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EDITORIAL

Understanding serum inflammatory markers in pediatric *Mycoplasma pneumoniae* pneumonia

Basavraj S Nagoba, Shree V Dhotre, Ajay M Gavkare, Sachin S Mumbre, Pradnya S Dhotre

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Abstract

This editorial reflects on the research, which investigates the potential of serum markers to predict the severity of *Mycoplasma pneumoniae* infections. *Mycoplasma pneumoniae* pneumonia (MPP) is a prevalent cause of respiratory infections in children, often leading to significant morbidity. Predicting the severity of MPP can significantly enhance patient management and outcomes. This editorial reviews the role of specific laboratory markers: (1) Lactate dehydrogenase; (2) Interleukin (IL)-6; (3) IL-10; (4) Tumor necrosis factor-α; and (5) D-dimer in predicting the severity of MPP in pediatric patients. Elevated levels of these markers are strongly associated with severe cases of MPP, providing clinicians with valuable tools for early diagnosis and targeted intervention.

Key Words: *Mycoplasma pneumoniae* pneumonia; Pediatric; Severity prediction; Laboratory markers; Clinical management

Core Tip: This editorial underscores the significance of laboratory markers in predicting the severity of *Mycoplasma pneumoniae* pneumonia (MPP) in children. Elevated levels of lactate dehydrogenase, interleukin (IL)-6, IL-10, tumor necrosis factor-α, and D-dimer are identified as critical indicators of severe MPP. Utilizing these markers can aid in the early identification of severe cases, facilitating timely intervention and improving clinical outcomes in pediatric patients.

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INTRODUCTION

Mycoplasma pneumoniae pneumonia (MPP) is a significant cause of respiratory infections in children, leading to substantial morbidity and occasionally severe complications. Early and accurate prediction of MPP severity is crucial for optimizing patient management and improving outcomes. This editorial explores the role of specific laboratory markers; lactate dehydrogenase (LDH), interleukin (IL)-6, IL-10, tumor necrosis factor-α (TNF-α), and D-dimer; in predicting the severity of MPP in paediatric patients.

Wang *et al*[1] published a notable study that highlights the predictive value of serum inflammatory markers in assessing the severity of MPP in children. By analyzing clinical manifestations and laboratory data from 160 children (80 with severe MPP and 80 with mild MPP), the research offers valuable insights into the role of inflammatory cytokines in the progression of disease.

EPIDEMIOLOGY

MPP is a common respiratory infection in children, particularly those aged 5-15 years. It accounts for up to 40% of community-acquired pneumonia cases in this age group[2]. The infection is highly contagious, spreading through respiratory droplets, and can lead to outbreaks in schools and childcare settings. Seasonal variations are noted, with higher incidence rates in the late summer and early fall[3].

According to Bradley *et al*[4], community-acquired pneumonia in children often presents as MPP, especially during these peak seasons, making it imperative to understand and predict the severity of this condition.

Pathophysiology

Mycoplasma pneumoniae is a small, wall-less bacterium that attaches to the respiratory epithelium, causing inflammation and damage[5]. The immune response to this pathogen involves both cellular and humoral components, leading to the production of various cytokines and inflammatory markers[6]. The severity of MPP can be influenced by the host's immune response and the bacterial load.

The pathogenesis of MPP includes direct cytotoxic effects of the pathogen and immune-mediated damage. Studies indicate that the bacterium can induce a robust immune response, causing a cytokine storm in severe cases, which is characterized by elevated levels of IL-6, IL-10, TNF-α, and other inflammatory markers[7].

Clinical presentation

Children with MPP typically present with a range of symptoms, from mild respiratory discomfort to severe pneumonia. Common symptoms include a persistent dry cough, fever, malaise, and headache[8]. In severe cases, patients may develop complications such as pleural effusion, respiratory failure, or extrapulmonary manifestations like encephalitis and hemolytic anemia[9].

A study by Jain *et al*[10] found that MPP often presents with nonspecific symptoms that overlap with other respiratory infections, complicating the initial clinical assessment. Moreover, extrapulmonary manifestations, though less common, can significantly impact patient morbidity and require comprehensive management strategies.

Diagnostic dilemmas

Diagnosing MPP can be challenging due to its nonspecific clinical presentation and the limitations of current diagnostic methods. PCR and serological tests are commonly used but may not always provide timely or definitive results[11]. The identification of reliable laboratory markers that correlate with disease severity is essential for improving diagnostic accuracy and patient management[2].

The utility of LDH, IL-6, IL-10, TNF-α, and D-dimer as biomarkers for severe MPP has been supported by various studies. Elevated levels of these markers have been consistently associated with more severe disease presentations and poorer outcomes[12]. Additionally, these biomarkers can be measured quickly and easily in clinical settings, providing real-time data to guide therapeutic decisions.

Therapeutic strategies

Treatment of MPP typically involves the use of macrolide antibiotics, such as azithromycin or clarithromycin[9]. In cases of macrolide-resistant *Mycoplasma pneumoniae*, alternative antibiotics like doxycycline or fluoroquinolones may be used [13]. Supportive care, including hydration, antipyretics, and respiratory support, is crucial in managing severe cases.

Recent guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of United States emphasize the importance of early and appropriate antibiotic therapy to mitigate complications and improve outcomes [4]. Moreover, adjunctive therapies targeting the inflammatory response, such as corticosteroids, have been explored, though their routine use remains controversial[14].

Clinical implications

The identification of elevated levels of LDH, IL-6, IL-10, TNF-α, and D-dimer as markers of severe MPP has significant clinical implications. These markers can help clinicians to identify patients at higher risk of severe disease, allowing for timely and targeted therapeutic interventions[1]. Early identification and treatment of severe MPP can reduce the risk of complications and improve patient outcomes[3].

Furthermore, integrating these biomarkers into clinical practice can enhance the precision of severity assessments and facilitate personalized treatment approaches. Studies have demonstrated that early and aggressive intervention in patients with elevated biomarker levels can significantly reduce morbidity and healthcare costs[15].

EDITORIAL COMMENTS

The role of laboratory markers in predicting MPP severity represents a promising advancement in paediatric respiratory medicine. LDH, IL-6, IL-10, TNF-α, and D-dimer are readily available and routinely measured in clinical practice, making them practical tools for clinicians. Future research should focus on validating these findings in larger, multicenter studies and exploring the potential for incorporating these markers into clinical decision-making algorithms.

Additionally, the development of predictive models incorporating these biomarkers could further enhance clinical decision-making. For example, a scoring system based on biomarker levels and clinical parameters could provide a comprehensive risk assessment, guiding treatment intensity and resource allocation.

CONCLUSION

Early prediction of severity of MPP using laboratory markers such as LDH, IL-6, IL-10, TNF-α, and D-dimer can significantly enhance patient management and outcomes in pediatric populations. These markers provide valuable insights into disease progression, enabling timely and targeted interventions. As our understanding of MPP pathophysiology and its clinical implications evolves, incorporating these markers into routine clinical practice holds the potential to improve care for children with this common and potentially severe infection.

Future studies should aim to standardize the measurement and interpretation of these biomarkers across different clinical settings. Additionally, investigating the interplay between these markers and other clinical factors could provide a more nuanced understanding of MPP severity and its determinants. Collaborative efforts and multicenter trials will be essential to translate these findings into widespread clinical practice.

FOOTNOTES

Author contributions: Nagoba BS designed the overall concept and outline of the manuscript; Dhotre SV, Gavkare AM, Mumbre SS, and Dhotre PS contributed to the discussion and design of the manuscript; Nagoba BS, Dhotre SV and Gavkare AM contributed to the writing, and editing the manuscript and review of literature; all of the authors read and approved the final version of the manuscript to be published.

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REFERENCES

1 **Wang LP**, Hu ZH, Jiang JS, Jin J. Serum inflammatory markers in children with Mycoplasma pneumoniae pneumonia and their predictive value for Mycoplasma severity. *World J Clin Cases* 2024; **12**: 4940-4946 [PMID: 39109035 DOI: 10.12998/wjcc.v12.i22.4940]

2 **Zhang Y**, Zhou Y, Li S, Yang D, Wu X, Chen Z. The Clinical Characteristics and Predictors of Refractory Mycoplasma pneumoniae Pneumonia in Children. *PLoS One* 2016; **11**: e0156465 [PMID: 27227519 DOI: 10.1371/journal.pone.0156465]

3 **Jain S**, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, Stockmann C, Anderson EJ, Grijalva CG, Self WH, Zhu Y, Patel A, Hymas W, Chappell JD, Kaufman RA, Kan JH, Dansie D, Lenny N, Hillyard DR, Haynes LM, Levine M, Lindstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, Wunderink RG, Edwards KM, Pavia AT, McCullers JA, Finelli L; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015; **372**: 835-845 [PMID: 25714161 DOI: 10.1056/NEJMoa1405870]

4 **Bradley JS**, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH Jr, Moore MR, St Peter SD, Stockwell JA, Swanson JT; Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011; **53**: e25-e76 [PMID: 21880587 DOI: 10.1093/cid/cir531]

5 **Waites KB**, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. *Clin Microbiol Rev* 2004; **17**: 697-728 [PMID: 15489344 DOI: 10.1128/CMR.17.4.697-728.2004]

6 **Waites KB**, Xiao L, Liu Y, Balish MF, Atkinson TP. Mycoplasma pneumoniae from the Respiratory Tract and Beyond. *Clin Microbiol Rev* 2017; **30**: 747-809 [PMID: 28539503 DOI: 10.1128/CMR.00114-16]

7 **Liu B**, Chang X, Yan N. Clinical analysis of the epidemiology and changes in inflammatory indexes of Mycoplasma pneumonia in acute and recovery stage pediatric patients. *Transl Pediatr* 2022; **11**: 1645-1655 [PMID: 36345443 DOI: 10.21037/tp-22-416]

8 **Atkinson TP**, Balish MF, Waites KB. Epidemiology, clinical manifestations, pathogenesis and laboratory detection of Mycoplasma pneumoniae infections. *FEMS Microbiol Rev* 2008; **32**: 956-973 [PMID: 18754792 DOI: 10.1111/j.1574-6976.2008.00129.x]

9 **Principi N**, Esposito S. Management of severe community-acquired pneumonia of children in developing and developed countries. *Thorax* 2011; **66**: 815-822 [PMID: 20965930 DOI: 10.1136/thx.2010.142604]

10 **Jain S**, Finelli L; CDC EPIC Study Team. Community-acquired pneumonia among U.S. children. *N Engl J Med* 2015; **372**: 2167-2168 [PMID: 26017833 DOI: 10.1056/NEJMc1504028]

11 **Kutty PK**, Jain S, Taylor TH, Bramley AM, Diaz MH, Ampofo K, Arnold SR, Williams DJ, Edwards KM, McCullers JA, Pavia AT, Winchell JM, Schrag SJ, Hicks LA. Mycoplasma pneumoniae Among Children Hospitalized With Community-acquired Pneumonia. *Clin Infect Dis* 2019; **68**: 5-12 [PMID: 29788037 DOI: 10.1093/cid/ciy419]

12 **Zhu Z**, Zhang T, Guo W, Ling Y, Tian J, Xu Y. Clinical characteristics of refractory Mycoplasma pneumoniae pneumonia in children treated with glucocorticoid pulse therapy. *BMC Infect Dis* 2021; **21**: 126 [PMID: 33509121 DOI: 10.1186/s12879-021-05830-4]

13 **Morozumi M**, Takahashi T, Ubukata K. Macrolide-resistant Mycoplasma pneumoniae: characteristics of isolates and clinical aspects of community-acquired pneumonia. *J Infect Chemother* 2010; **16**: 78-86 [PMID: 20094751 DOI: 10.1007/s10156-009-0021-4]

14 **Yang EA**, Kang HM, Rhim JW, Kang JH, Lee KY. Early Corticosteroid Therapy for Mycoplasma pneumoniae Pneumonia Irrespective of Used Antibiotics in Children. *J Clin Med* 2019; **8**: 726 [PMID: 31121867 DOI: 10.3390/jcm8050726]

15 **Tong L**, Huang S, Zheng C, Zhang Y, Chen Z. Refractory Mycoplasma pneumoniae Pneumonia in Children: Early Recognition and Management. *J Clin Med* 2022; **11**: 2824 [PMID: 35628949 DOI: 10.3390/jcm11102824]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Genetic variation features of neonatal hyperbilirubinemia caused by inherited diseases

Jin-Ying You, Ling-Yun Xiong, Min-Fang Wu, Jun-Song Fan, Qi-Hua Fu, Ming-Hua Qiu

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Abstract

BACKGROUND

Genetic factors play an important role in neonatal hyperbilirubinemia (NH) caused by genetic diseases.

AIM

To explore the characteristics of genetic mutations associated with NH and analyze the correlation with genetic diseases.

METHODS

This was a retrospective cohort study. One hundred and five newborn patients diagnosed with NH caused by genetic diseases were enrolled in this study between September 2020 and June 2023 at the Second Affiliated Hospital of Xiamen Medical College. A 24-gene panel was used for gene sequencing to analyze gene mutations in patients. The data were analyzed *via* Statistical Package for the Social Sciences 20.0 software.

RESULTS

Seventeen frequently mutated genes were found in the 105 patients. *Uridine 5'-diphospho-glucuronosyltransferase 1A1* (*UGT1A1*) variants were identified among the 68 cases of neonatal Gilbert syndrome. In patients with sodium taurocholate cotransporting polypeptide deficiency, the primary mutation identified was *Na+/taurocholate cotransporting polypeptide Ntcp* (*SLC10A1*). *Adenosine triphosphatase 7B* (*ATP7B*) mutations primarily occur in patients with hepatolenticular degeneration (Wilson's disease). In addition, we found that *UGT1A1* and *glucose-6-phosphate dehydrogenase* mutations were more common in the high-risk group than in the low-risk group, whereas mutations in *SLC10A1*, *ATP7B*, and *heterozygous 851del4 mutation* were more common in the low-risk group.

CONCLUSION
Genetic mutations are associated with NH and significantly increase the risk of disease in affected newborns.

Key Words: Hyperbilirubinemia; Gene mutation; Neonates; Genetic polymorphisms; Inherited diseases

Core Tip: Variations in the frequency and distribution of gene mutations are observed in neonatal hyperbilirubinemia (NH) caused by inherited diseases, with *uridine 5'-diphospho-glucuronosyltransferase 1A1* mutations prevalent in neonatal Gilbert syndrome cases, *Na+/taurocholate cotransporting polypeptide Ntcp* mutations in sodium taurocholate cotransporting polypeptide deficiency patients, and *Adenosine triphosphatase* mutations in Wilson's disease. The distinct genetic profiles between the high-risk and low-risk groups suggest the potential utility of genetic screening for risk stratification and early intervention in NH.

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INTRODUCTION

Neonatal hyperbilirubinemia (NH) is one of the most common clinical issues in newborns, with an incidence as high as 60% in healthy full-term infants[1,2]. Most cases are physiological and mild and often do not require treatment. However, it can also be associated with certain underlying conditions. Severe cases can lead to bilirubin encephalopathy without timely treatment, resulting in intellectual impairment, damage to the nervous and auditory systems, and even death[3].

The aetiology of NH is complex, and different cases of hyperbilirubinemia can have single or mixed causes. Known pathogenic factors include ABO blood group or Rh blood group incompatibility, infections, and delayed meconium passage[4-6]. However, there are also cases where the cause of jaundice is unclear. For patients with NH of unknown cause, identifying the underlying etiology is crucial for timely diagnosis and effective treatment. In some instances, abnormally elevated bilirubin levels may indicate underlying genetic factors, where genetic mutations may play a pivotal role[7,8].

With the rapid advancement of gene mutation detection technologies, the significance of genetic factors in NH has attracted increasing attention. Long *et al*[9] detected *Uridine 5'-diphospho-glucuronosyltransferase 1A1* (*UGT1A1*) gene mutations in infants with hyperbilirubinemia *via* methods such as polymerase chain reaction (PCR). They reported that the *UGT1A1* 211G>A mutation is associated with NH in Asians. In another study, *UGT1A1* variants were recognized as potential risk factors for prolonged jaundice and hyperbilirubinemia, particularly among full-term, exclusively breastfed infants of Chinese descent, *via glucose-6-phosphate dehydrogenase* (*G6PD*) enzyme quantification assays[10]. However, previous studies have focused primarily on detecting single genes *via* traditional methods such as PCR. However, comprehensive studies exploring the broader genetic landscape of NH in which multiple genes are targeted remain scarce. This highlights the need for further investigations and more extensive genomic analyses. In clinical practice, high-throughput sequencing for neonatal genetic screening could facilitate the identification of genetic variants associated with hyperbilirubinemia, offering valuable guidance for clinical diagnosis and treatment.

Some studies have shown that several genetic disorders can lead to hyperbilirubinemia, including Dubin-Johnson syndrome (DJS), Crigler–Najjar syndrome, Gilbert syndrome (GS), and Lucey–Driscoll syndrome[11]. With the advancement of genetic testing technologies, the crucial role of genetic mutations in the occurrence of NH is increasingly recognized. GS is a common genetic disorder characterized by elevated levels of bilirubin in the blood[12]. Its main feature is mutations in the *UGT1A1* gene, which is involved in bilirubin metabolism. Research has indicated that mutations in the *UGT1A1* gene lead to decreased bilirubin metabolism capacity, thereby increasing the risk of NH[13]. Crigler–Najjar syndrome is a rare but severe genetic disorder characterized by high levels of bilirubin in the blood. Its aetiology is also associated with mutations in the *UGT1A1* gene[14]. In addition, other genetic mutations related to bilirubin metabolism, such as *OATP transporters* (*SLCO1B1*), *heterozygous 851del4 mutation* (*SLC25A13*), and *biliverdin reductase A* (*BLVRA*)[15-17], are associated with NH. These findings indicate that genetic mutations play a significant role in the pathogenesis of NH, providing important clues for a deeper understanding of the genetic basis and pathological mechanisms of this disease. However, previous studies have focused mainly on exploring the correlation between specific gene variants and patients with hyperbilirubinemia, and a systematic exploration of the association between more unknown genes and NH in large-scale populations is lacking.

Given the potential complexity and clinical significance of NH, a thorough understanding of the associated genetic mutations is crucial for elucidating the genetic basis of this condition, guiding clinical diagnosis, and formulating individualized treatment. Therefore, this study aims to explore genetic mutations associated with NH comprehensively and investigate the correlation between these mutations and the pathogenesis of the disease. These results provide a

foundation for future clinical practice and genetic counseling, offering a deeper understanding and guidance for the prevention and treatment of NH.

MATERIALS AND METHODS

Study population and data collection

We prospectively collected data from 105 newborn patients who were diagnosed with NH caused by genetic diseases between September 2020 and June 2023 at the Second Affiliated Hospital of Xiamen Medical College. The inclusion criteria were as follows: (1) They were diagnosed with NH caused by genetic diseases; and (2) They had undergone genetic testing. The exclusion criteria were as follows: Individuals with hyperbilirubinemia who did not undergo 24-gene panel testing. Whole blood samples were collected from all patients and stored at -20 °C for genetic sequencing. The study was conducted in accordance with the Helsinki Declaration and approved by the Clinical Research Ethics Committee of the Second Affiliated Hospital of Xiamen Medical College (No. 2020039). Informed consent was obtained from all the legal guardians of the study participants.

Targeted panel sequencing and genetic analysis

Targeted panel sequencing of 23 genes, including: (1) *Adenosine triphosphatase* (*ATP*)*-binding cassette transporters* (*ABCB11*); (2) *ATP-binding cassette subfamily C member 2* (*ABCC2*); (3) *ATP-binding cassette sub-family D member 3* (*ABCD3*); (4) *Trihydroxycoprostanoyl-CoA oxidase* (*ACOX2*); (5) *ATP7B*; (6) *UGT1A1*; (7) *Cytochrome P450, Family 7, Subfamily B, Polypeptide 1* (*CYP7B1*); (8) *G6PD*; (9) *Beta-globin gene* (*HBB*); (10) *3β-hydroxy-Δ5-C27-steroid oxidoreductase* (*HSD3B7*); (11) *Jagged 1* (*JAG1*); (12) *Niemann-Pick type C 1* (*NPC1*); (13) *NPC2*; (14) *NOTCH2*; (15) *SMase gene* (*SMPD1*); (16) *Glucocerebrosidase*; (17) *ABCB4*; (18) *Farnesoid X receptor* (*NR1H4*); (19) *Monoclonal antibody P504S*; (20) *Aldo-keto reductase family 1 member D1*; (21) *ATP8B1*; (22) *Na+/taurocholate cotransporting polypeptide Ntcp* (*SLC10A1*); and (23) *SLC25A13,* was performed for each patient. Genomic DNA was extracted from whole-blood samples *via* a QIAamp DNA Blood Mini Kit (Qiagen) according to the manufacturer's protocol. Genomic DNA fragments were enriched for targeted panel sequencing (Agilent ClearSeq Inherited Disease Kit; Agilent). After enrichment, the DNA libraries underwent next-generation sequencing (Illumina HiSeq 2000/2500 platform). The sequencing data were first processed to remove low-quality reads and adapter sequences. Burrows-Wheeler Aligner software was then used to align the sequencing reads to the human reference genome (version hg19). Genome analysis toolkit software was subsequently employed to identify single nucleotide variants and insertions/deletions within the aligned reads. Annotation analysis was conducted *via* databases including the 1000 Genomes Project, ExAC, gnomAD, ClinVar, Human Gene Mutation Database (HGMD) Professional, and local databases.

Statistical analysis

Statistical Package for the Social Sciences 20.0 was used for data analysis. The continuous variables in the data group are expressed as the means ± SD. Count data are presented as frequencies and percentages. The Pearson χ^2 test was used, and $P < 0.05$ was considered statistically significant.

RESULTS

General clinical characteristics

A total of 105 newborns with hyperbilirubinemia caused by genetic diseases (54 males and 43 females) were included in this study (Table 1). Among these patients, the birth weight was 2.01-4.10 kg, with an average of 3.25 kg ± 0.82 kg, and the gestational age was 36-41 weeks, with an average of 38 weeks ± 2 weeks. The occurrence of hyperbilirubinemia ranged from 1 day to 60 days, with an average of 16.5 days. There were 87 full-term infants, 9 preterm infants, and 9 unknown. Seventy-three infants were fully breastfed, 24 were mixed fed, and 8 were unknown. The peak value of total serum bilirubin (TSB) was 291-722.39 μmol/L, with an average of 398.07 μmol/L ± 55.09 μmol/L. Among them, 68 patients (64.7%) had GS, 14 patients (13.3%) had sodium taurocholate cotransporting polypeptide deficiency (NTCP) deficiency, and 9 patients (8.6%) had Citrin deficiency. There were five cases each of *G6PD* deficiency, Niemann-Pick disease (NPD), Wilson's disease, and congenital bile acid synthesis disorders (4.8%). There were four cases (3.8%) of progressive familial intrahepatic cholestasis and four cases (3.8%) of Alagille syndrome. Three patients (2.9%) had DJS, and two patients (1.9%) had thalassemia.

Genetic spectrum of the study participants

We tested the samples through a 24-gene panel, and variants defined as pathogenic or likely pathogenic (LP) were selected for analysis. Among the 105 patients, 75 (71.4%) were pathogenic or LP variant carriers. In a study of 82 patients, a total of 17 pathogenic mutated genes were detected, including: (1) *ABCB11*; (2) *ABCC2*; (3) *ABCD3*; (4) *ACOX2*; (5) *ATP7B*; (6) *UGT1A1*; (7) *CYP7B1*; (8) *G6PD*; (9) *HBB*; (10) *HSD3B7*; (11) *JAG1*; (12) *NPC1*; (13) *NR1H4*; (14) *ATP8B1*; (15) *SLC10A1*; (16) *SLC25A13*; and *SMPD1* (Figure 1). Among these genes, *UGT1A1* (77.3%) had the highest mutation frequency, accounting for 67.2% (39/58) of the heterozygous mutations and 32.7% (19/58) of the homozygous mutations. The gene with the highest frequency was *SLC10A1* (18.7%), which included 92.9% (13/14) of the genes with heterozygous mutations and 7.1% (1/14) with homozygous mutations. This was followed by genes that were entirely heterozygous

Table 1 Demographic and clinical characteristics of the study population, *n* (%)

Variable	Patient cohorts (*n* = 105)
Sex	
Female	43
Male	54
Gestational age (weeks)	38 ± 2
birth weight (kg)	3.25 ± 0.82 (2.01-4.10)
Age of onset (days)	
1-3 days	59
4-7 days	11
≥ 8 days	6
Feeding pattern	
Full breastfeeding	73
Mix feeding	24
Premature birth	
Yes	9
No	87

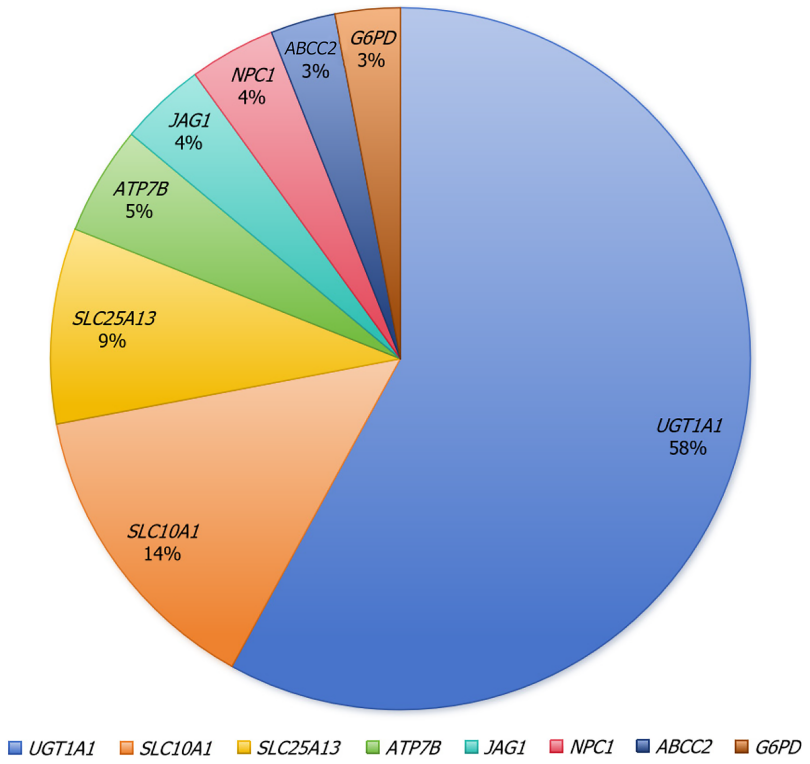

Figure 1 Results for the percentage of mutated genes in 105 patients. *UGT1A1*: *Uridine 5'-diphospho-glucuronosyltransferase 1A1*; *SLC10A1*: *Na+/taurocholate cotransporting polypeptide Ntcp*; *SLC25A13*: *Heterozygous 851del4 mutation*; *ATP7B*: *Adenosine triphosphatase 7B*; *JAG1*: *Jagged 1*; *NPC1*: *Niemann-Pick type C 1*; *ABCC2*: *Adenosine triphosphatase-binding cassette subfamily C member 2*; *G6PD*: *Glucose-6-phosphate dehydrogenase*.

mutations: (1)*SLC25A13* (12%); and (2) *ATP7B* (6.7%). The remaining genes were low-frequency pathogenic genes, including: (1) *JAG1* (5.3%); (2) *NPC1* (5.3%); (3) *ABCC2* (4.0%); and (4) G6PD (4.0%). These gene mutations are associated with the onset of NH caused by genetic diseases.

Analysis of genetic factors in NHs

We analyzed the molecular genetic factors of hyperbilirubinemia caused by genetic diseases, and the list of gene

mutations is shown in Table 2. Among the 17 detected genetic diseases, GS is the most common, and through diagnostic analysis, 4 different *UGT1A1* variants were identified among the 71 cases of neonatal GS. The most common variant was p.Gly71Arg (84.5%), followed by p.Pro364Leu (9.9%) and p.Tyr486Asp (2.8%). The three known mutations were classified as pathogenic according to the HGMD standards/guidelines. The p.Pro451Leu mutation is a variant of uncertain significance identified for the first time. The primary mutation identified in patients with NTCP deficiency is *SLC10A1* (p.Ser267Phe). *ATP7B* mutations primarily occur in patients with hepatolenticular degeneration (Wilson's disease), among which there are four variants of uncertain clinical significance: (1) P.Asp1164Asn; (2) P.Arg827Gln; (3) P.Thr935Met; and (4) P.Cys157Phe. Mutations in *G6PD* are associated with hemolytic anemia due to G6PD deficiency. When considering NPD, the *HSD3B7* (p.Ser738Ter and p.Gln81His), *SMPD1* (p.Leu124Arg), and *ABCD3* (p.Ala321Val) gene mutation rates were 12.2% (28/230) and 9.6% (22/230), respectively. In patients with DJS, mutations occur in the *ABCC2* gene. Among these mutations, p.Gln93Ter is classified as LP, and the other two novel variants (p.Arg1310Gly and p.Glu881del) are classified as variants of uncertain significance. Additionally, we identified several rare mutations, including *HBB* mutations in patients with thalassemia, *ACOX2* mutations in patients with type 1 congenital bile acid synthesis disorder, and *SMPD1* mutations in patients with neonatal DJS.

Gene mutations and their distribution in high-risk patients

Patients were classified into high-risk and low-risk groups based on a total bilirubin level of 342 μmol/L. First, we analyzed the correlation between clinical characteristics and TSB levels. Our bivariate analysis results of the clinical characteristics are shown in Table 3. Exclusive breastfeeding was shown to be associated with severe TSB ($P < 0.05$). Sex, feeding method, birth weight, and gestational age were unrelated to TSB. An analysis of the frequency of genetic mutations in the high-risk and low-risk groups was conducted. The results revealed that the proportions of *UGT1A1* and *G6PD* mutations were greater in the high-risk group, whereas mutations in *SLC10A1*, *ATP7B*, and *SLC25A13* were more common in the low-risk group (Figure 2). The results of the bivariate analysis of gene mutation and the TSB are shown in Table 4. None of the genes were associated with severe TSB.

DISCUSSION

NH is a common condition in newborns, and its pathogenesis involves abnormalities in the bilirubin metabolism pathway[18]. In recent years, more studies have shown a close association between hyperbilirubinemia and genetic mutations[19]. These mutations affect the function of related genes, leading to abnormalities in bilirubin metabolism. In this study, we explored the relationships between hyperbilirubinemia caused by inherited diseases and genetic mutations and analyzed their potential clinical significance.

UGT1A1 is an enzyme responsible for conjugating bilirubin with glucuronic acid. Genetic variants of *UGT1A1* that result in reduced enzyme activity and expression are associated with nonhemolytic hyperbilirubinemia syndromes, such as GS and Crigler-Najjar (CN) syndrome type I and type II (referred to as CN I and CN II, respectively)[20-22]. Previous studies confirmed that the prevalence of *UGT1A1* gene mutations in patients with hyperbilirubinemia is significantly greater than that in healthy controls, suggesting that *UGT1A1* gene mutations play an important role in the pathogenesis of hyperbilirubinemia[23]. Additionally, research by Mazur-Kominek *et al*[24] has shown that *UGT1A1* mutations are among the key causes of NH. These mutations decrease the expression level of the *UGT1A1* gene, thereby reducing the rate of bilirubin metabolism and increasing the concentration of bilirubin in the blood, ultimately leading to hyperbilirubinemia. The present study revealed that *UGT1A1* has the highest mutation frequency in patients with hyperbilirubinemia, which is consistent with previous research results. Furthermore, our study revealed that the mutation frequency of *UGT1A1* in high-risk bilirubin patients was greater than that in low-risk patients. The *ATP7B* gene is one of the genes that encode copper-transporting proteins in the human genome. The protein encoded by this gene is an ATPase that plays a critical role in maintaining the body's balance and metabolism of copper ions. Previous studies have suggested that mutations in the *ATP7B* gene may affect the structure or function of the ATP7B protein, leading to abnormal copper accumulation in the liver and resulting in Wilson's disease[25,26]. Wilson's disease may cause liver diseases such as liver fibrosis and cirrhosis, which may interfere with the metabolism and excretion of bilirubin, ultimately leading to hyperbilirubinemia[27]. Our research revealed that the mutation frequency of the *ATP7B* gene was greater in the high-risk bilirubin patient group. These findings suggest that *ATP7B* plays an important role in hyperbilirubinemia. Our study also revealed common mutations in *G6PD* among patients with high bilirubin levels. Functional loss mutations in the *G6PD* gene cause G6PD deficiency. G6PD deficiency is a significant risk factor for NH[28]. Several studies have indicated that infants with G6PD deficiency are prone to severe neonatal jaundice[29-31]. Elevated levels of bilirubin in the blood and ineffective bilirubin clearance in the liver can also lead to the accumulation of serum bilirubin, resulting in NH. This condition is more common and severe in infants with G6PD deficiency[32]. Furthermore, studies have indicated that variations in the *UGT1A1* gene are risk factors for NH in infants with G6PD deficiency[33]. The *ABCC2* gene is located on chromosome 10q24 and encodes multidrug resistance-associated protein 2 (MRP2). Studies have confirmed that conjugate hyperbilirubinemia is the most obvious consequence of mutations in ABCC2 that lead to DJS[34].

We identified several rare mutations, including *HBB* mutations in patients with beta-thalassemia, *ACOX2* mutations in patients with type 1 congenital bile acid synthesis disorder, and *SMPD1* mutations in patients with DJS. The *HBB* gene encodes the beta-globin chain of hemoglobin. Beta-thalassemia is an inherited blood disorder caused by mutations in the *HBB* gene, resulting in impaired synthesis of beta-globin, leading to hemolytic anemia and chronic anemia, and hemolysis may lead to hyperbilirubinemia[35]. The *ACOX2* gene encodes acyl-coenzyme an oxidase 2, which is key in the bile acid synthesis pathway. Defects in *ACOX2* can block bile acid synthesis, leading to bile stasis and hyperbilirubinemia[36]. The

Table 2 List of pathogenic/likely pathogenic variants in patients

Gene	Cytogenetic location	Mutation variant	Amino acid variant	Type of gene	Allele frequency
Uridine 5'-diphospho-glucuronosyltransferase 1A1	Chr2: 234669144	C.211G>A	P.Gly71Arg	Het/hom	0.152
	Chr2: 234676872	C.1091C>T	P.Pro364 Leu	Het	0.012
	Chr2: 234681059	C.1456T>G	P.Tyr486Asp	PAT	0.001
	Chr2: 234680955	C.1352C>T	P.Pro451 Leu	Het	0.005
Na+/taurocholate cotransporting polypeptide Ntcp	Chr14: 70245193	C.800C>T	P.Ser267Phe	Het/hom	0.078
heterozygous 851del4 mutation	Chr7: 95818684	C.852_855delTATG	P.Met285ProfsTer2	Het	0.004
	Chr7: 95813702	C.1064G>A	P.Arg355Gln	Het	3.48^{E-04}
	Chr7: 95775896	C.1424G>A	P.Arg475Gln	Het	-
	Chr7: 95751240	C.1638_1660dup	P.Ala554GlyfsTer17	Het	0.0013
ATP 7B	Chr13: 52515283	C.3490G>A	P.Asp1164Asn	Het	-
	Chr13: 52524503	C.2480G>A	P.Arg827Gln	Het	5.80^{E-4}
	Chr13: 52523859	C.2804C>T	P.Thr935Met	Het	0.002
	Chr13: 52548886	C.470G>T	P.Cys157Phe	Het	-
	Chr13: 52524515	C.2468A>G	P.Glu823Gly	Het	1.16^{E-4}
	Chr13: 52534313	C.2092A>C	P.Ile698 Leu	Het	-
Glucose-6-phosphate dehydrogenase	ChrX: 153774276	C.185A>G	P.His62Arg	Hemi	0.002
	ChrX: 153763476	C.482G>T	P.Gly161Val	Het	6.03^{E-4}
	ChrX: 153760484	C.1466G>T	P.Arg489 Leu	Het	0.008
	ChrX: 153760472	C.1478G>A	P.Arg493His	Hemi	0.005
Beta-globin gene	Chr11: 5246931	C.341T>A	P.Val114Glu	Het	2.32^{E-4}
Cytochrome P450, Family 7, Subfamily B, Polypeptide 1	Chr8: 65536958	C.259+2T>C		Het	1.16^{E-4}
ATP-binding cassette subfamily C member 2	Chr10: 101552060	C.277C>T	P.Gln93Ter	Het	1.16^{E-4}
Jagged 1	Chr20: 10622442	C.2671G>A	P.Ala891Thr	Het	-
Niemann-Pick type C 1	Chr18: 21116653	C.3229C>T	P.Arg1077Ter	Het	-
Farnesoid X receptor	Chr12: 100926359	C.569T>A	P.Met190 Lys	Het	-
3β-hydroxy-Δ5-C27-steroid oxidoreductase	Chr16: 30998260	C.631C>T	P.Arg211Cys	Het	-
	Chr18: 21123451	C.2213C>A	P.Ser738Ter	Het	1.16^{E-4}
	Chr18: 21152082	C.243G>C	P.Gln81His	Het	-
ATP 8B1	Chr18: 55351421	C.1477G>A	P.Val493Ile	Het	7.11^{E-4}
	Chr20: 10629285	C.1481A>G	P.Asn494Ser	Het	-
Trihydroxycoprostanoyl-CoA oxidase	Chr3: 58512313	C.1226G>A	P.Arg409His	Het	0.002
	Chr3: 58508322	C.1533A>G	P.Ile511Met	Het	5.78^{E-4}
SMase gene	Chr11: 6412666	C.371T>G	P.Leu124Arg	Het	3.47^{E-4}
	Chr10: 101604163	C.3928C>G	P.Arg1310Gly	Het	-
	Chr12: 100904723	C.247C>G	P.Pro83Ala	Het	5.78^{E-04}
	Chr10: 101590078	C.2643_2645delAGA	P.Glu881del	Het	-
ATP-binding cassette transporters	Chr2: 169830310	C.1349T>C	P.Met450Thr	Het	4.65^{E-4}
	Chr11: 5247153	C.316-197C>T		Het	-
ATP-binding cassette sub-family D member 3	Chr1: 94933490	C.262C>T	P.Leu88Phe	Het	0.001

	Chr18: 21136571	C.962C>T	P.Ala321Val	Het	3.67^{E-4}
	Chr20: 10623197	C.2511T>G	P.Asp837Glu	Het	-

ATP: Adenosine triphosphatase.

Table 3 The correlation between clinical characteristics and total serum bilirubin levels

	Hyperbilirubinemia		
Factors	**Total serum bilirubin ≥ 342 μmol/L**	**Total serum bilirubin < 342 μmol/L**	***P* value**
Gender			
Female	17	26	0.67
Male	18	36	
Exclusive breastfeeding			
Yes	31	42	0.027
No	4	20	
Gestational age (week)	38.9 ± 1.26	38.6 ± 1.43	0.170
Birth weight (kg)	3.19 ± 0.41	3.16 ± 0.41	0.38
P			
Yes	2	7	0.48
No	33	54	

Table 4 Gene mutation analysis between high and low total serum bilirubin groups

	Hyperbilirubinemia		
Mutation	**Total serum bilirubin ≥ 342 μmol/L**	**Total serum bilirubin < 342 μmol/L**	***P* value**
Uridine 5'-diphospho-glucuronosyltransferase 1A1			
G/A	32	11	0.32
C/T	4	3	
T/G	1	1	
Na+/taurocholate cotransporting polypeptide Ntcp			
C/T	6	7	NA
Heterozygous 851del4 mutation			
C.852_855delTATG	2	3	0.57
C.1638_1660dup	0	1	
G/A	0	1	
Adenosine triphosphatase 7B			
G/T	1	0	0.26
A/C	1	0	
G/A	0	1	
C/T	0	1	
Glucose-6-phosphate dehydrogenase			
G/T	1	2	0.32
G/A	1	0	
A/G	0	1	

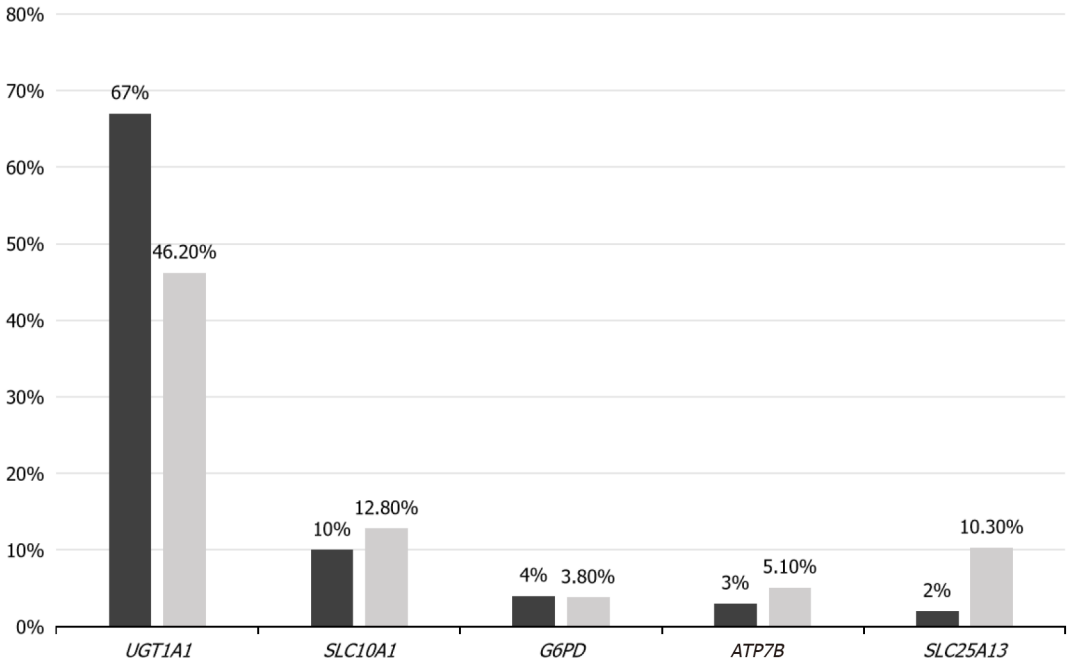

Figure 2 Analysis of the percentage of genes between the high and low total serum bilirubin groups. The blue bars represent the high-risk group with a total bilirubin level greater than 342 μmol/L. The orange bars correspond to the high-risk group with a total bilirubin level of less than 342 μmol/L. *UGT1A1*: *Uridine 5'-diphospho-glucuronosyltransferase 1A1*; *SLC10A1*: *Na+/taurocholate cotransporting polypeptide Ntcp*; *SLC25A13*: *Heterozygous 851del4 mutation*; *ATP7B* : *Adenosine triphosphatase 7B*; *G6PD*: *Glucose-6-phosphate dehydrogenase*.

SMPD1 gene encodes acid sphingomyelinase, which maintains lysosomal function by degrading lysosomal membranes in the lysosome. DJS is a rare genetic disorder caused by mutations in the *SMPD1* gene, resulting in impaired acid sphingomyelinase activity, obstruction of bilirubin excretion, and hyperbilirubinemia[37]. Identifying these rare mutations emphasizes the genetic variations of hyperbilirubinemia, where different gene mutations may lead to varying types of hyperbilirubinemia. Further investigation of these rare mutations will help us better understand the patho-genesis of hyperbilirubinemia and provide new clues and methods for diagnosing and treating related diseases[38].

Genetic screening is a valuable tool for identifying neonates who may be at increased risk for hyperbilirubinemia because of mutations or polymorphisms in genes involved in bilirubin metabolism, such as the *UGT1A1* gene and *SLCO1B1* gene[17]. Early identification of these genetic risk factors allows for the stratification of neonates into high-risk and low-risk categories. This stratified approach enables more tailored monitoring and intervention strategies[39,40]. High-risk infants can be prioritized for more frequent bilirubin level checks and earlier therapeutic interventions, such as phototherapy, thereby reducing the risk of severe complications such as phototherapy[41]. Moreover, low-risk infants may avoid unnecessary interventions, contributing to more efficient use of healthcare resources. Based on genetic screening, clinicians can develop more personalized treatment plans. By identifying susceptibility genes for hyperbilirubinemia, high-risk individuals who may develop severe hyperbilirubinemia can be identified early, allowing for more aggressive preventive and intervention measures[42]. This precision medicine strategy enhances the effectiveness of early interventions and reduces the incidence of severe complications.

This study has certain limitations. First, the limited number of cases may restrict the reliability and generalizability of the study results. Second, there are challenges in collecting clinical data on NH, including issues related to the quality and completeness of case data, which may affect the reliability of the study results. Additionally, differences in the number of samples available for analysis between different groups may also lead to experimental biases. Therefore, in the future, larger sample sizes and more comprehensive studies are needed to determine the correlation between genomic variations and the severity of hyperbilirubinemia.

CONCLUSION

There is a close association between hyperbilirubinemia and genetic mutations, where genetic mutations affect the normal functioning of bilirubin metabolism pathways, leading to hyperbilirubinemia. Research on genetic mutations related to hyperbilirubinemia not only helps us understand the pathogenesis of hyperbilirubinemia in depth but also provides new insights for its prevention, diagnosis, and treatment. Future studies should continue to explore the relationship between hyperbilirubinemia and genetic mutations to promote advancements in clinical practice, ultimately improving the prognosis of infants with hyperbilirubinemia.

FOOTNOTES

Author contributions: You JY conceived and designed the study; Xiong LY wrote the manuscript; Wu MF, Fan JS, Fu QH, and Qiu MH collected data and performed bioinformatics analysis; You JY and Xiong LY edited and revised the manuscript; all of the authors read and approved the final version of the manuscript to be published.

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REFERENCES

1 **Sarici SU**. Incidence and etiology of neonatal hyperbilirubinemia. *J Trop Pediatr* 2010; **56**: 128-129 [PMID: 19502601 DOI: 10.1093/tropej/fmp041]
2 **Mitra S**, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. *Br J Hosp Med (Lond)* 2017; **78**: 699-704 [PMID: 29240507 DOI: 10.12968/hmed.2017.78.12.699]
3 **Lee HY**, Ithnin A, Azma RZ, Othman A, Salvador A, Cheah FC. Glucose-6-Phosphate Dehydrogenase Deficiency and Neonatal Hyperbilirubinemia: Insights on Pathophysiology, Diagnosis, and Gene Variants in Disease Heterogeneity. *Front Pediatr* 2022; **10**: 875877 [PMID: 35685917 DOI: 10.3389/fped.2022.875877]
4 **Dennery PA**, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med* 2001; **344**: 581-590 [PMID: 11207355 DOI: 10.1056/NEJM200102223440807]
5 **Ip S**, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, Maisels MJ, Lau J; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. *Pediatrics* 2004; **114**: e130-e153 [PMID: 15231986 DOI: 10.1542/peds.114.1.e130]
6 **Huang MJ**, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. *Pediatr Res* 2004; **56**: 682-689 [PMID: 15319464 DOI: 10.1203/01.PDR.0000141846.37253.AF]
7 **Kaplan M**. Genetic interactions in the pathogenesis of neonatal hyperbilirubinemia: Gilbert's Syndrome and glucose-6-phosphate dehydrogenase deficiency. *J Perinatol* 2001; **21** Suppl 1: S30-34; discussion S35 [PMID: 11803413 DOI: 10.1038/sj.jp.7210630]
8 **Lin R**, Wang X, Wang Y, Zhang F, Wang Y, Fu W, Yu T, Li S, Xiong M, Huang W, Jin L. Association of polymorphisms in four bilirubin metabolism genes with serum bilirubin in three Asian populations. *Hum Mutat* 2009; **30**: 609-615 [PMID: 19243019 DOI: 10.1002/humu.20895]
9 **Long J**, Zhang S, Fang X, Luo Y, Liu J. Neonatal hyperbilirubinemia and Gly71Arg mutation of UGT1A1 gene: a Chinese case-control study followed by systematic review of existing evidence. *Acta Paediatr* 2011; **100**: 966-971 [PMID: 21272068 DOI: 10.1111/j.1651-2227.2011.02176.x]
10 **Yang Z**, Lin F, Xu JX, Yang H, Wu YH, Chen ZK, Xie H, Huang B, Lin WH, Wu JP, Ma YB, Li JD, Yang LY. UGT1A1*6 mutation associated with the occurrence and severity in infants with prolonged jaundice. *Front Pediatr* 2022; **10**: 1080212 [PMID: 36605758 DOI: 10.3389/fped.2022.1080212]
11 **Radlović N**. Hereditary hyperbilirubinemias. *Srp Arh Celok Lek* 2014; **142**: 257-260 [PMID: 24839786 DOI: 10.2298/sarh1404257r]
12 **Arnold JC**, Otto G, Kraus T, Kommerell B, Theilmann L. Gilbert's syndrome--a possible cause of hyperbilirubinemia after orthotopic liver transplantation. *J Hepatol* 1992; **14**: 404 [PMID: 1500702 DOI: 10.1016/0168-8278(92)90191-q]
13 **Tomerak RH**, Helal NF, Shaker OG, Yousef MA. Association between the Specific UGT1A1 Promoter Sequence Variant (c-3279T>G) and Unconjugated Neonatal Hyperbilirubinemia. *J Trop Pediatr* 2016; **62**: 457-463 [PMID: 27318112 DOI: 10.1093/tropej/fmw031]
14 **Abdellaoui N**, Abdelmoula B, Abdelhedi R, Kharrat N, Tabebi M, Rebai A, Bouayed Abdelmoula N. Novel combined UGT1A1 mutations in Crigler Najjar Syndrome type I. *J Clin Lab Anal* 2022; **36**: e24482 [PMID: 35527687 DOI: 10.1002/jcla.24482]
15 **Liu J**, Long J, Zhang S, Fang X, Luo Y. Polymorphic variants of SLCO1B1 in neonatal hyperbilirubinemia in China. *Ital J Pediatr* 2013; **39**: 49 [PMID: 24090270 DOI: 10.1186/1824-7288-39-49]

16 **Wang H**, Shu S, Chen C, Huang Z, Wang D. Novel mutations in the SLC25A13 gene in a patient with NICCD and severe manifestations. *J Pediatr Endocrinol Metab* 2015; **28**: 471-475 [PMID: 25381944 DOI: 10.1515/jpem-2014-0278]

17 **Fan J**, He HY, Li HH, Wu PL, Tang L, Deng BY, Dong WH, Wang JH. Associations between UGT1A1, SLCO1B1, SLCO1B3, BLVRA and HMOX1 polymorphisms and susceptibility to neonatal severe hyperbilirubinemia in Chinese Han population. *BMC Pediatr* 2024; **24**: 82 [PMID: 38279097 DOI: 10.1186/s12887-024-04537-0]

18 **Abbey P**, Kandasamy D, Naranje P. Neonatal Jaundice. *Indian J Pediatr* 2019; **86**: 830-841 [PMID: 30790186 DOI: 10.1007/s12098-019-02856-0]

19 **Zhou J**, Yang C, Zhu W, Chen S, Zeng Y, Wang J, Zhao H, Chen Y, Lin F. Identification of Genetic Risk Factors for Neonatal Hyperbilirubinemia in Fujian Province, Southeastern China: A Case-Control Study. *Biomed Res Int* 2018; **2018**: 7803175 [PMID: 30298137 DOI: 10.1155/2018/7803175]

20 **Cozzi L**, Nuti F, Degrassi I, Civeriati D, Paolella G, Nebbia G. Gilbert or Crigler-Najjar syndrome? Neonatal severe unconjugated hyperbilirubinemia with P364L UGT1A1 homozygosity. *Ital J Pediatr* 2022; **48**: 59 [PMID: 35436954 DOI: 10.1186/s13052-022-01251-4]

21 **Maruo Y**, Nakahara S, Yanagi T, Nomura A, Mimura Y, Matsui K, Sato H, Takeuchi Y. Genotype of UGT1A1 and phenotype correlation between Crigler-Najjar syndrome type II and Gilbert syndrome. *J Gastroenterol Hepatol* 2016; **31**: 403-408 [PMID: 26250421 DOI: 10.1111/jgh.13071]

22 **Kraemer D**, Scheurlen M. [Gilbert disease and type I and II Crigler-Najjar syndrome due to mutations in the same UGT1A1 gene locus]. *Med Klin (Munich)* 2002; **97**: 528-532 [PMID: 12371080 DOI: 10.1007/s00063-002-1180-6]

23 **Kim JJ**, Oh J, Kim Y, Lee KA. Genetic Spectrum of UGT1A1 in Korean Patients with Unconjugated Hyperbilirubinemia. *Ann Lab Med* 2020; **40**: 281-283 [PMID: 31858773 DOI: 10.3343/alm.2020.40.3.281]

24 **Mazur-Kominek K**, Romanowski T, Bielawski K, Kiełbratowska B, Preis K, Domżalska-Popadiuk I, Słomińska-Frączek M, Sznurkowska K, Renke J, Plata-Nazar K, Śledzińska K, Sikorska-Wiśniewska G, Góra-Gębka M, Liberek A. Association between uridin diphosphate glucuronosylotransferase 1A1 (UGT1A1) gene polymorphism and neonatal hyperbilirubinemia. *Acta Biochim Pol* 2017; **64**: 351-356 [PMID: 28399191 DOI: 10.18388/abp.2016_1450]

25 **Wang J**, Tang L, Xu A, Zhang S, Jiang H, Pei P, Li H, Lv T, Yang Y, Qian N, Naidu K, Yang W. Identification of mutations in the ATP7B gene in 14 Wilson disease children: Case series. *Medicine (Baltimore)* 2021; **100**: e25463 [PMID: 33879678 DOI: 10.1097/MD.0000000000025463]

26 **Balashova MS**, Tuluzanovskaya IG, Glotov OS, Glotov AS, Barbitoff YA, Fedyakov MA, Alaverdian DA, Ivashchenko TE, Romanova OV, Sarana AM, Scherbak SG, Baranov VS, Filimonov MI, Skalny AV, Zhuchenko NA, Ignatova TM, Asanov AY. The spectrum of pathogenic variants of the ATP7B gene in Wilson disease in the Russian Federation. *J Trace Elem Med Biol* 2020; **59**: 126420 [PMID: 31708252 DOI: 10.1016/j.jtemb.2019.126420]

27 **Lucena-Valera A**, Ruz-Zafra P, Ampuero J. Wilson's disease: overview. *Med Clin (Barc)* 2023; **160**: 261-267 [PMID: 36697289 DOI: 10.1016/j.medcli.2022.12.016]

28 **Liu H**, Liu W, Tang X, Wang T. Association between G6PD deficiency and hyperbilirubinemia in neonates: a meta-analysis. *Pediatr Hematol Oncol* 2015; **32**: 92-98 [PMID: 24684295 DOI: 10.3109/08880018.2014.887803]

29 **Nannelli C**, Bosman A, Cunningham J, Dugué PA, Luzzatto L. Genetic variants causing G6PD deficiency: Clinical and biochemical data support new WHO classification. *Br J Haematol* 2023; **202**: 1024-1032 [PMID: 37415281 DOI: 10.1111/bjh.18943]

30 **Olusanya BO**, Emokpae AA, Zamora TG, Slusher TM. Addressing the burden of neonatal hyperbilirubinaemia in countries with significant glucose-6-phosphate dehydrogenase deficiency. *Acta Paediatr* 2014; **103**: 1102-1109 [PMID: 24990658 DOI: 10.1111/apa.12735]

31 **Isa HM**, Mohamed MS, Mohamed AM, Abdulla A, Abdulla F. Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency. *Korean J Pediatr* 2017; **60**: 106-111 [PMID: 28461823 DOI: 10.3345/kjp.2017.60.4.106]

32 **Huang CS**, Chang PF, Huang MJ, Chen ES, Chen WC. Glucose-6-phosphate dehydrogenase deficiency, the UDP-glucuronosyl transferase 1A1 gene, and neonatal hyperbilirubinemia. *Gastroenterology* 2002; **123**: 127-133 [PMID: 12105841 DOI: 10.1053/gast.2002.34173]

33 **Wang M**, Chen T, Chen R, Bi Z, Peng J, Shao Q, Li J. Neonatal jaundice caused by compound mutations of SLC10A1 and a novel UGT1A1 gene. *Clin Res Hepatol Gastroenterol* 2024; **48**: 102340 [PMID: 38588793 DOI: 10.1016/j.clinre.2024.102340]

34 **Ottosson A**, Edvinsson L, Sjögren A, Löwenhielm P. Digoxin, magnesium, and potassium levels in a forensic autopsy material of sudden death from ischemic heart disease. *Z Rechtsmed* 1988; **101**: 27-36 [PMID: 3218385 DOI: 10.1186/s13023-020-1346-4]

35 **Jiang H**, Zhou JY, Li J, Li DZ. Unstable Hemoglobin Variants: The Need for Clinical Vigilance in Infants with Congenital Jaundice. *Hemoglobin* 2019; **43**: 60-62 [PMID: 31092072 DOI: 10.1080/03630269.2019.1582429]

36 **Vilarinho S**, Sari S, Mazzacuva F, Bilgüvar K, Esendagli-Yilmaz G, Jain D, Akyol G, Dalgiç B, Günel M, Clayton PT, Lifton RP. ACOX2 deficiency: A disorder of bile acid synthesis with transaminase elevation, liver fibrosis, ataxia, and cognitive impairment. *Proc Natl Acad Sci U S A* 2016; **113**: 11289-11293 [PMID: 27647924 DOI: 10.1073/pnas.1613228113]

37 **Grasko Y**, Hooper AJ, Burnett JR, Watts GF. A novel missense SMPD1 gene mutation, T460P, and clinical findings in a patient with Niemann-Pick disease type B presenting to a lipid disorders clinic. *Ann Clin Biochem* 2014; **51**: 615-618 [PMID: 24643943 DOI: 10.1177/0004563214527067]

38 **Xia H**, Zhang Z, Luo C, Wei K, Li X, Mu X, Duan M, Zhu C, Jin L, He X, Tang L, Hu L, Guan Y, Lam DCC, Yang J. MultiPrime: A reliable and efficient tool for targeted next-generation sequencing. *Imeta* 2023; **2**: e143 [PMID: 38868227 DOI: 10.1002/imt2.143]

39 **Yang H**, Li H, Xia Q, Dai W, Li X, Liu Y, Nie J, Yang F, Sun Y, Feng L, Yang L. UGT1A1 variants in Chinese Uighur and Han newborns and its correlation with neonatal hyperbilirubinemia. *PLoS One* 2022; **17**: e0279059 [PMID: 36520959 DOI: 10.1371/journal.pone.0279059]

40 **Cui Z**, Shen W, Sun X, Li Y, Liu Y, Sun Z. Developing and evaluating a predictive model for neonatal hyperbilirubinemia based on UGT1A1 gene polymorphism and clinical risk factors. *Front Pediatr* 2024; **12**: 1345602 [PMID: 38487473 DOI: 10.3389/fped.2024.1345602]

41 **Bhutani VK**; Committee on Fetus and Newborn; American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2011; **128**: e1046-e1052 [PMID: 21949150 DOI: 10.1542/peds.2011-1494]

42 **Xu JX**, Lin F, Wu YH, Chen ZK, Ma YB, Yang LY. Etiology analysis for term newborns with severe hyperbilirubinemia in eastern Guangdong of China. *World J Clin Cases* 2023; **11**: 2443-2451 [PMID: 37123300 DOI: 10.12998/wjcc.v11.i11.2443]

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ORIGINAL ARTICLE

Retrospective Study

Prediction of cyanotic and acyanotic congenital heart disease using machine learning models

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Abstract

BACKGROUND

Congenital heart disease is most commonly seen in neonates and it is a major cause of pediatric illness and childhood morbidity and mortality.

AIM

To identify and build the best predictive model for predicting cyanotic and acyanotic congenital heart disease in children during pregnancy and identify their potential risk factors.

METHODS

The data were collected from the Pediatric Cardiology Department at Chaudhry Pervaiz Elahi Institute of Cardiology Multan, Pakistan from December 2017 to October 2019. A sample of 3900 mothers whose children were diagnosed with

cyanotic or acyanotic congenital heart disease was taken. Multivariate outlier detection methods were used to identify the potential outliers. Different machine learning models were compared, and the best-fitted model was selected using the area under the curve, sensitivity, and specificity of the models.

RESULTS

Out of 3900 patients included, about 69.5% had acyanotic and 30.5% had cyanotic congenital heart disease. Males had more cases of acyanotic (53.6%) and cyanotic (54.5%) congenital heart disease as compared to females. The odds of having cyanotic was 1.28 times higher for children whose mothers used more fast food frequently during pregnancy. The artificial neural network model was selected as the best predictive model with an area under the curve of 0.9012, sensitivity of 65.76%, and specificity of 97.23%.

CONCLUSION

Children having a positive family history are at very high risk of having cyanotic and acyanotic congenital heart disease. Males are more at risk and their mothers need more care, good food, and physical activity during pregnancy. The best-fitted model for predicting cyanotic and acyanotic congenital heart disease is the artificial neural network. The results obtained and the best model identified will be useful for medical practitioners and public health scientists for an informed decision-making process about the earlier diagnosis and improve the health condition of children in Pakistan.

Key Words: Congenital heart disease; Cyanotic heart disease; Acyanotic heart disease; Logistic regression model; Artificial neural network

Core Tip: In this study, to identify and build the best model for predicting cyanotic and acyanotic congenital heart disease in children during pregnancy and identify their risk factors, we employed machine learning models and compared their performance to choose the best one. We also used multivariate outlier detection methods to determine the outlier cases. The best fit model for congenital heart disease was the artificial neural network model. Children having a positive family history are at very high risk of having cyanotic and acyanotic congenital heart disease.

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INTRODUCTION

Congenital heart disease (CHD) is most commonly seen in neonates[1] and is a major cause of pediatric illness and childhood morbidity and mortality[2]. CHD is usually the result of the abnormal embryonic development of a normal structure during the early stage of embryonic or fetal development[3]. The incidence of CHD is 8 to 10 per 1000 births in Pakistan and nearly about 50000 children are affected by CHD each year[4]. The prevalence of CHD was 4 per 1000 live births in Karachi, Pakistan and 41.7% of children had cyanotic CHD and 58.3% had acyanotic CHD[5]. Acyanotic CHD was more common than cyanotic CHD and both conditions were found to have a higher incidence in males as compared to females[6,7].

In underdeveloped countries, families of children with CHD are faced with many health care and socioeconomic problems[1]. Late diagnosis of CHD carries a high risk of avoidable morbidity, mortality, and handicap. Problem identification and modification at an early stage were crucial in avoiding complexity, improving quality of life, and reducing mortality[2]. Awareness among parents about the disease can reduce the delay in the identification of disease, which can undoubtedly prevent mortality and morbidity in the subjects[8]. In rural areas of Pakistan, the prevalence of CHD was very high as compared to urban areas[9]. There were several fetal factors associated with CHD, like premature birth, stillbirth, and low birth weight. Low birth weight, family history of CHD, maternal co-morbidities, and consanguineous marriage were associated with CHD[10]. Physical activity, nutrition, partner interaction, access to basic health care facilities, calories in food, environment, and housing conditions during pregnancy reduce the risk factors of cyanotic and acyanotic CHD[11]. The prevalence of CHD was 9.3 per 1000 Live births in Asia and 8 to 10 per 1000 Live births worldwide; 60.6% of cases were acyanotic CHD and 38.6% were cyanotic CHD[12]. The prevalence of CHD for Whites was significantly higher than for Blacks or Mexican Americans. The prevalence rate of CHD in children aged 5 to 15 years has been reported as 2 per 1000 in Sudan, 3 per 1000 in Uganda, and 3.6 per 1000 in Nigeria[13]. In India, the prevalence of CHD was reported from 8.5 to 13.6 per 1000 live births, and the 10% infant mortality was due to CHD. Acyanotic CHD was present in 79% of CHD children, 21% had cyanotic CHD, and 82.9% were diagnosed between 0 to 3 years of age. Parental age, illness during pregnancy, and advanced maternal age were found to be risk factors for CHD[14,15]. The

prevalence of CHD was 5 to 10 per 1000 live births and 10.01 per 1000 in school children in Alexandria, Egypt. Parental consanguinity, positive family history, and maternal health during pregnancy were high-risk factors for CHD[16]. CHD was the most common birth defect in China and the prevalence was 7 to 8 per 1000 live births; it shows about 100000 to 150000 new cases annually. The mental stress in the mother, number of previous pregnancies, maternal infection, and education level of the mother were the risk factors for CHD[17]. CHD risk was higher among those children who had a family history of heart disease[18].

The CHD prevalence in Asia, Europe, and Africa was found to be 9.3 per 1000, 8.2 per 1000, and 1.9 per 1000 live births, respectively. The CHD prevalence was reported to be higher in the Asian region as compared with other regions[19]. Smoking status in mothers and mental stress in mothers during pregnancy were found highly associated with CHD in children[20]. The increase in the risk of CHD was associated with poor socioeconomic status, family income, occupation, and education level of mothers[21]. In Brazil, CHD was most common in newborns and reached 1% of the population of Brazil. Socioeconomic status and family income are important factors in child development, and indirectly, they affect the process and outcome of child development with home type, nutrition quality, availability of school, health care, and medical facilities[22]. CHD is associated with physical inactivity and obesity in children and adolescents. To reduce the risk of obesity and heart disease in children and adolescents, it must be necessary to adopt a healthy lifestyle[23]. The environment and lifestyle factors also influence children with CHD[24].

In recent years, machine learning models have emerged as crucial tools in revolutionizing disease prediction and diagnosis. These advanced analytical models have transformed the way that healthcare professionals approach patient care, enabling early detection, accurate diagnosis, and personalized treatment[25]. The artificial neural network (ANN) model is vital in disease prediction due to their ability to learn from vast amounts of complex data, identify suitable patterns and correlations that may elude human clinicians, adapt to new data and improve prediction accuracy over time, and provide tailored recommendations for patient care[26]. The ANN models, inspired by the human brain's structure and function, have shown remarkable promise in disease prediction due to their ability to mimic human brain function, capacity to analyze complex relationships between variables, and identification of non-linear patterns and interactions [27]. The present study aimed to identify the risk factors for cyanotic and acyanotic CHD in children, predict cyanotic and acyanotic CHD in children at the time of pregnancy, and suggest the best machine learning-based predictive model.

MATERIALS AND METHODS

Study design and sample

A retrospective study design was used, and data was collected from the outpatient department, inpatient department, and ward of the Pediatric Department at the Institute of Cardiology Multan, Pakistan from December 2017 to October 2019. The data of the present study were collected from 3900 mothers whose children were diagnosed with cyanotic and acyanotic CHD by echocardiography. The sample of the current study attained a greater than 80% power of the test.

Patients' consent and ethics approval

The study was approved by the Departmental Ethics Committee and Board of Advanced Studies, Bahauddin Zakariya University, Multan, Pakistan. Also, we have taken permission from the hospital and all the families included in the study were volunteers and were well informed about the study and the confidentiality of their identity.

Operational definition of variables

The data was collected by the principal author. With the discussion of medical practitioners and based on literature survey, different factors were isolated and these factors are described as diabetes in family (diabetes in first-order relatives), smoking status in the family (smoking in first-order relatives), family history of heart disease (family history of heart disease in first-order relatives), anemia in mother during pregnancy, physically active mother during pregnancy (the mother can walk at least two and half hour in a week), use of fast food, low-calorie food, and staple food during pregnancy (mothers eating fast food more than once a week, mothers consuming less than 2000 calories per day, and mothers using cereal grain and tubers as staple food). Nutrition status during pregnancy (good nutrition: Protein more than 5 ounces, fruits up to 2 cups, vegetables up to 3 cups, grains up to 6 ounces, and dairy up to 3 cups; normal nutrition: Protein up to 5 ounces, fruits up to 1.5 cups, vegetables up to 2.5 cups, grains up to 5 ounces, and dairy up to 2.5 cups. Less than normal nutrition is considered as poor nutrition), monthly income of family, education level of parents, dwelling area (the area of the child was categorized into rural and urban areas), home environment during pregnancy, health condition of other people living in home (respiratory infections, asthma, lead poisoning, injuries, and mental health), mother interaction with their partner during pregnancy, quality of basic health care facilities during pregnancy (well-trained and motivated staff, accurate medical record, water, energy, sanitation, hand hygiene, and waste disposal facilities which are functional, reliable, and safe; adequate stocks of medicines, supplies, and equipment that is safe, effective, timely, efficient, and equitable), access to health care facilities (is there any government hospital or medical unit and government doctor available in their surroundings), housing tenure (house is rented or owned), housing condition (the good condition of house contained: Being dry, safe, and hygienic, good ventilation, good sanitation, good heating, good lighting, good facilities of cooking, availability of suitable storage for food, and good access to shop and facilities). The dependent/outcome variable was the type of CHD, which was categorized as cyanotic and acyanotic.

Data management and analysis

For data analyses, R was used. Categorical data are presented as frequencies and percentages. The data were randomly divided into two parts for modeling and validation: The first part (85%) was used for training the model, and the second part (15%) was used for validation of the model. For multivariate outlier detection in the generalized linear model, different measurements were used, *i.e.*, Cook's distance[28], modified Cook's distance[29], leverage[30], Andrew's Pregibon[31], Welsch's distance[32], and covariance ratio[33]. Those cases were considered outliers that were jointly identified by all the above methods. The prediction performance for predicting the type of CHD was evaluated using subset logistic regression (SLR)[34], subset logistic regression after deletion (SLRAD), and the machine learning model ANN[35]. The performance of the models was compared using the area under the receiver operating characteristic (ROC) curve (AUC) and its 95% confidence interval, sensitivity, and specificity. In ANN models, the best generalization is achieved by using a model whose complexity is the most appropriate to produce an adequate fit of the data. In Supplementary material, the mathematical and procedural details of the diagnostic measures of outliers and all models are described.

RESULTS

There were 53.6% of males and 46.6% of females who had acyanotic CHD, and 54.5% of males and 45.5% of females who had cyanotic CHD. The children with acyanotic CHD who had a family history of diabetes accounted for 36.0%, and 40.3% of children with cyanotic CHD had a family history of diabetes. The results of univariate analyses are presented in Table 1.

Figure 1 shows the graphs of influential diagnostic measures for CHD. In this figure, the circles show the observation of the data, the red line shows the cut point of the measure, and the points along with the observation number that are beyond the cut point were identified as influential observations for each measure. We delete those observations that were commonly identified as outliers by all the diagnostic measures.

The results of the logistic regression analysis is given in Table 2. The results of SLR showed that family history of heart disease, use of fast-food during pregnancy, use of staple food during pregnancy, poor nutrition during pregnancy, low family monthly income, uneducated parents, urban area, poor quality of health care facilities, rented house, and poor housing condition were significant risk factors for CHD. The results of SLRAD showed that family history of heart disease, use of fast-food during pregnancy, poor nutrition during pregnancy, low family monthly income, uneducated father, urban area, poor quality of health care facilities, rented house, and poor housing conditions were significant risk factors for CHD.

Figure 2 shows the weight of each input variable, and the weights were obtained by the ANN model for CHD through normalizing importance. According to importance, the most important risk factors for CHD were obtained: Father's education, family income, father's occupation, health condition, mother's education, nutrition, and number of children in family. In all the important factors, mother's education, nutrition status, and number of children in family had positive weight, while father's education, family income, father's occupation, and health condition had negative weight.

Figure 3 demonstrates the sequence of each predictor and describes the final ANN fitted model for CHD, which was generated by plotting each risk factor by normalized importance. In the ANN model for CHD, there were 20 input variables, 4 hidden variables, and 1 output variable.

Table 3 shows the comparison of all models by AUC and its 95% confidence interval, sensitivity, and specificity. The results showed that the ANN model had the highest AUC at 0.901 (95%CI: 0.892–0.910) with a sensitivity and specificity of 65.76% and 97.23%, respectively. The SLRAD model had the second highest AUC at 0.886 (95%CI: 0.876-0.896), with a sensitivity of 57.69% and specificity of 98.69%. The SLRM model had the third-highest AUC at 0.860 (95%CI: 0.849-0.871) with a sensitivity of 49.62% and specificity of 98.38%. Figure 4 also shows that the ANN model had the highest diagnostic accuracy for CHD.

DISCUSSION

The results of the current study show that acyanotic CHD is more common in children as compared to cyanotic CHD, which is consistent with the findings of a previous study done in Pakistan[6]. Our results show that the odds of having cyanotic CHD was 1.28 times higher for children whose mothers used fast food during pregnancy as compared to those whose mothers did not use. The odds of having cyanotic CHD was 6.22 times higher for children whose father was uneducated as compared to those whose father was educated. The odds of having cyanotic CHD was 1.49 times higher for children whose mothers had normal housing conditions as compared to those whose mothers had good housing conditions. Children who had a family history of heart disease had 0.55 times the odds of having acyanotic CHD as compared to those who had not. Children whose mothers used the staple food during pregnancy had 0.79 times the odds of having acyanotic CHD as compared to those whose mother did not. Male children were more affected by cyanotic and acyanotic CHD as compared to female children. A study in China has similar findings[17]. The result of our study shows that family history of heart disease is a risk factor for CHD, in agreement with the results of the studies in Egypt and China[16,18]. The result of the model comparison shows that the ANN model had the highest diagnostic accuracy. The result of analysis based on the ANN, the best-selected model, shows that father's education, family income, father's occupation, health condition of other people's living in home, mother's education, nutrition, and number of children in family are risk factors for cyanotic and acyanotic CHD in children. A study in China also concluded that mother's

Table 1 Descriptive analysis of categorical data of congenital heart disease, *n* (%)

Variable	Category	Acyanotic	Cyanotic	Variable	Category	Acyanotic	Cyanotic
Gender	Female	1258 (46.4)	518 (45.5)	Father's education	Uneducated	1102 (40.7)	702 (59.0)
	Male	1452 (53.6)	672 (54.5)		Primary/middle	1220 (45.0)	354 (29.7)
Diabetes	No	1734(64.0)	710 (59.7)		Secondary/higher	326 (12.0)	118 (9.9)
	Yes	976 (36.0)	480 (40.3)		Graduate	52 (1.9)	12 (1.0)
Smoking	No	1318 (48.6)	664 (55.8)		Masters or higher	10 (0.4)	4 (0.3)
	Yes	1392 (51.4)	526 (44.2)	Father's occupation	Dead/ unemployed	4 (0.1)	4 (0.3)
Family History	No	858 (31.7)	510 (42.9)		Labour/former	1866 (68.9)	826 (69.4)
	Yes	1852 (68.3)	680 (57.1)		Private job	194 (7.2)	20 (1.7)
Anemia during pregnancy	No	2598 (95.9)	1150 (96.6)		Small business	620 (22.9)	328 (27.6)
	Yes	112 (4.1)	40 (3.4)		Civil servant	26 (1.0)	12 (1.0)
Inactive	No	800 (29.5)	342 (28.7)	Area	Rural	1604 (59.2)	878 (73.8)
	Yes	1910 (70.5)	848 (71.3)		Urban	1106 (40.8)	312 (26.2)
Fast food during pregnancy	No	1356 (50.0)	486 (40.8)	Home environment	Poor	1650 (60.9)	518 (43.5)
	Yes	1354 (50.0)	704 (59.2)		Normal	590 (21.8)	400 (33.6)
Low-calorie food during pregnancy	No	1036 (38.2)	472 (39.7)		Good	470 (17.3)	272(22.9)
	Yes	1674 (61.8)	718 (60.3)	Health condition	Poor	602 (22.2)	402 (33.8)
Nutrition during pregnancy	Poor	1558 (57.5)	492 (41.3)		Normal	1660 (61.3)	522 (43.9)
	Normal	532 (19.6)	382 (32.1)		Good	448 (16.5)	266 (22.4)
	Good	620 (22.9)	316 (26.6)	Interaction with partner during pregnancy	Poor	1592 (58.7)	498 (41.8)
Staple food during pregnancy	No	1720 (63.5)	692 (58.2)		Normal	558 (20.6)	392 (32.9)
	Yes	990 (36.5)	498 (41.8)		Good	560 (20.7)	300 (25.2)
Income	< 10000	20 (0.70)	18 (1.5)	Health care quality	Poor	1540 (56.8)	506 (42.5)
	10000 to 20000	2076 (76.6)	956 (80.3)		Normal	660 (24.4)	414 (34.8)
	> 20000	614 (22.7)	216(18.2)		Good	510 (18.8)	270 (22.7)
Mother's education	Uneducated	1492 (55.1)	690 (58.0)	Health care access	No	2034 (75.1)	770 (64.7)
	Primary/middle	1002 (37.0)	404 (33.9)		Yes	676 (24.9)	420 (35.3)
	Secondary/higher	200 (7.4)	90 (7.6)	Housing tenure	Owned	2628 (97.0)	1164 (97.8)
	Graduate	8 (0.3)	6 (0.5)		Rented	82 (3.0)	26 (2.2)
	Masters or higher	8 (0.3)	0 (0.0)	Housing condition	Poor	630 (23.2)	528 (44.4)
					Normal	1742 (64.3)	548 (46.1)
					Good	338 (12.5)	114 (9.6)

education level is a risk factor for CHD[17,21]. A study in Pakistan also supports our findings, *i.e.*, health condition of other people living in home, and quality and access to basic health care facilities are risk factors of cyanotic and acyanotic CHD in children[11].

The field of machine learning has undergone significant advancements in recent years, leading to a surge in the development of innovative models that can accurately predict disease[36]. The ANN and machine learning models can analyze medical images, genetic data, and patient information to predict the risk factors of disease, detect early warning signs, and recommend preventive measures[37]. In the current study, we used different machine learning models to predict cyanotic and acyanotic CHD in children. One recent study reported that the neural network model is an accurate decision support tool in diagnosing CHD[38]. Another study shows that the ANN model yields the best accuracy while predicting CHD in children[39]. The results of another study show that the best predictive model for CHD children was machine learning models and the AUC values for those models ranged from 0.81 to 0.83[40].

Table 2 Multivariate logistic regression models by using stepwise selection approach

Variable	Categories[4]	SLR		SLRAD	
		OR	95%CI	OR	95%CI
(Intercept)	-	2.006	0.300-13.400	0.000	-
History	Yes	0.551[1]	0.463-0.656	0.541[1]	0.454-0.646
Fast food	Yes	1.289[2]	1.027-1.618	1.331[2]	1.056-1.677
Staple food	Yes	0.794[3]	0.609-1.034	0.803	0.615-1.049
Nutrition	Normal	0.668	0.345-1.294	0.698	0.382-1.273
	Poor	0.621[2]	0.409-0.942	0.571[1]	0.382-0.853
Children	-	1.368[1]	1.267-1.476	1.365[1]	1.264-1.473
Family income	< 20000	0.276[1]	0.124-0.614	0.263[1]	0.118-0.588
	10000 to 20000	0.396[2]	0.181-0.866	0.390[2]	0.177-0.857
Mother education	Master or higher	0.000	0-2.96E+163	0.998	-
	Primary/middle	0.474	0.129-1.744	3.96E+05	-
	Secondary/higher	0.781	0.208-2.933	7.09E+05	-
	Uneducated	0.300[3]	0.082-1.106	2.58E+05	-
Father's education	Master or higher	0.391	0.053-2.907	0.000	-
	Primary/middle	1.984	0.779-5.053	2.630[3]	0.907-7.624
	Secondary/higher	1.950	0.775-4.909	2.599[3]	0.902-7.489
	Uneducated	6.221[1]	2.395-16.160	8.516[1]	2.875-25.225
Father's occupation	Dead/unemployed	0.672	0.101-4.478	8.65E+05	-
	Labour/former	0.336[2]	0.123-0.914	0.736	0.196-2.768
	Private job	0.082[1]	0.026-0.259	0.145[1]	0.035-0.611
	Small business	0.465	0.168-1.292	0.986	0.259-3.761
Dwelling area	Urban	0.582[1]	0.478-0.710	0.554[1]	0.453-0.678
Partner interaction	Normal	1.060	0.583-1.927	-	-
	Poor	0.732	0.496-1.081	-	-
Quality of health care facilities	Normal	0.468[2]	0.25-0.878	0.409[1]	0.226-0.743
	Poor	0.682	0.421-1.104	0.503[1]	0.316-0.802
Housing tenure	Rented	0.511[2]	0.276-0.946	0.437[2]	0.227-0.841
Housing condition	Normal	1.498[2]	1.053-2.131	1.554[2]	1.086-2.225
	Poor	2.852[1]	2.04-3.987	3.004[1]	2.136-4.225

[1]Significance at 1%;
[2]Significant at 5%;
[3]Significant at 10%.
[4]Reference categories are: Family history "no", use of fast food "no", use of staple food "no", nutrition "good", partner interaction "good", quality of health care facilities "good", housing condition "good", family income "< 10000", father's education "primary/middle", father's occupation "civil servant", and housing tenure "owned".

CONCLUSION

Children having a family history of heart disease are at very high risk of developing cyanotic and acyanotic CHD. The incidence of cyanotic CHD can be reduced by limiting fast food during pregnancy. Similarly, reducing the number of children can also minimize the incidence of CHD. Moreover, mothers with an uneducated partner and poor housing conditions are at high risk of birthing a child having cyanotic CHD. Similarly, the incidence of acyanotic CHD can be reduced by adopting good dietary habits (high nutrition food and rich calorie food) during pregnancy. Families with low income, uneducated mothers, and those living in urban areas are at higher risk of birthing a child having cyanotic CHD. The best fit model for our data is ANN, which can be used for earlier diagnostics. This prediction model can help medical

Table 3 Performance comparison of models

Model	AUC	95%CI	Sensitivity	Specificity
SLRM	86.01	0.849–0.871	49.62	98.38
SLRAD	88.57	0.876-0.896	57.69	98.69
ANN	90.12	0.892–0.910	65.76	97.23

AUC: Area under the curve; SLR: Logistic regression; SLRAD: Subset logistic regression after deletion; ANN: Artificial neural network.

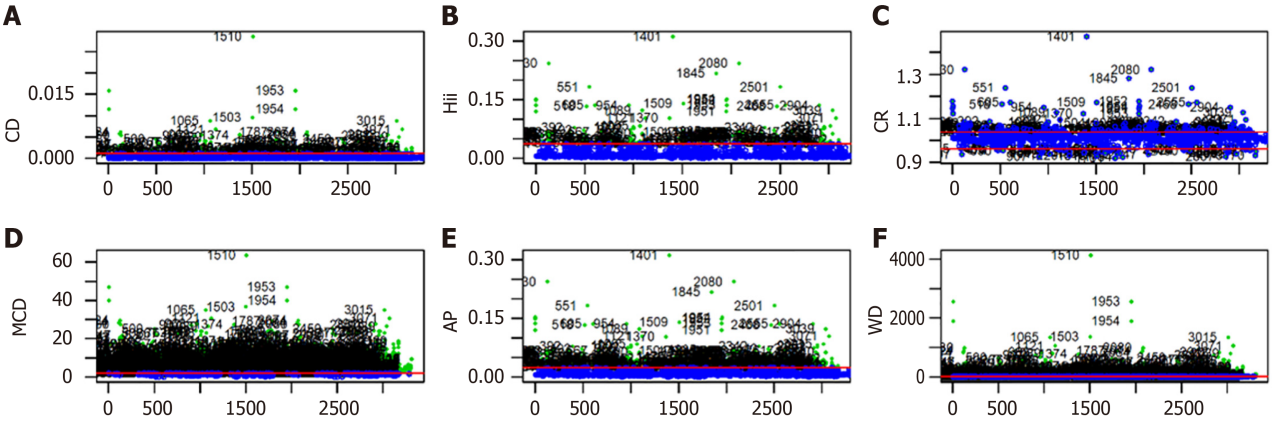

Figure 1 Graphs of influential diagnostic measures. A: Detection using Cook's distance method; B: Detection using leverage method; C: Detection using covariance ratio method; D: Detection using modified Cook's distance method; E: Detection using Andrew's Pregibon method; F: Detection using Walsh's distance method.

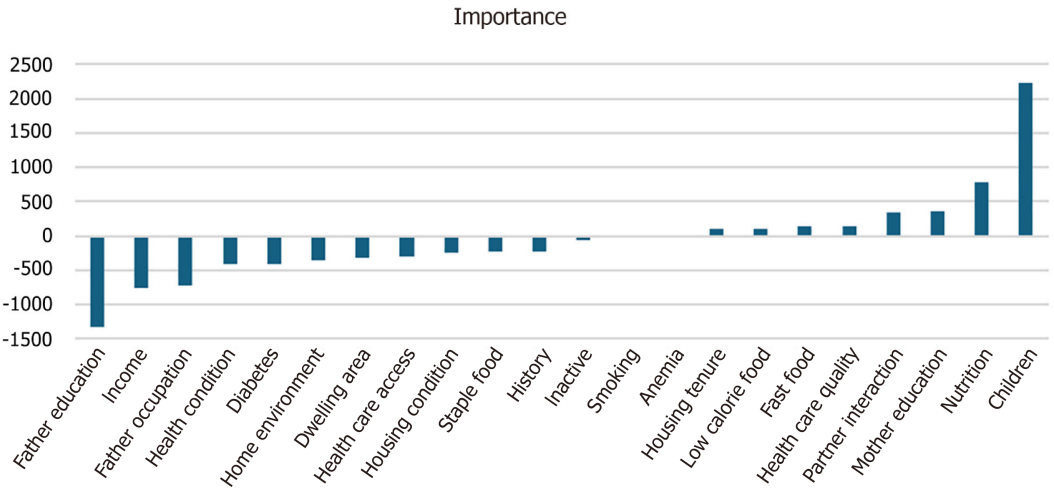

Figure 2 Weights according to importance of variables by artificial neural network.

practitioners and experts to identify the risk and make earlier diagnoses of cyanotic and acyanotic CHD during pregnancy, which will improve healthcare.

Limitations and future directions

The accuracy of the models may be limited by the quality and availability of the regional data. This can be improved by using large nationwide data. For future studies, investigating new features and feature engineering techniques can help improve model performance. Developing models that are more interpretable can help clinicians understand why certain predictions are made. Validating the models prospectively can help establish their clinical utility. Comparing the performance of different machine learning models can help identify the best approach.

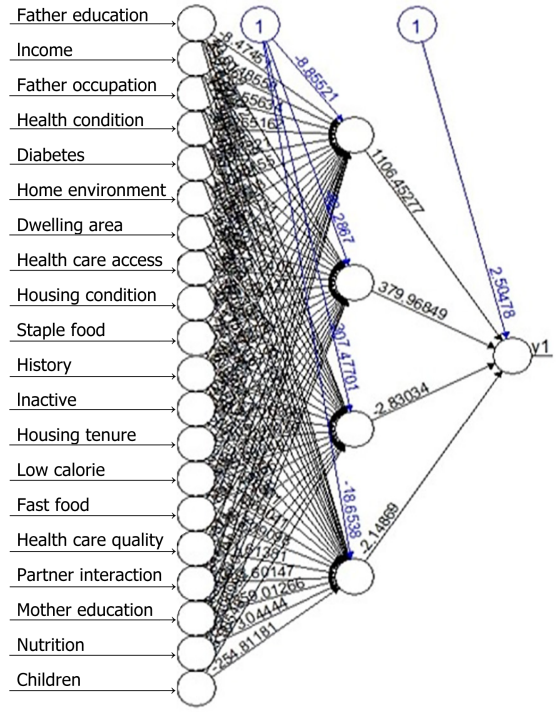

Figure 3 Modeling structure of artificial neural network with weights of each node.

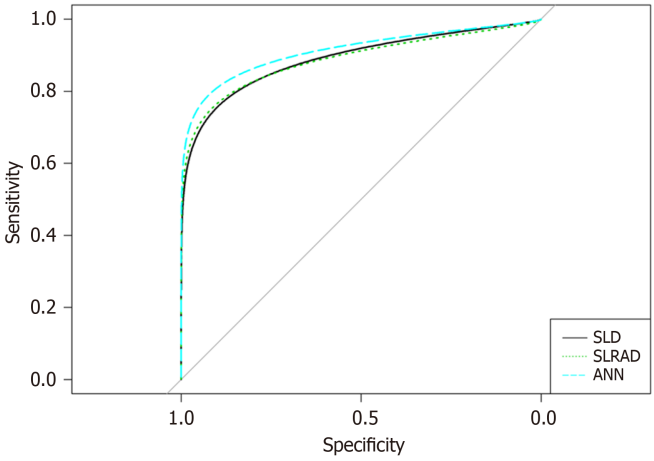

Figure 4 Receiver operating characteristic curves for comparison of subset logistic regression, subset logistic regression after deletion, and artificial neural network model. SLR: Subset logistic regression; SLRAD: Subset logistic regression after deletion; ANN: Artificial neural network.

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FOOTNOTES

Author contributions: Shahid S, Khurram H, and Lim A conceptualized and designed the research; Shahid S and Khurram H organized the dataset, performed statistical analysis and data interpretation, and wrote the first draft of the manuscript with the help of Lim A; Khurram H and Lim A played important and indispensable roles in the experimental design, data interpretation, and manuscript preparation as the co-corresponding authors; Shahid S and Khurram H made crucial and indispensable contributions towards the completion of the project and were thus qualified as the co-first authors of the paper; Lim A proofread the draft and gave valuable suggestions to improve the manuscript; Shabbir MF reviewed the final draft from a medical perspective. Billah B reviewed the final draft from a statistical perspective. All authors contributed to the manuscript revision, and read and approved the final draft.

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REFERENCES

1 **Shabana NA**, Shahid SU, Irfan U. Genetic Contribution to Congenital Heart Disease (CHD). *Pediatr Cardiol* 2020; **41**: 12-23 [PMID: 31872283 DOI: 10.1007/s00246-019-02271-4]
2 **Mohammad N**, Shaikh S, Memon S, Das H. Spectrum of heart disease in children under 5 years of age at Liaquat University Hospital, Hyderabad, Pakistan. *Indian Heart J* 2014; **66**: 145-149 [PMID: 24581115 DOI: 10.1016/j.ihj.2013.12.041]
3 **Balat MS**, Sahu SK. Congenital heart disease: factor affecting it and role of RBSK in dealing with situation. *Int J Community Med Public Health* 2018; **5**: 4437 [DOI: 10.18203/2394-6040.ijcmph20183990]
4 **Humayun KN**, Atiq M. Clinical profile and outcome of cyanotic congenital heart disease in neonates. *J Coll Physicians Surg Pak* 2008; **18**: 290-293 [PMID: 18541084]
5 **Masood N**, Sharif M, Asghar R, Qamar M, Hussain I. Frequency of congenital heart diseases at Benazir Bhutto Hospital Rawalpindi. *Ann Pak Inst Med Sci* 2010; **6**: 120-123
6 **Farooqui R**, Haroon UF, Niazi A, Rehan N, Butt T, Niazi M. Congenital heart diseases in neonates. *JRMC* 2010; **14**: 31-33
7 **Pathan IH**, Bangash SK, Khawaja AM. Spectrum of heart defects in children presenting for paediaric cardiac surgery. *Pak Heart J* 2016; 49
8 **Hussain M**, Hussain S, Krishin J, Abbasi S. Presentation of congestive cardiac failure in children with ventricular septal defect. *J Ayub Med Coll Abbottabad* 2010; **22**: 135-138 [PMID: 22455281]
9 **Rizvi SF**, Mustafa G, Kundi A, Khan MA. Prevalence of congenital heart disease in rural communities of Pakistan. *J Ayub Med Coll Abbottabad* 2015; **27**: 124-127 [PMID: 26182756]
10 **Ul Haq F**, Jalil F, Hashmi S, Jumani MI, Imdad A, Jabeen M, Hashmi JT, Irfan FB, Imran M, Atiq M. Risk factors predisposing to congenital heart defects. *Ann Pediatr Cardiol* 2011; **4**: 117-121 [PMID: 21976868 DOI: 10.4103/0974-2069.84641]
11 **Shahid S**, Akbar A. Conventional and non-conventional risk factors of cyanotic and acyanotic congenital heart diseases in children of southern Punjab, Pakistan. *Pak Heart J* 2020; **53** [DOI: 10.47144/phj.v53i2.1698]
12 **Pate N**, Jawed S, Nigar N, Junaid F, Wadood AA, Abdullah F. Frequency and pattern of congenital heart defects in a tertiary care cardiac hospital of Karachi. *Pak J Med Sci* 2016; **32**: 79-84 [PMID: 27022350 DOI: 10.12669/pjms.321.9029]
13 **Aman W**, Sherin A, Hafizullah M. Frequency of congenital heart diseases in patients under the age of twelve years at Lady Reading Hospital Peshawar. *JPMI* 2006; **20**
14 **Kapoor R**, Gupta S. Prevalence of congenital heart disease, Kanpur, India. *Indian Pediatr* 2008; **45**: 309-311 [PMID: 18451451]
15 **Abqari S**, Gupta A, Shahab T, Rabbani MU, Ali SM, Firdaus U. Profile and risk factors for congenital heart defects: A study in a tertiary care hospital. *Ann Pediatr Cardiol* 2016; **9**: 216-221 [PMID: 27625518 DOI: 10.4103/0974-2069.189119]
16 **Settin A**, Almarsafawy H, Alhussieny A, Dowaidar M. Dysmorphic Features, Consanguinity and Cytogenetic Pattern of Congenital Heart Diseases: a pilot study from Mansoura Locality, Egypt. *Int J Health Sci (Qassim)* 2008; **2**: 101-111 [PMID: 21475491]
17 **Liu S**, Liu J, Tang J, Ji J, Chen J, Liu C. Environmental risk factors for congenital heart disease in the Shandong Peninsula, China: a hospital-based case-control study. *J Epidemiol* 2009; **19**: 122-130 [PMID: 19398851 DOI: 10.2188/jea.je20080039]
18 **Pei L**, Kang Y, Zhao Y, Yan H. Prevalence and risk factors of congenital heart defects among live births: a population-based cross-sectional survey in Shaanxi province, Northwestern China. *BMC Pediatr* 2017; **17**: 18 [PMID: 28086762 DOI: 10.1186/s12887-017-0784-1]
19 **van der Linde D**, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011; **58**: 2241-2247 [PMID: 22078432 DOI: 10.1016/j.jacc.2011.08.025]
20 **Feng Y**, Yu D, Yang L, Da M, Wang Z, Lin Y, Ni B, Wang S, Mo X. Maternal lifestyle factors in pregnancy and congenital heart defects in offspring: review of the current evidence. *Ital J Pediatr* 2014; **40**: 85 [PMID: 25385357 DOI: 10.1186/s13052-014-0085-3]
21 **Yu D**, Feng Y, Yang L, Da M, Fan C, Wang S, Mo X. Maternal socioeconomic status and the risk of congenital heart defects in offspring: a meta-analysis of 33 studies. *PLoS One* 2014; **9**: e111056 [PMID: 25347676 DOI: 10.1371/journal.pone.0111056]

22 **Mari MA**, Cascudo MM, Alchieri JC. Congenital Heart Disease and Impacts on Child Development. *Braz J Cardiovasc Surg* 2016; **31**: 31-37 [PMID: 27074272 DOI: 10.5935/1678-9741.20160001]

23 **Barbiero SM**, D'Azevedo Sica C, Schuh DS, Cesa CC, de Oliveira Petkowicz R, Pellanda LC. Overweight and obesity in children with congenital heart disease: combination of risks for the future? *BMC Pediatr* 2014; **14**: 271 [PMID: 25323400 DOI: 10.1186/1471-2431-14-271]

24 **Wacker-Gussmann A**, Oberhoffer-Fritz R. Cardiovascular Risk Factors in Childhood and Adolescence. *J Clin Med* 2022; **11** [PMID: 35207409 DOI: 10.3390/jcm11041136]

25 **Alowais SA**, Alghamdi SS, Alsuhebany N, Alqahtani T, Alshaya AI, Almohareb SN, Aldairem A, Alrashed M, Bin Saleh K, Badreldin HA, Al Yami MS, Al Harbi S, Albekairy AM. Revolutionizing healthcare: the role of artificial intelligence in clinical practice. *BMC Med Educ* 2023; **23**: 689 [PMID: 37740191 DOI: 10.1186/s12909-023-04698-z]

26 **Byeon H**, Gc P, Hannan SA, Alghayadh FY, Soomar AM, Soni M, Bhatt MW. Deep neural network model for enhancing disease prediction using auto encoder based broad learning. *SLAS Technol* 2024; **29**: 100145 [PMID: 38750819 DOI: 10.1016/j.slast.2024.100145]

27 **Taherdoost H**. Deep Learning and Neural Networks: Decision-Making Implications. *Symmetry* 2023; **15**: 1723 [DOI: 10.3390/sym15091723]

28 **Belle V**, Papantonis I. Principles and Practice of Explainable Machine Learning. *Front Big Data* 2021; **4**: 688969 [PMID: 34278297 DOI: 10.3389/fdata.2021.688969]

29 **Shahid S**. Statistical Modeling of Epidemiology of Cardiovascular Diseases in Children (Doctoral dissertation, Bahauddin Zakariya University Multan, Pakistan). 2022

30 **Belsley DA**, Kuh E, Welsch RE. Regression diagnostics: Identifying influential data and sources of collinearity. New York and Chichester: John Wiley & Sons, 1980 [DOI: 10.1002/0471725153]

31 **Bagheri A**, Midi H, Imon A. The Effect of Collinearity-influential Observations on Collinear Data Set: A Monte Carlo Simulation Study. *J App Sci* 2010; **10**: 2086-2093 [DOI: 10.3923/jas.2010.2086.2093]

32 **Van den Broeck J**, Cunningham SA, Eeckels R, Herbst K. Data cleaning: detecting, diagnosing, and editing data abnormalities. *PLoS Med* 2005; **2**: e267 [PMID: 16138788 DOI: 10.1371/journal.pmed.0020267]

33 **Ullah MA**, Pasha GR. The origin and developments of influence measures in regression. *PJS* 2009; **25**

34 **Hosmer DW**, Lemeshow S, Sturdivant RX. Applied logistic regression. Canada: Jhon Wiley & Sons, 2013 [DOI: 10.1002/9781118548387]

35 **Shahid S**, Khurram H, Billah B, Akbar A, Shehzad MA, Shabbir MF. Machine learning methods for predicting major types of rheumatic heart diseases in children of Southern Punjab, Pakistan. *Front Cardiovasc Med* 2022; **9**: 996225 [PMID: 36312229 DOI: 10.3389/fcvm.2022.996225]

36 **Shivahare BD**, Singh J, Ravi V, Chandan RR, Alahmadi TJ, Singh P, Diwakar M. Delving into Machine Learning's Influence on Disease Diagnosis and Prediction. *TOPHJ* 2024; **17** [DOI: 10.2174/0118749445297804240401061128]

37 **Kumar Y**, Koul A, Singla R, Ijaz MF. Artificial intelligence in disease diagnosis: a systematic literature review, synthesizing framework and future research agenda. *J Ambient Intell Humaniz Comput* 2023; **14**: 8459-8486 [PMID: 35039756 DOI: 10.1007/s12652-021-03612-z]

38 **Hoodbhoy Z**, Jiwani U, Sattar S, Salam R, Hasan B, Das JK. Diagnostic Accuracy of Machine Learning Models to Identify Congenital Heart Disease: A Meta-Analysis. *Front Artif Intell* 2021; **4**: 708365 [PMID: 34308341 DOI: 10.3389/frai.2021.708365]

39 **Rani S**, Masood S. Predicting congenital heart disease using machine learning techniques. *JDMSC* 2020; **23**: 293-303 [DOI: 10.1080/09720529.2020.1721862]

40 **Guo K**, Fu X, Zhang H, Wang M, Hong S, Ma S. Predicting the postoperative blood coagulation state of children with congenital heart disease by machine learning based on real-world data. *Transl Pediatr* 2021; **10**: 33-43 [PMID: 33633935 DOI: 10.21037/tp-20-238]

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ORIGINAL ARTICLE

Retrospective Study

Molecular profiles and long-term outcomes of Thai children with hepatic glycogen storage disease in Thailand

Jaravee Vanduangden, Rungnapa Ittiwut, Chupong Ittiwut, Teerasak Phewplung, Anapat Sanpavat, Palittiya Sintusek, Kanya Suphapeetiporn

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Abstract

BACKGROUND

Thus far, genetic analysis of patients clinically diagnosed with glycogen storage diseases (GSDs) in Thailand has not been reported.

AIM
To evaluate the clinical and biochemical profiles, molecular analysis and long-term outcomes of Thai children diagnosed with hepatic GSD.

METHODS
Children aged < 18 years diagnosed with hepatic GSD and followed up at King Chulalongkorn Memorial Hospital were recruited. Whole-exome sequencing (WES) was performed to identify the causative gene variants. Medical records were assessed.

RESULTS
All eight children with histopathologically confirmed diagnosis were classified by WES into subtypes Ia (n = 1), III (n = 3), VI (n = 3), and IX (n = 1). A total number of 10 variants were identified including *G6PC* (n = 1), *AGL* (n = 4), *PYGL* (n = 5), and *PHKA2* (n = 1). *AGL* had two novel variants. The clinical manifestations were hepatomegaly (n = 8), doll-like facies (n = 3), wasting (n = 2), and stunting (n = 5). All patients showed hypoglycemia, transaminitis, and dyslipidemia. The mainstay of treatment was cornstarch supplementation and high-protein and low-lactose-fructose diet. After a median follow-up time of 9.59 years, height turned to normal for age in 3/5 patients and none had malnutrition. Liver enzymes, blood sugar, and lipid profiles improved in all.

CONCLUSION
Hepatomegaly, transaminitis, and hypoglycemia are the hallmarks of GSD confirmed by liver histopathology. Molecular analysis can confirm the diagnosis or classify the subtype that might benefit from personalized treatment, prognosis, and long-term care.

Key Words: Storage disease; Hypoglycemia; Pediatric; Whole exome sequencing; Novel variants; Thailand

Core Tip: Hepatic glycogen storage diseases (GSDs) are rare but treatable conditions. While liver histopathology is helpful for diagnosis, it cannot differentiate between GSD subtypes. Data on long-term outcomes with extensive nutritional management are limited. This study evaluates the clinical and biochemical profiles, molecular analysis, and long-term outcomes of Thai children with hepatic GSDs, identifying two novel causative variants. The findings indicate that extensive nutritional management, including frequent uncooked cornstarch supplementation, a high-protein diet, and a low lactose-fructose diet, yields favorable outcomes across GSD subtypes. However, tailored management, particularly for GSD types III and VI, can further enhance quality of life and minimize complications.

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INTRODUCTION

Glycogen storage diseases (GSDs) are rare inherited disorders that affect glycogen metabolism, with a global incidence of approximately < 1 in 100000[1]. The pathogenesis of GSDs involves defects in the enzymes responsible for breaking down glycogen, resulting in the storage of glycogen in mainly the liver, muscle, and heart[1]. GSDs have 23 subtypes that can be broadly classified into hepatic GSDs or muscle GSDs depending on the primary system affected. Hepatic GSDs include types 0a, I, III, IV, VI, and IX and Fanconi–Bickel syndrome that are inherited in an autosomal recessive manner, except for type IXa, which is an X-linked recessive disorder. Genetic analysis is ultimately responsible for the final identification of GSD subgroups given the diversity of clinical and laboratory findings[1]. Because GSDs are treatable conditions, prompt and accurate diagnosis are essential for the commencement of targeted therapy tailored to the subtypes, preventing permanent injury and improving the quality of life of the patients.

Worldwide, molecular genetic studies of GSD subtypes have increased, particularly in several Asian nations including China[2-4], India[5,6], and Pakistan[7]. Thus far, no studies have conducted genetic analysis of patients clinically diagnosed with GSDs in Thailand. Therefore, this study sought to delineate the clinical and genetic attributes of hepatic GSDs in Thai children. By conducting comprehensive assessments of clinical profiles, laboratory studies—including liver histology—and long-term outcomes following treatment, this research not only enhances our understanding of GSDs in the Thai population but also contributes valuable insights into the phenotypic variability, potential genetic mutations, and therapeutic responses associated with these disorders. Ultimately, the findings could inform improved diagnostic and treatment strategies for GSDs in Thailand and similar contexts, paving the way for future research and better healthcare outcomes for affected individuals.

MATERIALS AND METHODS

Participants

The study population included children aged < 18 years who were diagnosed with hepatic GSDs at the time of their initial diagnosis and regularly followed up at King Chulalongkorn Memorial Hospital, Thailand, between January 2010 and September 2023.

Written informed assent and/or informed consent for this study were obtained from the patients and/or their parents. In addition, genetic counseling and informed consent were provided to all participants and their guardians before collecting blood samples for genetic analysis. This study was approved by the Institute Research Board at Chulalongkorn University, Bangkok, Thailand (No. 0678/65).

Clinical data

Data were extracted from the electronic medical records, which included the clinical profiles at the time of presentation, biochemical profiles (fasting blood glucose, uric acid, complete blood count, liver function test, lipids, creatinine, lactate dehydrogenase, lactate, creatine kinase, and coagulogram), radiological parameters, liver histopathology, nutritional and medical therapy, and outcomes at the end of the follow-up period.

In every outpatient visit, the growth parameters of all patients were monitored, and the weight-for-length/height in children aged < 5 years and the *Z*-scores for height and body mass index (BMI) were employed for children aged 5–19 years, according to the growth chart that was established by the World Health Organization.

Definition

Growth and nutrition status: Overweight was defined as the weight-for-length/height > 2 SD in children aged < 5 years and BMI-for-age > 1 SD in children aged 5–19 years. Obesity was defined as weight-for-length/height > 3 SD in children aged < 5 years and BMI-for-age > 2 SD in children aged 5–19 years. Wasting was defined as weight-for-length/height < −2 SD in children aged < 5 years and BMI-for-age < −2 SD in children aged 5–19 years. Stunting referred to length/height-for-age < −2 SD.

Biochemical results: Hypoglycemia is defined if blood sugar less than 60 mg/dL. Hyperuricemia is defined if serum uric acid is 5.9 mg/dL for < 9 years (both genders), 6.1 mg/dL for 9–11 years (both genders), 7.0 mg/dL (males), and 6.2 mg/dL (females) for 12–14 years. Dyslipidemia is defined if cholesterol ≥ 200 mg/dL or low density lipoprotein ≥ 130mg/dL, high density lipoprotein < 40 mg/dL, triglyceride ≥ 100 mg/dL in children aged less than 9 years and triglyceride ≥ 130 mg/dL in children aged between 9-19 years. Transaminase is defined if aspartate aminotransferase or alanine aminotransferase > 40 U/L. Hyperbilirubinemia is defined if total bilirubin > 2mg/dL. Anemia is defined if hemoglobin < 11 g/dL for age 6 months-5 years, < 11.5 g/dL for age > 5-12 years and female adolescent, < 12 g/dL for male adolescent.

Molecular data analysis

After obtaining informed consent, 3 mL of peripheral blood was collected from patients and their available parents. Genomic DNA was extracted from peripheral blood leukocytes using the Puregene blood kit (Qiagen, Hilden, Germany). Whole-exome sequencing (WES) was performed. Briefly, DNA was used to create a library for Illumina sequencing, specifically focusing on the exome (coding regions of genes). The library was enriched for exonic regions using a specific kit. Finally, the captured libraries were sequenced using a NextSeq2000 instrument. The sequencing data for single-nucleotide variants and insertions/deletions (indels) were analyzed. The variants were filtered based on the following criteria: (1) Location within exons or nearby introns of GSD-related genes[4]; (2) Nonsynonymous changes (altering the protein sequence); (3) Rarity in the Genome Aggregation Database (GnomAD); (4) Low frequency in Thai exome controls; (5) (for missense variants) Predicted to be damaging by SIFT and Polyphen protein prediction tools, and (6) Relevance to the symptoms of hepatic GSDs.

As mentioned, the bioinformatic pipeline employed for WES data analysis involved a multi-step filtering process to identify potentially pathogenic variants. All single nucleotide variants and indels were initially filtered based on their location within exons or flanking introns of genes relevant to GSD. Only non-synonymous variants were considered, and those with a minor allele frequency less than 1% in the 1000 Genomes Project and 0.1% in the GnomAD were retained. Additionally, variants were excluded if they were identified in more than 10 alleles in a control cohort of 5432 Thai exomes. For missense variants, predictions from SIFT and Polyphen were used to assess their potential impact on protein function. Finally, variants were prioritized if they were associated with the patients' phenotype or known to be involved in the disease under investigation. This rigorous filtering approach ensured the identification of the most likely pathogenic variants for further validation.

Statistical analysis

Continuous and categorical data were presented as median values, interquartile ranges, and proportions or percentages. Fisher's exact test was used to compare discrete data, and the Mann–Whitney *U* test was used to analyze continuous data. A *P*-value of < 0.05 indicated significance. STATA version 18 was used for all statistical analyses. The figures were made using GraphPad Prism version 9.2.0.

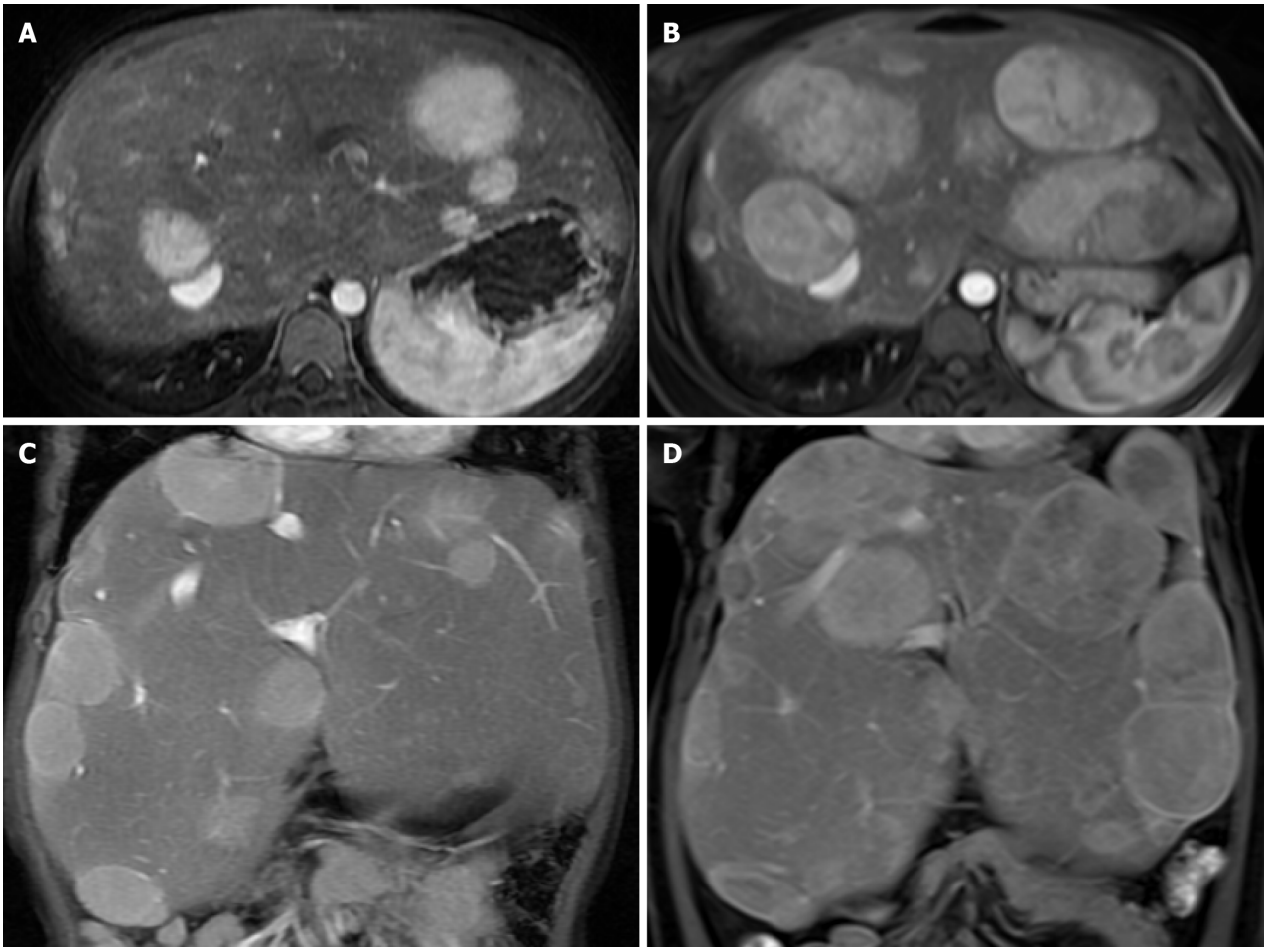

Figure 1 Axial post contrast arterial phase and coronal post contrast 3-minute delayed phase of a 15-year-old girl revealed multiple arterial and delayed enhancing nodules and masses scattering in both hepatic lobes with subsequent pathological proven hepatic adenomatosis. Thirteen years later; overall increasing sizes and numbers of multiple known hepatic adenomatosis scattering in both hepatic lobes, showing heterogeneous arterial enhancement and heterogeneous delayed enhancement. Noted some nodules in the right hepatic lobe decreased in sizes. A: Initial axial post contrast arterial phase; B: Thirteen-year-follow-up axial arterial enhancement; C: Initial coronal post contrast delayed phase; D: Thirteen-year-follow-up coronal delayed phase.

RESULTS

Patient characteristics and genetic diagnosis

A total of eight patients who were diagnosed with GSDs were recruited. Molecular analysis confirmed the diagnosis of GSDs and subtype identification. The median age at presentation was 2.18 (1.57–3.05) years, and 37.5% were male. However, the median time of diagnosis and molecular analysis were 1.56 (0.9–2.4) and 3.41 (2.78–6.49) years from the presentation, respectively. Two patients (25%) were from families of consanguineous couples. Based on the results of the molecular analysis, one patient each was classified into subtypes Ia (12.5%) and IX (12.5%), and three patients were classified into subtypes III (37.5%) and VI (37.5%) (Table 1). Ten variants were identified in *G6PC* (n = 1), *AGL* (n = 4), *PYGL* (n = 5), and *PHKA2* (n = 1). The compound heterozygous c.1611+1G>C and c.1735G>A variants in *AGL* identified in patient 4 were novel (Table 1). A comprehensive comparison of two novel *AGL* variants, including their allele frequencies in control databases, potential functional effects, and American College of Medical Genetics and Genomics (ACMG) classifications are demonstrated in Table 2[8]. Remarkably, the known c.2467C>T (p.Gln823Ter) mutation in *PYGL*[9] appears to be a potential hotspot, present in all three patients with *PYGL* mutations.

The first manifestations were abdominal distension from hepatomegaly (100%), doll-like facies (37.5%), wasting (25%), overweight (12.5%), stunting (62.5%), gastrointestinal bleeding (12.5%), epistaxis (12.5%), and jaundice (12.5%). Biochemical profiles at presentation were hypoglycemia (100%), transaminitis (100%), hyperuricemia (50%), anemia (25%), hypercholesterolemia (62.5%), hypertriglyceridemia (100%), and direct hyperbilirubinemia (50%) (Table 3). All patients had normal renal function. Liver ultrasonography revealed hepatomegaly with diffuse increased parenchyma echogenicity in all patients. One patient had multiple liver tumors, with magnetic resonance imaging revealing the feature of hepatic adenomatosis (Figure 1). Liver pathology exhibited hepatocyte ballooning with positive periodic acid-Schiff staining and diastase sensitivity in all patients (Figure 2).

Table 1 Genetic variants associated with glycogen storage disease

Patient number	Gene	WES	Variant	Amino acid	Exon/ Intron	Zygosity	Inheriting parent of allele[1]	Transcript	hg19 coordinate	Ref.
GSD Ia										
5	*G6PC*	Duo	c.648G>T	p.Leu216Leu	Exon 5	Homozygous or Hemizygous[2]	Mother	NM_000151.4	chr17:41063017 G>T	[21]
GSD III										
3	*AGL*	Trio	c.2578delG	p.Val860LeufsTer8	Exon 20	Homozygous	Father and mother	NM_000642.3	chr1:100350156 delG	Clinvar RCV003060970.1[3]
4	*AGL*	Singleton	c.1611+1G>C	N/A	Intron 12	Heterozygous	Unknown	NM_000642.3	chr1:100343385 G>C	Novel[4]
			c.1735G>A	p.Glu579Lys	Exon 13	Heterozygous	Unknown	NM_000642.3	chr1:100345602 G>A	Novel[4]
6	*AGL*	Trio	c.1735+1G>T	N/A	Intron 13	Homozygous	Father and mother	NM_000642.3	chr1:100345603 G>T	[22]
GSD VI										
2	*PYGL*	Trio	c.514C>T	p.Arg172Ter	Exon 4	Heterozygous	Father	NM_002863.5	chr14:51398405 G>A	[9]
			c.2467C>T	p.Gln823Ter	Exon 20	Heterozygous	Mother	NM_002863.5	chr14:51372187 G>A	[9]
7	*PYGL*	Singleton	c.2467C>T	p.Gln823Ter	Exon 20	Heterozygous	Unknown	NM_002863.5	chr14:51372187 G>A	[9]
			c.932G>A	p.Arg311His	Exon 8	Heterozygous	Unknown	NM_002863.5	chr14:51383747 C>T	[23]
8	*PYGL*	Trio	c.1726C>T	p.Arg576Ter	Exon 14	Heterozygous	Father	NM_002863.5	chr14:51378916 G>A	[24][5]
			c.2467C>T	p.Gln823Ter	Exon 20	Heterozygous	Mother	NM_002863.5	chr14:51372187 G>A	[9]
GSD IX										
1	*PHKA2*	Trio	c.2746C>T	p.Arg916Trp	Exon 25	hemizygous	Mother	NM_000292.3	chrX:18924673 G>A	[25]

[1]Biallelic variants identified by singleton exome sequencing analysis will be reported as "parental origin unknown.
[2]The duo exome sequencing performed on patient #5 and the mother, due to the unavailability of the father's DNA, has shown that the zygosity of the *G6PC*:c.648G>T variant cannot be distinguished between homozygous (inherited from both parents) and hemizygous (inherited from the mother only).
[3]Although no individuals with *AGL*-related conditions have been previously reported in the literature with this variant, ClinVar classifies the *AGL*:c.2578delG variant as pathogenic (Accession: RCV003060970.1) based on a submission ID: SCV003456543.1 by Invitae.
[4]Novel: a novel variant means that it is not present in the public database including literatures in pubmed, GRCh38/hg38 or GRCh37/hg19 gnomAD, and Clinvar databases.
[5]No reports of the *PYGL*:c.932G>A (p.Arg311His) variant exist in patients with glycogen storage disease type VI. However, the literature on colorectal carcinoma documents its presence[24].
WES: Whole-exome sequencing; GSD: Glycogen storage diseases.

Because genetic analysis was unavailable at the time of diagnosis and the diagnosis of GSD was initially based on clinical presentations and liver histopathology, the mainstay of treatment was to normalize blood sugar and other biochemical profiles. Cornstarch supplementation was advocated in all patients, given 1–7.2 g/kg/day twice to five times a day depending on the result of random blood glucose, in conjunction with a high-protein diet (1.5–3 g/kg/day) and

Table 2 Comparison of novel *AGL* variants based on allele frequency and functional impact

Variant	GRCh37/hg19 gnomAD	GRCh38/hg38 gnomAD	5432 Thai exomes	Potential functional impact	Reported in other GSD cases	ACMG classification
c.1611+1G>C (p.?)	Not identified	Not identified	Not identified	Potentially disruptive to splicing due to its location at the splice donor site. May lead to aberrant mRNA processing and protein expression	Not reported	Likely pathogenic (PVS1, PM2)
c.1735G>A (p.Glu579Lys)	Not identified	Identified in 1 out of 1461034 alleles	Not identified	Missense mutation resulting in a Glu579Lys amino acid change within the transferase catalytic domain. May affect enzyme activity or protein stability	Not reported	Variant of uncertain significance (PM2, PP3)

ACMG: American College of Medical Genetics and Genomics; GSD: Glycogen storage diseases.

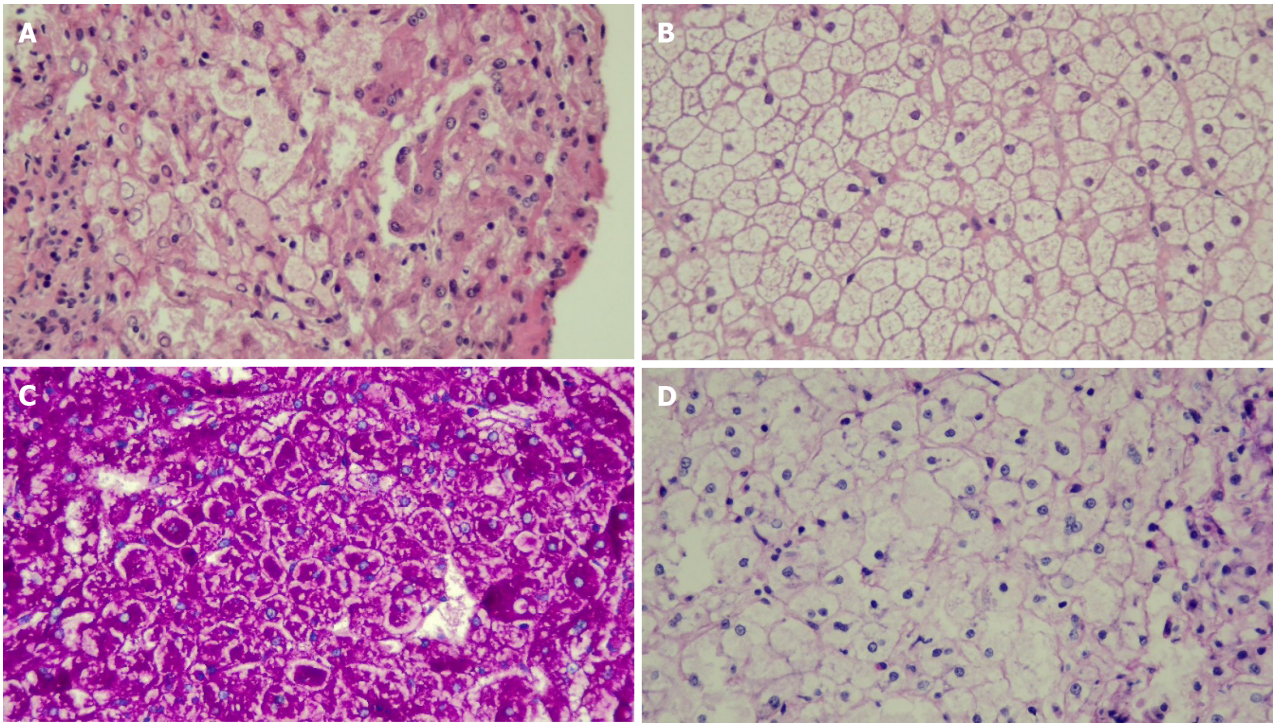

Figure 2 Light microscopy of liver histopathology with high-power magnification (× 40). A: Patient 6 [glycogen storage disease (GSD) type III] hematoxylin and eosin stain (HE) shows swelling of hepatocytes; B: Patient 7 (GSD type VI) HE stain shows swelling of hepatolcytes with some material deposit inside; C: Patient 7 with periodic acid-Schiff (PAS) staining; D: Patient 7 with PAS-diastase (PAS-D) staining. Hepatocytes were stained with PAS and were mostly digested by PAS-D.

low-lactose–fructose ingestion. One of them (patient 5, GSD type I) had hyperuricemia that required allopurinol (Table 3). All patients had regular follow-up appointments every 3–6 months. Nearly all patients demonstrated good compliance with the uncooked cornstarch prescription, except for patients 1 (GSD type I), 2 (GSD type VI), and 5 (GSD type XI). Despite poor compliance, patient 2 (GSD type VI) had normal liver enzyme levels, lipid profiles, and growth at the last follow-up. By contrast, patients 1 (GSD type I) and 5 (GSD type XI) had better biochemical profiles but exhibited stunted growth from diagnosis through the last follow-up. Patients 3, 4, and 6 (GSD type III) experienced frequent hypoglycemia, requiring cornstarch supplementation of up to 7.2 g/kg/day (patient 3) and up to five times a day. Despite good compliance, patients 3 and 6 had persistent transaminitis and dyslipidemia, and patient 3 was also overweight.

All eight patients remain alive, with a median follow-up period of 9.59 (1.20–10.56) years. For the outcome at the end of follow-up, patients 1 and 5 still had stunting (25%), but none had wasting. However, patients 1, 3, and 8 were overweight, with BMI Z-score 1.2 SD (37.5%). Liver function, blood sugar, and lipid profiles improved in all patients. Transaminitis turned to normal in 3 (37.5%) patients. Blood sugar improved in all patients; however, two of them (25%) still had hypoglycemia with prolonged fasting time (patients 3 and 6; GSD type III). Patients 2 and 4 diagnosed with GSD types III and VI could omit uncooked corn starch before bedtime as determined by their genetic subtype analysis without hypoglycemia from their random blood glucose. Hypercholesterolemia was observed in 2 (25%) patients, and hypertriglyceridemia was noted in 2 (25%) patients. Hyperuricemia was found in 4 (50%) patients (Table 4 and Figure 3).

Table 3 Patient characteristics, biological profiles at the time of clinical diagnosis and at the last of follow-up

Patient number	Sex	Age at clinical Dx (year)	Time from clinical Dx to molecular Dx (year)	First presentation	Growth and nutritional status	Biochemical result						Follow-up time (year)	Clinical and biological profiles at the last follow-up						
						AST (U/L)	ALT (U/L)	BS (mg/dL)	TC (mg/dL)	TG (mg/dL)	Uric Acid (mg/dL)		Growth and nutritional status	AST (U/L)	ALT(U/L)	BS (mg/dL)	TC (mg/dL)	TG (mg/dL)	Uric Acid (mg/dL)
GSD I																			
5	F	14.7	12.52	Hepatomegaly, recurrent epistaxis	Wasting/ stunting	118	67	53	210	376	8.6	13.8	Stunting	33	28	58	179	396	9.7
GSD III																			
3	F	3.02	8.49	Hepatomegaly	Normal	4302	1341	48	241	622	5.1	11.5	Overweight	510	375	72	205	124	8
4	F	1.43	12.22	Hepatomegaly	Normal	629	547	20	138	119	3.3	12.3	Normal	33	28	78	137	63	5.8
6	M	2.62	3.06	Hepatomegaly, doll-like facies	Stunting	1878	854	30	180	231	6.1	3.1	Normal	626	408	35	184	203	6.8
GSD VI																			
2	F	1.75	9.24	Hepatomegaly	Wasting	746	736	56	305	335	6.9	12.5	Normal	15	14	83	137	89	6.1
7	F	3.08	2.08	Hepatomegaly	Stunting	72	64	92	256	189	4.3	2.1	Normal	55	40	72	226	104	5.9
8	M	1.35	1.10	Hepatomegaly, doll-like facies	Overweight/ stunting	920	665	55	246	303	3.9	1.8	Overweight	72	90	86	170	100	5.4
GSD IX																			
1	M	1.7	2.75	Hepatomegaly, doll-like facies	Stunting	1531	439	34	145	159	5.3	6.48	Overweight/stunting	161	78	84	145	97	5.2

GSD: Glycogen storage disease; F: Female; M: Male, Dx: Diagnosis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BS: Blood sugar; TC: Total cholesterol; TG: Triglyceride.

One patient with GSD type I had increasing size of the hepatic adenomatosis but normal liver enzyme, requiring liver transplantation (waiting list) (Figure 1). For other comorbidities, none had hypertension, chronic kidney disease, delayed motor development, seizure due to hypoglycemia, or hypertrophic cardiomyopathy.

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate the clinical and molecular characteristics of hepatic GSDs in Thai children. The most common hepatic GSDs in this study are types III and VI. The known c.2467C>T

Table 4 Biochemical profiles at the diagnosis and the last follow-up, median (25th-75th percentiles)

Blood test	At the diagnosis	At the last follow-up	*P* value
Hb (mg/dL)	11.9 (10.1-12.2)	12.9 (11.8-13.1)	0.072
WBC	11140 (9975-14020)	9415 (8600-10690)	0.046
Platelet	386000 (325500-457500)	377500 (327000-448000)	1
Blood sugar (mg/dL)	55 (30-87)	72 (58-83.5)	0.248
Total cholesterol	241 (138-256)	174.5 (137-194.5)	0.132
Triglyceride (mg/dL)	231 (159-335)	105.5 (94.5-163.5)	0.037
LDL (mg/dL)	141 (88-211)	94 (83.5-122)	0.165
HDL (mg/dL)	24 (10-32)	39.5 (35-41)	0.004
Uric acid (mg/dL)	5.1 (3.9-6.5)	6 (5.6-7.55)	0.148
ALT (U/L)	665 (67-854)	59 (28-232.5)	0.021
AST (U/L)	833 (374-1704)	63.5 (33-335.5)	0.007
Total bilirubin (mg/dL)	0.39 (0.24-0.99)	0.53 (0.43-0.70)	0.462
Direct bilirubin (mg/dL)	0.22 (0.10-0.41)	0.22 (0.16-0.28)	1
Globulin (mg/dL)	3.1 (2.8-3.4)	3.4 (2.85-4.05)	0.354
Albumin (mg/dL)	4.3 (4.0-4.5)	4.4 (4.25-4.4)	0.335
GGT	169 (66.2-251)	59 (31.5-136)	0.156
Blood urea nitrogen	12 (8-14)	10.5 (9.5-13.5)	0.771
Creatinine	0.25 (0.21-0.4)	0.41 (0.26-0.55)	0.072

Hb: Hemoglobin; WBC: White blood cell count; LDL: Low density lipoprotein; HDL: High density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.

(p.Gln823Ter) mutation in *PYGL* appears to be a potential hotspot, present in all three individuals with GSD type VI. All patients presented with hepatomegaly, hypoglycemia, hypercholesterolemia and transaminitis. Liver histopathology was used to confirm the diagnosis with high accuracy. The improvement in lipid profiles, growth parameters, and liver enzymes in most patients proposed that nutritional management had yielded favorable long-term outcomes. In addition, molecular analysis successfully classified GSD subtypes and identified two novel *AGL* variants, expanding the mutational spectrum.

In the present study, the hallmarks of GSDs included the triad of hepatomegaly, transaminitis, and hypoglycemia that were consistent with the studies in India and Pakistan by Kumar *et al*[6] (n = 57) and Ahmed *et al*[7] (n = 55), in which all of them had marked abdominal distension probably from hepatomegaly. Liang *et al*[4] studied in Chinese children (n = 49), and all of them had the triad, and Beyzaei *et al*[10] (n = 14) studied in Iranian cases of GSDs, and all of them had hepatomegaly and transaminitis. As a result, the triad is useful to narrow the diagnosis that should be confirmed using liver biopsy or molecular analysis. In regions where molecular analysis is inaccessible, liver biopsy might be considered for timely management. However, guidelines for the specific management according to hepatic GSD subtypes have been established for hepatic GSD types I[11], III[12], IV[13], VI[14], and IX[14] that help physicians target or personalize management. In addition, long-term complications appear to differ among types, for example, hepatic adenoma can occur in GSD types I, III, and IV[15]. Thus, monitoring complications of GSD subtypes is cost-benefit and saves time leading to a better quality of life of patients. Many mimic diseases from GSDs should be considered, such as congenital disorder of glycosylation, lysosomal disorders, and mitochondrial disorders[16-18]. Consequently, in centers with limited resources, molecular analysis must be subsequently performed by sending specimens to facilities capable of confirming the diagnosis and classifying subtypes for tailored treatment[19]. In addition, understanding patients' genetic background is beneficial for counseling and family planning.

In this study, most Thai children with GSDs had types III and VI, in contrast with findings from China[2-4,8], Iran[10], India[5,6], Parkistan[7], Spain[19], and Italy[20] where GSD type VI is relatively rare. GSD type III, common in many countries, is associated with recurrent hypoglycemic seizures, leading to delayed development. However, in this study, Thai children with GSD type III did not experience seizures or demonstrate significant developmental delays. Notably, one child with GSD type III (with a novel causative variant) achieved good clinical and biochemical outcomes, and uncooked cornstarch supplementation was stopped during adolescence. For GSD type IX, our patient exhibited improved biochemical profiles but continued to experience growth retardation at age 9, consistent with reports from the ACMG [14]. This finding contrasts with that of a larger study in China where nearly all patients with GSD type IXa (n = 17) had mild disorders and favorable outcomes, often achieving normal growth by adolescence without cornstarch supple-

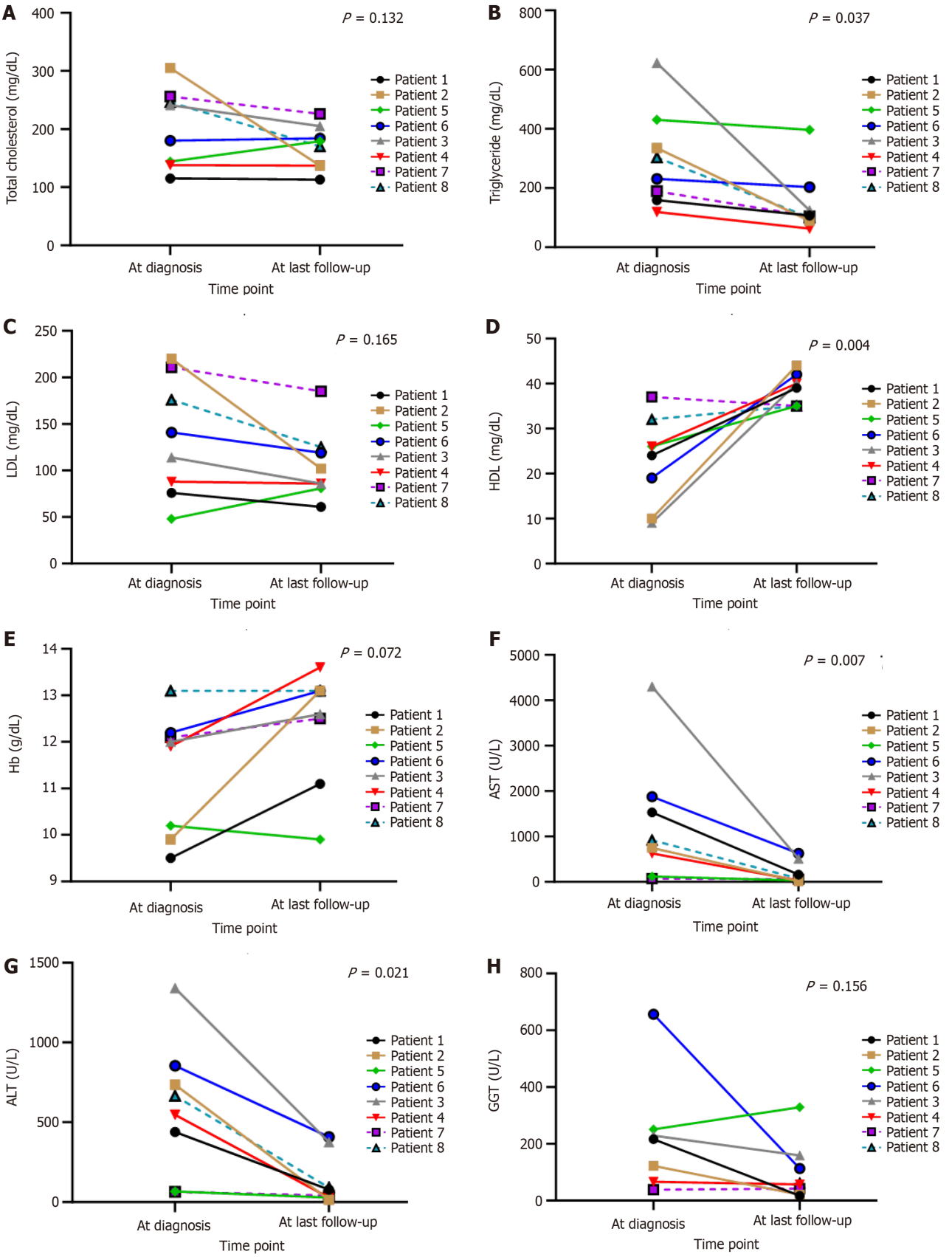

Figure 3 Biological profiles at diagnosis and the last follow-up. A: Total cholesterol; B: Triglyceride; C: Low density lipoprotein; D: High density lipoprotein; E: Hemoglobin; F: Aspartate aminotransferase; G: Alanine aminotransferase; H: Gamma-glutamyl transferase. Hb: Hemoglobin; LDL: Low density lipoprotein; HDL: High density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.

mentation[2]. Patients with GSD type VI, although less reported in Asia, generally have better outcomes than those with GSD types I, III, and XI. Clinical symptoms and biochemical profiles often improve into adulthood with specific nutritional therapy, which helps preserve growth, improve glycemic control, and prevent liver complications. In this study, three children with GSD type VI had normal growth, and two had normal liver enzymes and lipid profiles after extensive nutritional management. One child, who had poor compliance with uncooked cornstarch but adhered to a high-protein diet, also achieved good clinical and biochemical outcomes, indicating that tapering treatment for GSD type VI may be reasonable. In addition, the known c.2467C>T (p.Gln823Ter) mutation in *PYGL* appears to be a potential hotspot, present in all three individuals with GSD type VI, and could be considered the screening mutation for patients suspected of GSDs in Thailand.

Nutritional management is the mainstay of treatment, particularly cornstarch supplementation for GSD type I because of frequent fasting hypoglycemia. However, cornstarch might not be necessary if patients with GSD type III reach adolescence[12], and only bedtime cornstarch might be considered in GSD types VI and IX. In addition to nutritional management, a comprehensive, long-term care approach involving the surveillance of disease sequelae based on GSD subtypes is recommended. Therefore, the precise diagnosis of GSD subtypes can enhance the quality of life, not only by enabling more targeted nutritional management but also by addressing the potential involvement of other organs[12,13].

In this, all patients received similar nutritional management and long-term surveillance with multidisciplinary teams in all aspects of growth, metabolic, cardiac, and liver complications. The treatment outcome was favorable, with nearly normal growth and significant improvement in the biochemical profiles of lipid and liver enzymes. However, after genetic analysis, two of our patients were diagnosed with GSD types III and VI and experienced frequent hypoglycemia during their toddler years. As they grow (aged 11 and 14 years), hypoglycemia subsequently improves, allowing them to discontinue both daytime and nighttime cornstarch supplementation, with only occasional home blood sugar monitoring. These findings highlight the genetic heterogeneity of GSDs, affirming the use of WES in the diagnosis and clinical decision-making. A high-protein diet is also advocated in patients with GSD types VI and XI as a protective effect against overweight/obesity and insulin resistance[20]. This dietary approach was advised for all patients with GSD in this study, with favorable outcomes; however, its generalizability across all GSD types warrants further study.

This study has several limitations, primarily due to the small sample size, which resulted in low statistical power and limitations in the generalizability of the findings to all patients with GSDs. A multicenter study focusing on Thai children with GSDs could provide valuable insights, particularly if it includes investigations into genotype–phenotype correlations, explores novel therapeutic approaches, and evaluates long-term outcomes, particularly given the increased availability of genetic analysis in recent times. In addition, hypoglycemia, a hallmark of the disease, may be present from birth and can go undetected, potentially affecting child development—a factor not deeply explored in this study. Finally, the age at diagnosis and treatment duration among patients may confound the observed improvements in patients' growth and biochemical profiles.

CONCLUSION

The findings of this study indicate that key features of liver GSDs encompass hepatomegaly, transaminitis, and hypoglycemia. Stunting or growth retardation is commonly observed. Although a liver biopsy can confirm the diagnosis, it is unable to identify the specific GSD subtype. Therefore, molecular diagnosis using WES plays a crucial role in determining the GSD subtype, facilitating tailored treatment for patient subgroups. After the treatment of our patients, notable enhancements were observed in blood sugar levels, aspartate transaminase, alanine transaminase, and lipid profiles. Moreover, height and BMI improved after treatment. This underscores the significance of effective nutritional management in optimizing patient outcomes.

FOOTNOTES

Author contributions: Suphapeetiporn K, Sintusek P and Vanduangden J designed the manuscript, wrote the manuscript; Suphapeetiporn K, Sintusek P collected the data and drafted the manuscript; Ittiwut R and Ittiwut C analyzed the sequencing data and wrote the manuscript; Phewplung T prepared and provided the liver tumor images; Sanpavat A interpreted and prepared the histopathology images. All authors have read and approved the final manuscript.

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Informed consent statement: Written informed assent and/or informed consent for this study were obtained from the patients and/or their parents.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: Correspondence and requests for materials should be addressed to Palittiya Sintusek.

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REFERENCES

1 **Weinstein DA**, Steuerwald U, De Souza CFM, Derks TGJ. Inborn Errors of Metabolism with Hypoglycemia: Glycogen Storage Diseases and Inherited Disorders of Gluconeogenesis. *Pediatr Clin North Am* 2018; **65**: 247-265 [PMID: 29502912 DOI: 10.1016/j.pcl.2017.11.005]
2 **Zhang J**, Yuan Y, Ma M, Liu Y, Zhang W, Yao F, Qiu Z. Clinical and genetic characteristics of 17 Chinese patients with glycogen storage disease type IXa. *Gene* 2017; **627**: 149-156 [PMID: 28627441 DOI: 10.1016/j.gene.2017.06.026]
3 **Dong R**, Wei X, Zhang K, Song F, Lv Y, Gao M, Wang D, Ma J, Gai Z, Liu Y. Genotypic and phenotypic characteristics of 12 chinese children with glycogen storage diseases. *Front Genet* 2022; **13**: 932760 [PMID: 36105079 DOI: 10.3389/fgene.2022.932760]
4 **Liang Y**, Du C, Wei H, Zhang C, Zhang M, Hu M, Fang F, Luo X. Genotypic and clinical analysis of 49 Chinese children with hepatic glycogen storage diseases. *Mol Genet Genomic Med* 2020; **8**: e1444 [PMID: 32772503 DOI: 10.1002/mgg3.1444]
5 **Poojari V**, Shah I, Shetty NS, Mirani S, Tolani D. Clinical profile and outcome of glycogen storage disease in Indian children. *Trop Doct* 2021; **51**: 189-192 [PMID: 33106122 DOI: 10.1177/0049475520961935]
6 **Kumar TV**, Bhat M, Narayanachar SG, Narayan V, Srikanth AK, Anikar S, Shetty S. Molecular and clinical profiling in a large cohort of Asian Indians with glycogen storage disorders. *PLoS One* 2022; **17**: e0270373 [PMID: 35834487 DOI: 10.1371/journal.pone.0270373]
7 **Ahmed S**, Akbar F, Ali AJ, Afroze B. Clinical, pathological and molecular spectrum of patients with glycogen storage diseases in Pakistan. *J Pediatr Endocrinol Metab* 2022; **35**: 373-385 [PMID: 34989216 DOI: 10.1515/jpem-2021-0575]
8 **Yu T**, Fu H, Yang A, Liang Y. Clinical and Functional Characterization of Novel AGL Variants in Two Families with Glycogen Storage Disease Type III. *Int J Endocrinol* 2023; **2023**: 6679871 [PMID: 37287601 DOI: 10.1155/2023/6679871]
9 **Liu B**, Wu B, Lu Y, Zhang P, Xiao F, Li G, Wang H, Dong X, Liu R, Li Y, Xie X, Zhou W, Wang J, Lu Y. A Novel, Recurrent, 3.6-kb Deletion in the PYGL Gene Contributes to Glycogen Storage Disease Type VI. *J Mol Diagn* 2020; **22**: 1373-1382 [PMID: 32961316 DOI: 10.1016/j.jmoldx.2020.08.006]
10 **Beyzaei Z**, Ezgu F, Geramizadeh B, Imanieh MH, Haghighat M, Dehghani SM, Honar N, Zahmatkeshan M, Jassbi A, Mahboubifar M, Alborzi A. Clinical and genetic spectrum of glycogen storage disease in Iranian population using targeted gene sequencing. *Sci Rep* 2021; **11**: 7040 [PMID: 33782433 DOI: 10.1038/s41598-021-86338-4]
11 **Kishnani PS**, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, Chung WK, Dagli AI, Dale D, Koeberl D, Somers MJ, Wechsler SB, Weinstein DA, Wolfsdorf JI, Watson MS; American College of Medical Genetics and Genomics. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med* 2014; **16**: e1 [PMID: 25356975 DOI: 10.1038/gim.2014.128]
12 **Kishnani PS**, Austin SL, Arn P, Bali DS, Boney A, Case LE, Chung WK, Desai DM, El-Gharbawy A, Haller R, Smit GP, Smith AD, Hobson-Webb LD, Wechsler SB, Weinstein DA, Watson MS; ACMG. Glycogen storage disease type III diagnosis and management guidelines. *Genet Med* 2010; **12**: 446-463 [PMID: 20631546 DOI: 10.1097/GIM.0b013e3181e655b6]
13 **Koch RL**, Soler-Alfonso C, Kiely BT, Asai A, Smith AL, Bali DS, Kang PB, Landstrom AP, Akman HO, Burrow TA, Orthmann-Murphy JL, Goldman DS, Pendyal S, El-Gharbawy AH, Austin SL, Case LE, Schiffmann R, Hirano M, Kishnani PS. Diagnosis and management of glycogen storage disease type IV, including adult polyglucosan body disease: A clinical practice resource. *Mol Genet Metab* 2023; **138**: 107525 [PMID: 36796138 DOI: 10.1016/j.ymgme.2023.107525]
14 **Kishnani PS**, Goldstein J, Austin SL, Arn P, Bachrach B, Bali DS, Chung WK, El-Gharbawy A, Brown LM, Kahler S, Pendyal S, Ross KM, Tsilianidis L, Weinstein DA, Watson MS; ACMG Work Group on Diagnosis and Management of Glycogen Storage Diseases Type VI and IX. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2019; **21**: 772-789 [PMID: 30659246 DOI: 10.1038/s41436-018-0364-2]
15 **Sintusek P**, Phewplung T, Sanpavat A, Poovorawan Y. Liver tumors in children with chronic liver diseases. *World J Gastrointest Oncol* 2021; **13**: 1680-1695 [PMID: 34853643 DOI: 10.4251/wjgo.v13.i11.1680]
16 **Jones MA**, Bhide S, Chin E, Ng BG, Rhodenizer D, Zhang VW, Sun JJ, Tanner A, Freeze HH, Hegde MR. Targeted polymerase chain reaction-based enrichment and next generation sequencing for diagnostic testing of congenital disorders of glycosylation. *Genet Med* 2011; **13**: 921-932 [PMID: 21811164 DOI: 10.1097/GIM.0b013e318226fbf2]
17 **DaRe JT**, Vasta V, Penn J, Tran NT, Hahn SH. Targeted exome sequencing for mitochondrial disorders reveals high genetic heterogeneity. *BMC Med Genet* 2013; **14**: 118 [PMID: 24215330 DOI: 10.1186/1471-2350-14-118]
18 **Fernández-Marmiesse A**, Morey M, Pineda M, Eiris J, Couce ML, Castro-Gago M, Fraga JM, Lacerda L, Gouveia S, Pérez-Poyato MS, Armstrong J, Castiñeiras D, Cocho JA. Assessment of a targeted resequencing assay as a support tool in the diagnosis of lysosomal storage disorders. *Orphanet J Rare Dis* 2014; **9**: 59 [PMID: 24767253 DOI: 10.1186/1750-1172-9-59]
19 **Vega AI**, Medrano C, Navarrete R, Desviat LR, Merinero B, Rodríguez-Pombo P, Vitoria I, Ugarte M, Pérez-Cerdá C, Pérez B. Molecular

diagnosis of glycogen storage disease and disorders with overlapping clinical symptoms by massive parallel sequencing. *Genet Med* 2016; **18**: 1037-1043 [PMID: 26913919 DOI: 10.1038/gim.2015.217]

20 **Tagliaferri F**, Massese M, Russo L, Commone A, Gasperini S, Pretese R, Dionisi-Vici C, Maiorana A. Hepatic glycogen storage diseases type 0, VI and IX: description of an italian cohort. *Orphanet J Rare Dis* 2022; **17**: 285 [PMID: 35854365 DOI: 10.1186/s13023-022-02431-5]

21 **Zheng BX**, Lin Q, Li M, Jin Y. Three novel mutations of the G6PC gene identified in Chinese patients with glycogen storage disease type Ia. *Eur J Pediatr* 2015; **174**: 59-63 [PMID: 24980439 DOI: 10.1007/s00431-014-2354-y]

22 **Perveen S**, Gupta N, Kumar M, Kaur P, Chowdhury MR, Kabra M. Spectrum of amyloglucosidase mutations in Asian Indian patients with Glycogen storage disease type III. *Am J Med Genet A* 2020; **182**: 1190-1200 [PMID: 32222031 DOI: 10.1002/ajmg.a.61547]

23 **Giannakis M**, Mu XJ, Shukla SA, Qian ZR, Cohen O, Nishihara R, Bahl S, Cao Y, Amin-Mansour A, Yamauchi M, Sukawa Y, Stewart C, Rosenberg M, Mima K, Inamura K, Nosho K, Nowak JA, Lawrence MS, Giovannucci EL, Chan AT, Ng K, Meyerhardt JA, Van Allen EM, Getz G, Gabriel SB, Lander ES, Wu CJ, Fuchs CS, Ogino S, Garraway LA. Genomic Correlates of Immune-Cell Infiltrates in Colorectal Carcinoma. *Cell Rep* 2016; **17**: 1206 [PMID: 27760322 DOI: 10.1016/j.celrep.2016.10.009]

24 **Luo X**, Duan Y, Fang D, Sun Y, Xiao B, Zhang H, Han L, Liang L, Gong Z, Gu X, Yu Y, Qiu W. Diagnosis and follow-up of glycogen storage disease (GSD) type VI from the largest GSD center in China. *Hum Mutat* 2022; **43**: 557-567 [PMID: 35143115 DOI: 10.1002/humu.24345]

25 **Beauchamp NJ**, Dalton A, Ramaswami U, Niinikoski H, Mention K, Kenny P, Kolho KL, Raiman J, Walter J, Treacy E, Tanner S, Sharrard M. Glycogen storage disease type IX: High variability in clinical phenotype. *Mol Genet Metab* 2007; **92**: 88-99 [PMID: 17689125 DOI: 10.1016/j.ymgme.2007.06.007]

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ORIGINAL ARTICLE

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Prevalence of obesity, determinants, and its association with hyperglycaemia among community dwelling older adolescents in India

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Abstract

BACKGROUND

Globally, obesity and diabetes mellitus (DM) are emergent public health concerns in the adolescent population. India, home to the largest adolescent population and the second largest diabetes cohort is experiencing rapid but unplanned urbanization, with accompanying unhealthy nutritional transition, and sedentary lifestyle.

AIM

To determine prevalence and determinants of obesity and hyperglycaemia and their association among community-dwelling older adolescents (15-19 years) in India.

METHODS

This cross-sectional analysis from the national family health survey-5 included data of 258028 adolescents aged 15-19 across India (2019-2021). The survey employed stratified two-stage sampling, with systematic random sampling in rural and urban areas. Statistical analysis included descriptive statistics, bivariate, and multivariable logistic regression, employing generalized linear models.

RESULTS

The weighted prevalence of DM was 1.09% including 0.77% [95% confidence interval (CI): 0.72-0.83] previously diagnosed and 0.32% (95%CI: 0.29-0.35) newly diagnosed cases detected on survey screening. On adjusted analysis, increasing age, higher education levels, higher wealth index, and overweight/obesity were the factors significantly associated with presence of DM. Only 61% of the adolescents with previously diagnosed DM were on anti-diabetes treatment. The weighted prevalence of overweight/obesity among older adolescents was 6.9% with significantly higher odds in the male sex, having higher educational levels,

urban residence, and those with a higher wealth index.

CONCLUSION
Nearly one in hundred older adolescents in India have diabetes, with one in three undiagnosed. Strengthening DM screening and treatment access among adolescents through public health programs is urgently warranted.

Key Words: Obesity; Hyperglycaemia; Adolescents; Diabetes; India

Core Tip: In resource-limited settings, 3 in 10 older adolescents with diabetes (DM) are undiagnosed due to lack of screening while only 6 in 10 older adolescents previously diagnosed with DM utilize anti-diabetes medication. Primary care physicians including paediatricians in outpatient settings should necessarily screen older adolescents with family history or those who are overweight or obese for DM. Furthermore, they should advise older adolescents to engage in regular physical activity and exercise to maintain normal body weight even in the absence of hyperglycaemia. Finally, medication adherence in older adolescents with DM should be assessed during each appointment accompanied with regular counselling.

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INTRODUCTION

Obesity and hyperglycaemia are rapidly emerging as critical public health concerns globally among adolescents. High body mass index (BMI) is positively correlated with Type 2 diabetes mellitus (T2DM) in adolescents, with estimates indicating a 13-fold higher risk of T2DM in obese adolescents compared to those with normal BMI[1-4]. Obesity in adolescence is also a strong predictor of obesity in adulthood[5].

India has the largest population of adolescents worldwide[6] and also the second largest diabetes mellitus (DM) cohort globally[7]. Increasing urbanization, consumption of unhealthy diets and decreased physical activity patterns[8,9] since childhood renders adolescents particularly susceptible to both increased BMI and lifestyle disorders especially T2DM. Genetic predisposition also enhances the risk, especially in the Indian population, which is more prone to insulin resistance and thereby T2DM even at lower levels of obesity compared to Caucasian populations[10].

Previous research has indicated the need for region-specific data in understanding the burden and determinants of diabetes in the adolescent population[11]. The prevalence of childhood obesity and overweight in India as *per* pooled evidence is 8.4%, and 12.4% respectively[12], although most of the existing data is derived from studies with small sample sizes and single-centre studies that lack representativeness while lacking generalizability. Furthermore, the linkage of adolescent BMI with hyperglycaemia and their sociodemographic and behavioural determinants have not been adequately explored in Indian health settings. We therefore conducted this study with the objectives of determining the prevalence and determinants of obesity and hyperglycaemia and their association among community-dwelling older adolescents (15-19 years) in India using data from a nationally representative dataset.

MATERIALS AND METHODS

Study design and data source

This study utilized data from the national family health survey-5 (NFHS-5), a nationally representative large-scale, multistage survey conducted in a representative sample of households across India between 2019 and 2021. NFHS-5 survey collected comprehensive information on India's population and health from 707 districts, 28 states, and eight union territories. The survey employed a stratified, two-stage sampling design to ensure the representativeness of the sample. In rural regions, primary sampling units (PSUs) were villages selected using probability proportional to size (PPS). Conversely, in urban areas, census enumeration blocks were chosen as PSUs through PPS systematic sampling. During the second stage, households were randomly chosen using systematic random sampling after a comprehensive mapping and household listing of the selected PSUs. Detailed information pertaining to the sampling, survey tools and data collection is available elsewhere[13].

Study sample

The present study included adolescents aged 15-19 years as the target population to estimate the prevalence of DM in this age-group. The study sample was derived from the NFHS-5 household dataset, which included a representative sample

of households from across the country.

Outcome variables

In NFHS-5, all individuals aged 15 years and older were invited to participate in a finger-stick blood glucose assessment [13]. Trained health investigators conducted random or fasting blood glucose testing using the Accu-Chek Performa glucometer along with glucose test strips. Threshold values were employed to identify DM using a random glucose test result of ≥ 200 mg/dL for individuals who were not in a fasting state and ≥ 126 mg/dL for individuals who reported fasting for ≥ 8 hours prior to the test.

An individual was categorized as having a previous DM diagnosis if they had answered affirmatively to the question, "Told high blood glucose on two or more occasions by doctor or health professionals?". Similarly, an individual was classified as using DM medication if they had indicated "yes" in response to the question, "Currently taking any prescribed medicine to lower blood glucose?". In our analysis, an individual was considered to have DM if they either exhibited elevated blood glucose levels, were previously diagnosed with DM, or were using medication to reduce their blood glucose levels. Further, we assessed treatment-seeking behaviour among adolescents with previously diagnosed DM, based on whether they reported taking medication to lower blood glucose.

Independent variables

The major socio-demographic variables considered, and their categories included age, sex (male or female), education levels (no education, primary, secondary or higher education), wealth index (poorest to richest), urban or rural residence, and household religion (Hindu, Muslim or others). Lifestyle factors included tobacco consumption (self-reported as yes or no) and alcohol use (self-reported as yes or no) among the adolescents. The type of healthcare facility accessed by the participant in the last 3 months was queried and categorized into four groups: None, public, private, and others (nongovernmental organization along with other facilities). In NFHS-5, the Seca 213 stadiometer was used to measure height and the Seca 874 digital scale was used to measure the weight of the participants. The World Health Organization growth reference standard was applied to ascertain the BMI z-scores in the adolescents[14]. For the current analysis, individuals were grouped into three categories: Overweight/obese (z-score > + 1 SD), normal (between + 1 and - 2 SD), and thin (> - 2 SD).

Statistical analysis

Descriptive statistics were employed to summarize the characteristics of the study participants. The mean and SD were reported for continuous variables, while frequency and percentages were reported for categorical variables. Bivariate analysis was conducted to examine the associations between the independent variables and the presence of DM among the adolescents.

We utilized the modified Poisson regression approach[15] to identify the determinants of DM among the adolescents. The model was fit using a generalized linear model with the Poisson family. Both unadjusted and adjusted rate ratios (RR) were reported along with their 95% confidence intervals (CI). Similar analysis was conducted to identify the predictors of overweight/obesity among adolescents. For treatment-seeking behaviour, multiple logistic regression was used to estimate odds ratios (ORs) and 95%CI for each predictor variable while adjusting for potential confounders. Adjusted models included variables that showed a significant association ($P < 0.05$) in the bivariate analysis, and model fit was assessed using appropriate tests. Pre-specified sampling weights were applied throughout the analysis to account for the survey design using the "svy" suffix. P value < 0.05 was considered statistically significant. Data analysis was conducted using Stata version 15.1 (StataCorp, College Station, TX, United States).

Ethical considerations

NFHS-5 was conducted in compliance with ethical guidelines and received approval from the ethics review board of the international institute of population sciences, Mumbai, India. Informed consent was obtained from all study participants, and data confidentiality was maintained throughout the analysis. We obtained the datasets through written permission from the Department of Homeland Security (DHS) which also approved the study proposal for this secondary data analysis. The NFHS-5 dataset is an anonymous publicly accessible dataset devoid of any personally identifiable information regarding the participants.

RESULTS

Characteristics of the study participants

The NFHS-5 dataset included a total of 258028 adolescents aged 15-19 years. Table 1 presents the demographic characteristics of the study participants. The mean (± SD) age of the adolescents was 16.99 (1.40) years, with nearly half (50.14%) being females. More than two-thirds of the adolescents resided in rural areas (70.4%), were Hindus by religion (80%) and had secondary education (83.93%). Most of the adolescents had a normal BMI (82.74%) and did not consume tobacco (96.19%) and alcohol (98.89%).

Prevalence of DM among older adolescents

The weighted prevalence of DM among the adolescents aged 15-19 years was estimated as per the operational definition with previously diagnosed DM observed among 0.77% (95%CI: 0.72-0.83) participants, while 0.32% (95%CI: 0.29-0.35)

Table 1 Socio-demographic and lifestyle characteristics of the study participants

Variables	Males, *n* = 129127[1]	Females, *n* = 128901[1]	Total, *n* = 258028[2]
Age in years, mean (SD)	16.97 (1.39)	17.00 (1.40)	16.99 (1.40)
Respondents' education, *n* = 257984			
No education	4185 (43.39)	5533 (56.61)	9718 (3.86)
Primary education	7442 (51.08)	7315 (48.92)	14757 (5.77)
Secondary education	110891 (50.33)	108314 (49.67)	219205 (83.93)
Higher education	6589 (46.51)	7715 (53.49)	14304 (6.44)
Religion, *n* = 139062			
Hindu	12631 (12.08)	91715 (87.92)	104346 (79.95)
Muslim	2116 (11.03)	17549 (88.97)	19665 (15.69)
Others	1903 (12.86)	13148 (87.14)	15051 (4.36)
Residence			
Urban	31058 (52.74)	28303 (47.26)	59361 (29.64)
Rural	98069 (48.65)	100598 (51.35)	198667 (70.36)
Wealth index			
Poorest	29734 (47.99)	31166 (52.01)	60900 (21.87)
Poorer	30774 (48.73)	31748 (51.27)	62522 (22.37)
Middle	26967 (49.64)	26970 (50.36)	53937 (20.69)
Richer	22600 (50.53)	22173 (49.47)	44773 (18.8)
Richest	19052 (53.45)	16844 (46.55)	35896 (16.26)
Tobacco consumption, *n* = 257580			
No	118792 (48.36)	126756 (51.64)	245548 (96.19)
Yes	9920 (86.28)	2112 (13.72)	12032 (3.81)
Alcohol usage, *n* = 257610			
No	125356 (49.39)	128255 (50.61)	253611 (98.89)
Yes	3380 (87.2)	619 (12.8)	3999 (1.11)
BMI, *n* = 134346			
Normal	12333 (10.78)	100459 (89.22)	112792 (82.74)
Thin	2333 (18.39)	10600 (81.61)	12933 (10.37)
Overweight/obese	1211 (13.47)	7410 (86.53)	8621 (6.88)
Health seeking behaviour in past 3 months, *n* = 139058			
None	13733 (13.01)	91180 (86.99)	104913 (74.07)
Public facility	1629 (8.06)	19130 (91.94)	20759 (14.13)
Private facility	1268 (10.04)	11740 (89.96)	13008 (11.48)
Other	20 (4.44)	358 (95.56)	378 (0.32)

Data are *n* (weighted %) unless otherwise indicated.
[1]Row-wise percentages.
[2]Column-wise percentages.
BMI: Body mass index.

were newly diagnosed with DM during survey screening. Overall, 1.09% (95%CI: 1.02-1.15) of adolescents had evidence of DM, as determined by either elevated blood glucose levels, self-reported status of the disease or anti-diabetes medication usage.

Determinants of DM among older adolescents

A binary logistic regression analysis was performed to identify the predictors of DM among the adolescents (Table 2). Upon unadjusted analysis, increasing age, higher education levels, higher wealth index and overweight/obesity were the factors associated with significantly higher odds of having DM among the adolescents. In this study, adjusted RR (aRR) for age was 1.09 (95%CI: 1.02-1.15) indicating that for every 1-year increase in age among the adolescents, the rate of DM increases by 8%. Similarly, a higher rate of having DM was found among those having overweight/obesity (aRR = 1.85; 95%CI: 1.46-2.34).

Treatment-seeking behaviour for older adolescents with DM

Among adolescents previously diagnosed with DM (n = 1744), 60.84% (95%CI: 57.38-64.20) reported taking anti-diabetes medications to lower their blood glucose levels (Table 3). Upon unadjusted logistic regression, adolescents of higher age, of highest educational status, of middle and richer wealth indices and those utilizing a health facility in the past 3 months had significantly higher odds of not taking anti-diabetes treatment despite being previously diagnosed with the condition. Upon adjusted analysis, middle wealth index (aOR = 2.13; 95%CI: 1.20-3.78), utilization of public facility (aOR = 1.76; 95%CI: 1.14-2.71) and private facility (aOR = 1.99; 95%CI: 1.14-3.47) showed significantly higher odds of not taking anti-diabetes treatment as compared to their counterparts.

Prevalence and determinants of overweight and/or obesity among older adolescents

The weighted prevalence of obesity among the older adolescents in this study was 1.70% (95%CI: 1.58-1.82), while for overweight was 5.20% (95%CI: 5.01-5.39). A binary logistic regression analysis was performed to identify the predictors of overweight and/or obesity among the adolescents (Table 4). Upon unadjusted analysis, all the variables included in the regression model were found to be significantly associated with overweight/obesity. Upon adjusted analysis, male sex (aRR = 1.10; 95%CI: 1.01-1.20), secondary education (aRR = 1.28; 95%CI: 1.06-1.54), higher education (aRR = 1.26; 95%CI: 1.02-1.56), Muslim religious household (aRR = 1.21; 95%CI: 1.10-1.34), other (non-Hindu) religions (aRR = 1.18; 95%CI: 1.04-1.33), urban residence (aRR = 1.28; 95%CI: 1.18-1.38), increasing wealth index (aRR for richest = 3.24; 95%CI: 2.86-3.67) and undiagnosed DM (aRR = 2.43; 95%CI: 1.82-3.24) were the significant predictors of overweight/obesity among the older adolescents.

Burden of DM among adolescents across various states and UTs of India

Figure 1 depicts the prevalence of DM among adolescents across various states and UTs of India. The highest prevalence was found in the UT of Ladakh (2.39%), followed by Dadra and Nagar Haveli (1.96%), Puducherry (1.94%) and the state of Tamil Nadu (1.76%). Lowest prevalence was found in Chandigarh (0.0%) and Goa (0.28%).

DISCUSSION

The present study observed a significant association with obesity/overweight and presence of DM in older adolescents in India corroborating the evidence from previous studies[16-18]. However, the prevalence of DM observed in this study (1.09%), was nearly eight times lower compared to an estimation using the glycated haemoglobin method in another large-scale national survey[16]. Furthermore, one in three adolescents with DM were undiagnosed and detected only on screening further indicative of the high burden of unrecognized DM in this vulnerable population which frequently remains asymptomatic. The study findings signify the need for screening older adolescents in India using the glycated haemoglobin method to obtain higher yields and achieve early detection to ensure timely initiation of effective anti-diabetes treatment to prevent or delay the onset of DM related microvascular and macrovascular complications[19,20].

In this study, each year increase from age of 15 onwards was associated with an 8% higher rate of DM indicating that as older adolescents transition into young adulthood, there is increased risk of developing DM particularly in the presence of overweight and obesity. Although increasing age is a well-established risk factor for DM worldwide[21], the increased risk of DM in late adolescence signifies a public health hazard that requires focused interventions for awareness generation and public health screening, strategies which are currently restricted to the > 30 age-group in the existing national program for non-communicable diseases in India[22]. Furthermore, in this study, the risk of DM was higher in the affluent adolescent subgroup possessing higher educational levels and having a higher wealth index which also correlated with their higher risk of obesity. Previously, epidemiological surveys have shown that affluent populations in long-term collaborations in low- and middle-income countries are likely to exhibit sedentary lifestyle that contribute to an increased risk of lifestyle disorders including DM[23]. The present study findings suggest a similar pattern of risk for DM may have occurrence even in the adolescent age-groups, although the absence of data on exercise and physical activity precludes estimation of the association of sedentarism on risk of DM.

The present study found that nearly 61% of the adolescents previously diagnosed with DM reported taking their prescribed anti-diabetes medications. Surprisingly, those who accessed either public or private health facilities in the past 3 months had significantly lower odds of utilizing anti-diabetes medication suggestive of missed opportunities and necessitating increased sensitization of healthcare providers for focusing on medication adherence in the adolescent patients with DM. The burden of overweight and obesity observed among adolescents in this study is also comparatively

Table 2 Distribution of factors associated with diabetes mellitus (previously and newly diagnosed cases)

Variables	DM absent, *n* = 221556	DM present, *n* = 2359	Unadjusted RR (95%CI)	Adjusted RR (95%CI)
Age in years, mean (SD)	16.98 (1.40)	17.11 (1.40)	1.07 (1.02-1.11)[a]	1.09 (1.02-1.15)[a]
Sex				
Male	105161 (98.87)	1168 (1.13)	Reference	-
Female	116395 (98.95)	1191 (1.05)	0.93 (0.83-1.04)	
Respondents' education				
No education	7785 (99.24)	73 (0.76)	Reference	Reference
Primary education	12239 (98.95)	142 (1.05)	1.38 (0.97-1.96)	1.14 (0.74-1.75)
Secondary education	189093 (98.91)	1987 (1.09)	1.43 (1.07-1.91)[a]	1.31 (0.91-1.88)
Higher education	12414 (98.83)	156 (1.17)	1.53 (1.09-2.15)[a]	1.13 (0.73-1.76)
Religion				
Hindu	98145 (98.95)	1006 (1.05)	Reference	-
Muslim	17820 (98.78)	210 (1.22)	1.17 (0.95-1.44)	
Others	14248 (98.85)	151 (1.15)	1.10 (0.81-1.49)	
Residence				
Urban	49616 (98.88)	562 (1.12)	Reference	-
Rural	171940 (98.93)	1797 (1.07)	0.96 (0.84-1.11)	
Wealth index				
Poorest	52225 (99.05)	486 (0.95)	Reference	Reference
Poorer	54247 (98.86)	612 (1.14)	1.19 (1.01-1.41)[a]	1.22 (0.97-1.53)
Middle	47012 (98.86)	523 (1.14)	1.20 (1.01-1.42)[a]	1.21 (0.97-1.52)
Richer	38521 (98.89)	428 (1.11)	1.16 (0.98-1.39)	1.11 (0.88-1.41)
Richest	29551 (98.93)	310 (1.07)	1.12 (0.93-1.36)	1.19 (0.92-1.54)
Tobacco consumption				
No	211095 (98.92)	2242 (1.08)	Reference	-
Yes	10087 (98.67)	115 (1.33)	1.23 (0.96-1.57)	
Alcohol usage				
No	217809 (98.91)	2332 (1.09)	Reference	-
Yes	3402 (99.12)	25 (0.88)	0.81 (0.47-1.38)	
BMI				
Normal	110800 (99.01)	1088 (0.99)	Reference	Reference
Thin	12659 (98.78)	153 (1.22)	1.24 (0.99-1.56)	1.24 (0.99-1.56)
Overweight/obese	8377 (98.13)	141 (1.87)	1.90 (1.50-2.40)[b]	1.85 (1.46-2.34)[b]
Health seeking behaviour in past 3 months				
None	97890 (98.92)	993 (1.08)	Reference	-
Public facility	19697 (98.78)	242 (1.22)	1.14 (0.93-1.39)	
Private facility	12261 (99.1)	128 (0.9)	0.84 (0.66-1.06)	
Other	361 (99.4)	4 (0.6)	0.56 (0.18-1.73)	

Data are *n* (%) unless otherwise indicated.
[a]$P < 0.05$.
[b]$P < 0.001$.
BMI: Body mass index; CI: Confidence interval; DM: Diabetes mellitus; RR: Rate ratio.

Table 3 Distribution of factors associated with treatment status in diabetes mellitus (previously diagnosed cases)

Variables	On treatment, *n* = 1088	Not on treatment, *n* = 656	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Age in years, mean (SD)	17.00 (1.39)	17.24 (1.42)	1.13 (1.03-1.24)[a]	1.08 (0.95-1.24)
Sex				
Male	553 (63.81)	308 (36.19)	Reference	-
Female	535 (57.93)	348 (42.07)	1.28 (0.98-1.67)	
Respondents' education				
No education	38 (70.58)	16 (29.42)	Reference	Reference
Primary education	66 (57.18)	44 (42.82)	1.80 (0.75-4.29)	1.61 (0.53-4.88)
Secondary education	922 (61.92)	547 (38.08)	1.48 (0.70-3.09)	1.10 (0.44-2.78)
Higher education	62 (48.58)	48 (51.42)	2.54 (1.07-6.04)[a]	1.77 (0.59-5.32)
Religion				
Hindu	445 (59.12)	289 (40.88)	Reference	-
Muslim	99 (63.13)	54 (36.87)	0.84 (0.48-1.47)	
Others	83 (53.26)	43 (46.74)	1.27 (0.63-2.55)	
Residence				
Urban	238 (60.22)	172 (39.78)	Reference	-
Rural	850 (61.09)	484 (38.91)	0.96 (0.68-1.37)	
Wealth index				
Poorest	262 (69.36)	110 (30.64)	Reference	Reference
Poorer	271 (60.54)	177 (39.46)	1.48 (0.97-2.24)	1.12 (0.64-1.97)
Middle	225 (55.31)	158 (44.69)	1.83 (1.21-2.77)[a]	2.13 (1.20-3.78)[a]
Richer	183 (54.72)	130 (45.28)	1.87 (1.22-2.87)[a]	1.45 (0.80-2.62)
Richest	147 (65.45)	81 (34.55)	1.19 (0.75-1.90)	1.17 (0.62-2.19)
Tobacco consumption				
No	1029 (60.67)	627 (39.33)	Reference	-
Yes	57 (63.97)	29 (36.03)	0.87 (0.48-1.57)	
Alcohol usage				
No	1075 (60.87)	649 (39.13)	Reference	-
Yes	11 (45.38)	7 (54.62)	1.87 (0.46-7.56)	
BMI				
Normal	506 (59.10)	311 (40.90)	Reference	-
Thin	71 (60.64)	46 (39.36)	0.94 (0.55-1.59)	
Overweight/obese	56 (59.81)	33 (40.19)	0.97 (0.54-1.74)	
Health seeking behaviour in past 3 months				
None	484 (63.34)	255 (36.66)	Reference	Reference
Public facility	97 (48.34)	87 (51.66)	1.85 (1.20-2.83)[a]	1.76 (1.14-2.71)[a]
Private facility	44 (47.45)	44 (52.55)	1.91 (1.11-3.30)[a]	1.99 (1.14-3.47)[a]
Other	2 (100)	0 (0)	-	-

Data are *n* (weighted %) unless otherwise indicated.
[a]$P < 0.05$.

BMI: Body mass index; CI: Confidence interval; DM: Diabetes mellitus; OR: Odds ratio. OR > 1 shows higher odds of not being on treatment for DM.

Table 4 Distribution of factors associated with overweight and/or obesity among older adolescents

Variables	Normal/thin, *n* = 125725	Overweight/obesity, *n* = 8621	Unadjusted RR (95%CI)	Adjusted RR (95%CI)
Age in years, mean (SD)	16.99 (1.40)	17.03 (1.42)	1.02 (1.001-1.04)[a]	1.01 (0.99-1.03)
Sex				
Male	14666 (92.11)	1211 (7.89)	1.17 (1.06-1.29)[a]	1.10 (1.01-1.20)[a]
Female	111059 (93.25)	7410 (6.75)	Reference	Reference
Respondents' education				
No education	5068 (96.24)	213 (3.76)	Reference	Reference
Primary education	7092 (95.48)	343 (4.52)	1.20 (0.97-1.50)	1.08 (0.86-1.35)
Secondary education	106285 (92.96)	7397 (7.04)	1.87 (1.57-2.24)[b]	1.28 (1.06-1.54)[a]
Higher education	7266 (91.25)	667 (8.75)	2.33 (1.91-2.85)[b]	1.26 (1.02-1.56)[a]
Religion				
Hindu	93663 (93.5)	6088 (6.5)	Reference	Reference
Muslim	16969 (91.78)	1353 (8.22)	1.27 (1.15-1.40)[b]	1.21 (1.10-1.34)[b]
Others	13385 (90.81)	1086 (9.19)	1.41 (1.25-1.60)[b]	1.18 (1.04-1.33)[a]
Residence				
Urban	26192 (89.28)	3028 (10.72)	1.97 (1.84-2.12)[b]	1.28 (1.18-1.38)[b]
Rural	99533 (94.57)	5593 (5.43)	Reference	Reference
Wealth index				
Poorest	31167 (96.82)	1013 (3.18)	Reference	Reference
Poorer	31730 (95.26)	1615 (4.74)	1.49 (1.33-1.67)[b]	1.45 (1.29-1.63)[b]
Middle	26511 (93.11)	1911 (6.89)	2.17 (1.93-2.43)[b]	2.00 (1.77-2.25)[b]
Richer	21175 (90.65)	2001 (9.35)	2.94 (2.63-3.29)[b]	2.49 (2.22-2.80)[b]
Richest	15142 (87.17)	2081 (12.83)	4.04 (3.61-4.51)[b]	3.24 (2.86-3.67)[b]
Tobacco consumption				
No	122540 (93.08)	8446 (6.92)	Reference	Reference
Yes	3108 (95.33)	168 (4.67)	0.67 (0.53-0.86)[a]	0.96 (0.74-1.25)
Alcohol usage				
No	124667 (93.1)	8563 (6.9)	Reference	Reference
Yes	992 (95.62)	52 (4.38)	0.64 (0.42-0.96)[a]	0.78 (0.50-1.21)
Incident DM				
No	124060 (93.21)	8430 (6.79)	Reference	Reference
Yes	331 (81.82)	57 (18.18)	2.68 (1.97-3.62)[b]	2.43 (1.82-3.24)[b]

Data are *n* (weighted %) unless otherwise indicated.
[a]$P < 0.05$.
[b]$P < 0.001$.
BMI: Body mass index; CI: Confidence interval; DM: Diabetes mellitus; RR: Rate ratio.

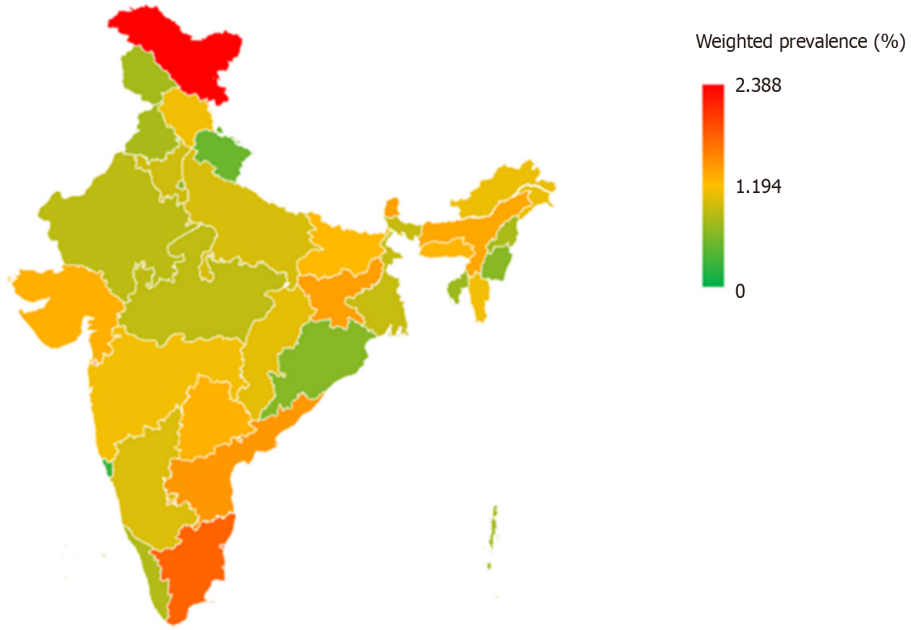

Figure 1 Heat map showing the prevalence of diabetes among adolescents across various states and union territories of India.

higher than estimates from the comprehensive national nutrition survey (2016-2018)[24]. We also observed male sex to be significantly associated with a higher risk of overweight/obesity compared to females, a finding consistent with previous studies conducted elsewhere[17,25,26]. Adolescents living in urban areas also had significantly higher odds of overweight and obesity suggestive of the effect of the urban environment characterized by increased accessibility to processed and unhealthy food options, coupled with sedentary lifestyles[27,28]. The strong association between DM and overweight/obesity underscores the potential deleterious long-term health consequences associated with adolescent obesity with emphasis on the need for early initiation of public health interventions to mitigate this risk.

Ensuring universal access to healthcare services in low-resource settings regardless of socioeconomic status or geographic location, is crucial in managing and mitigating the burden of DM in younger populations who are conventionally not screened for elevated blood sugar. We observed significant regional variations in the prevalence of DM across Indian states and territories suggestive of differential access and availability of healthcare services, variable efficiency of public health systems, and cultural and lifestyle factors heterogeneity contributing to the burden of obesity and hyperglycaemia in Indian adolescent populations. Consequently, tailored interventions that consider these regional differences will be instrumental in addressing this public health problem.

The strengths of the study include the large sample size and national representativeness with estimation of outcomes using standardized procedures by trained field personnel. However, the study also has certain limitations. Firstly, the cross-sectional nature of the NFHS-5 data restricts our ability to establish causality due to lack of temporal association. Longitudinal studies would enable investigating the causal pathways and confirming the directionality of these associations. Secondly, the reliance on self-reported data for certain variables, such as DM diagnosis and treatment, may introduce recall bias. Third, diagnosis of DM was based mostly on random blood sugar levels instead of glycated haemoglobin and fasting blood glucose levels, thereby reducing the sensitivity resulting in underestimation of the DM case burden. Third, the clinical relevance of the study is diminished by the small effect sizes and the inability to differentiate between type of DM, especially T1DM and T2DM cases which are distinct conditions with divergent risk factor profile and management strategies.

Based on the study's findings, we recommend primary care physicians including paediatricians in outpatient settings should necessarily screen older adolescents with family history or those who are overweight or obese for DM using either the fasting blood glucose test or the glycated haemoglobin method. Furthermore, they should advise older adolescents to engage in regular physical activity and exercise to maintain normal body weight even in the absence of hyperglycaemia. Finally, medication adherence in older adolescents with DM should be assessed during each appointment with appropriate counselling to achieve optimal adherence.

CONCLUSION

Nearly one in hundred older adolescents in India have DM, with significantly elevated risk of the disease in overweight and obese individuals. One in three adolescents with DM remain undiagnosed, while four in 10 adolescents with previously diagnosed DM are currently not on anti-diabetes treatment. Individuals from higher wealth quintile and those from urban areas have significantly elevated risk of obesity and DM. Tailored strategies for strengthening screening, confirmation of diagnosis, and adherence to anti-diabetes therapy of adolescents with DM warrant early incorporations in

India's national health programmes.

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REFERENCES

1 **WHO**. Obesity and overweight. [cited September 23 2024]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2 **Gurnani M**, Birken C, Hamilton J. Childhood Obesity: Causes, Consequences, and Management. *Pediatr Clin North Am* 2015; **62**: 821-840 [PMID: 26210619 DOI: 10.1016/j.pcl.2015.04.001]
3 **Sahoo K**, Sahoo B, Choudhury AK, Sofi NY, Kumar R, Bhadoria AS. Childhood obesity: causes and consequences. *J Family Med Prim Care* 2015; **4**: 187-192 [PMID: 25949965 DOI: 10.4103/2249-4863.154628]
4 **He QX**, Zhao L, Tong JS, Liang XY, Li RN, Zhang P, Liang XH. The impact of obesity epidemic on type 2 diabetes in children and adolescents: A systematic review and meta-analysis. *Prim Care Diabetes* 2022; **16**: 736-744 [PMID: 36184528 DOI: 10.1016/j.pcd.2022.09.006]
5 **Simmonds M**, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev* 2016; **17**: 95-107 [PMID: 26696565 DOI: 10.1111/obr.12334]
6 **UNICEF**. Adolescent development and participation. [cited September 23 2024]. Available from: https://www.unicef.org/india/what-we-do/adolescent-development-participation
7 **Pradeepa R**, Mohan V. Epidemiology of type 2 diabetes in India. *Indian J Ophthalmol* 2021; **69**: 2932-2938 [PMID: 34708726 DOI: 10.4103/ijo.IJO_1627_21]
8 **Hu FB**. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care* 2011; **34**: 1249-1257 [PMID: 21617109 DOI: 10.2337/dc11-0442]
9 **Weisman A**, Fazli GS, Johns A, Booth GL. Evolving Trends in the Epidemiology, Risk Factors, and Prevention of Type 2 Diabetes: A Review. *Can J Cardiol* 2018; **34**: 552-564 [PMID: 29731019 DOI: 10.1016/j.cjca.2018.03.002]
10 **Ali O**. Genetics of type 2 diabetes. *World J Diabetes* 2013; **4**: 114-123 [PMID: 23961321 DOI: 10.4239/wjd.v4.i4.114]
11 **Atre S**, Deshmukh S, Kulkarni M. Prevalence of type 2 diabetes mellitus (T2DM) in India: A systematic review (1994-2018). *Diabetes Metab Syndr* 2020; **14**: 897-906 [PMID: 32570014 DOI: 10.1016/j.dsx.2020.05.040]
12 **Ranjani H**, Mehreen TS, Pradeepa R, Anjana RM, Garg R, Anand K, Mohan V. Epidemiology of childhood overweight & obesity in India: A systematic review. *Indian J Med Res* 2016; **143**: 160-174 [PMID: 27121514 DOI: 10.4103/0971-5916.180203]
13 **International Institute for Population Sciences**. National Family Health Survey (NFHS-5) INDIA Report. [cited September 23 2024].

Available from: https://iipsindia.ac.in/content/national-family-health-survey-nfhs-5-india-report

14 **de Onis M**, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007; **85**: 660-667 [PMID: 18026621 DOI: 10.2471/blt.07.043497]

15 **Zou G**. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159**: 702-706 [PMID: 15033648 DOI: 10.1093/aje/kwh090]

16 **Kumar P**, Srivastava S, Mishra PS, Mooss ETK. Prevalence of pre-diabetes/type 2 diabetes among adolescents (10-19 years) and its association with different measures of overweight/obesity in India: a gendered perspective. *BMC Endocr Disord* 2021; **21**: 146 [PMID: 34233661 DOI: 10.1186/s12902-021-00802-w]

17 **Seema S**, Rohilla KK, Kalyani VC, Babbar P. Prevalence and contributing factors for adolescent obesity in present era: Cross-sectional Study. *J Family Med Prim Care* 2021; **10**: 1890-1894 [PMID: 34195121 DOI: 10.4103/jfmpc.jfmpc_1524_20]

18 **Praveen PA**, Tandon N. Childhood obesity and type 2 diabetes in India. *WHO South East Asia J Public Health* 2016; **5**: 17-21 [PMID: 28604392 DOI: 10.4103/2224-3151.206547]

19 **Cade WT**. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther* 2008; **88**: 1322-1335 [PMID: 18801863 DOI: 10.2522/ptj.20080008]

20 **Chawla A**, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab* 2016; **20**: 546-551 [PMID: 27366724 DOI: 10.4103/2230-8210.183480]

21 **GBD 2021 Diabetes Collaborators**. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2023; **402**: 203-234 [PMID: 37356446 DOI: 10.1016/S0140-6736(23)01301-6]

22 **Government of India Press Information Bureau**. Update on treatment of Diabetes. [cited September 23 2024]. Available from: https://pib.gov.in/pib.gov.in/Pressreleaseshare.aspx?PRID=1944600

23 **Owen N**, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging evidence for a new health risk. *Mayo Clin Proc* 2010; **85**: 1138-1141 [PMID: 21123641 DOI: 10.4065/mcp.2010.0444]

24 **Pandurangi R**, Mummadi MK, Challa S, Reddy NS, Kaliaperumal V, Khadar Babu C, Telikicherla UR, Pullakandham R, Geddam JJB, Hemalatha R. Burden and Predictors of Malnutrition Among Indian Adolescents (10-19 Years): Insights From Comprehensive National Nutrition Survey Data. *Front Public Health* 2022; **10**: 877073 [PMID: 35784251 DOI: 10.3389/fpubh.2022.877073]

25 **Shah B**, Tombeau Cost K, Fuller A, Birken CS, Anderson LN. Sex and gender differences in childhood obesity: contributing to the research agenda. *BMJ Nutr Prev Health* 2020; **3**: 387-390 [PMID: 33521549 DOI: 10.1136/bmjnph-2020-000074]

26 **Al-Haifi AR**, Al-Awadhi BA, Al-Dashti YA, Aljazzaf BH, Allafi AR, Al-Mannai MA, Al-Hazzaa HM. Prevalence of overweight and obesity among Kuwaiti adolescents and the perception of body weight by parents or friends. *PLoS One* 2022; **17**: e0262101 [PMID: 34982787 DOI: 10.1371/journal.pone.0262101]

27 **Bren d'Amour C**, Pandey B, Reba M, Ahmad S, Creutzig F, Seto K. Urbanization, processed foods, and eating out in India. *Global Food Security* 2020; **25**: 100361 [DOI: 10.1016/j.gfs.2020.100361]

28 **Squillacioti G**, De Petris S, Bellisario V, Borgogno Mondino EC, Bono R. Urban environment and green spaces as factors influencing sedentary behaviour in school-aged children. *Urban For Urban Green* 2023; **88**: 128081 [DOI: 10.1016/j.ufug.2023.128081]

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ORIGINAL ARTICLE

Observational Study

Visceral adiposity index, cardiorespiratory fitness, and fasting plasma glucose associations in adolescents

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Abstract

BACKGROUND

The global rise in the prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents is partly linked to the increasing rates of childhood obesity and physical inactivity.

AIM

To explore the independent relationships of visceral adiposity index (VAI) and cardiorespiratory fitness (CRF) with fasting plasma glucose (FPG) in adolescents.

METHODS

This descriptive cross-sectional study included 403 adolescents (202 boys and 201 girls) aged 11-19 years. Participants were evaluated for VAI, CRF, and FPG. Regression models, adjusted for age and maturity status, were used to assess the associations between VAI, CRF, and FPG.

RESULTS
The prevalence of T2DM risk was 15.3% (girls = 7.4%; boys = 7.9%). In boys, high VAI was positively associated with FPG (β = 0.190, P = 0.009), while low CRF was negatively associated with FPG (β = -0.206, P = 0.010). These associations persisted even after adjusting for CRF and VAI. However, no significant associations between VAI, CRF, and FPG were observed in girls (P > 0.05). Adolescents with high VAI and low fitness levels demonstrated poorer glycemic profiles.

CONCLUSION
Among boys, both VAI and CRF were independently associated with T2DM risk, with CRF showing a stronger association. These associations were not observed in girls. Promoting regular aerobic exercise and healthy diets may serve as essential public health promotion strategies in preventing and managing T2DM risk in adolescents.

Key Words: Adolescents; Abdominal adiposity; Fitness; Metabolic health; Primary prevention

Core Tip: The recent global rise in the prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents has been linked partly with the universal increase in childhood obesity and physical inactivity. There is paucity of information on the association of visceral adiposity index and cardiorespiratory fitness with risk of T2DM in Nigerian adolescents. This study unveiled the independent and joint associations of visceral adiposity index and cardiorespiratory fitness with the risk of T2DM in boys but not girls. It was recommended that health-promoting strategies that focus on favorable blood glucose levels, including healthy eating and aerobic-type activities should be encouraged among adolescents.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by elevated blood glucose levels, which is associated with significant complications and comorbidities, such as metabolic syndrome, cardiovascular disease, end-stage kidney disease, retinopathy, and limb amputation[1]. Globally, diabetes mellitus ranks as the 9th leading cause of death, with reports indicating that one in 11 adults worldwide is diagnosed with diabetes, with approximately 90% of these cases being T2DM[2]. In recent years, the prevalence of T2DM has surged among children and adolescents[3]. Traditionally regarded as a disease of adults, T2DM is increasingly recognized as a pediatric health issue, a trend that parallels the rise in childhood obesity and physical inactivity worldwide[4,5]. Screening and developing targeted interventions for high-risk adolescents should be prioritized as a crucial public health goal. Behavioral modifications, particularly those that promote increased physical activity and healthier eating habits, are essential strategies for combating this growing problem.

Impaired fasting plasma glucose (FPG) is an established biomarker for T2DM. Along with insulin resistance and impaired glucose tolerance, it is closely linked to obesity, particularly android obesity, in adolescents[6]. Waist circumference (WC) is commonly used to estimate visceral adipose tissue (VAT) in cardiometabolic disease (CMD) risk assessments; however, its limitation lies in the inability to differentiate subcutaneous from visceral fat. Recently, the visceral adiposity index (VAI), a novel sex-specific mathematical model based on anthropometric measures [body mass index (BMI) and WC] and blood lipid parameters [triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)], has been linked to VAT, adipokine levels, insulin resistance, and glucose disturbances in adults[7,8], and it was developed to estimate VAT dysfunction[9]. This method is gaining traction in public health research and clinical practice, with multiple studies identifying VAI as a predictor of CMD, including T2DM[2,10].

While several studies in the Caucasian population have demonstrated the detrimental health effects of VAI on T2DM risk in both adults[10,11] and youth[12,13], no study has explored the relationship between VAI and diabetes risk in African youth. Cardiorespiratory fitness (CRF), an objective measure of habitual physical activity, is considered a risk factor for T2DM and insulin resistance[11] and has been shown to positively impact CMD risk[14,15]. Recent reviews have also highlighted the efficacy of physical activity and CRF in managing T2DM in the general population[16]. However, it remains unclear whether the relationships among VAI, CRF, and diabetes risk in adolescents are independent or confounded by other factors. Furthermore, to our knowledge, no study has yet examined the combined association of VAI and CRF with diabetes risk in adolescents.

Adolescence is a critical developmental stage, often marked by unhealthy behavioral shifts such as increased social media use, smoking, drug and alcohol abuse, and other risky behaviors, which, if unchecked, can lead to pediatric non-communicable lifestyle diseases[17]. Both pediatric obesity and low physical fitness significantly increase the risk of CMD

in youth[14,18], with many of these risks persisting into adulthood[19].

This study aimed to investigate the association of VAI and CRF with FPG in Nigerian adolescents aged 11 years to 19 years. Specifically, the study examined the independent relationships of VAI and CRF with FPG among participants. The study identified the cardiometabolic risk factors most strongly associated with FPG. Additionally, the T2DM risk profiles of the participants were characterized. It was hypothesized that adolescents with high VAI and low CRF would be at greater risk of T2DM. This information could be crucial for developing effective primary prevention strategies.

MATERIALS AND METHODS

Study design and sample

This study utilized a descriptive observational cross-sectional design involving apparently healthy school boys and girls aged 11-19 years from secondary schools in Kogi East, North Central Nigeria. A total of 418 adolescents were selected using a multistage cluster and random sampling method across four secondary schools in the study area, applying the adjusted Taro Yamane sample size determination formula with 5% error rate[20].

$n = N/1 + (N \times e^2)$: $n = 125910/1 + (125910 \times 0.05^2) = 398.73$

Where: n = sample size; N = population; e = margin of error

In 2019, the population of secondary school students in Kogi East Senatorial District was 125910 (National Bureau of Statistics, 2022). The minimum sample size determined was 399 participants; however, the sample was increased to 418 to account for participant dropout and ensure representativeness. Detailed descriptions of the sampling procedure, inclusion criteria, study setting, and pilot tests have been previously published[14]. The purpose and test procedures were explained to participants after obtaining permission from the school heads. Data collection involved two visits: The first to familiarize participants with the test protocols and measure physical characteristics, and the second for clinical and biochemical measurements.

Data collection

Anthropometric characteristics were assessed using standardized methods[21]. The procedures for measuring physical characteristics, including stature, body mass, percent body fat, WC, BMI, and classifying participants into healthy weight and overweight categories based on the updated FitnessGram data[22], have been previously detailed[14]. Sexual maturity [maturity offset (MO)] was estimated using chronological age and stature based on the prediction equation by Moore *et al*[23]. Age-at-peak-height-velocity was estimated as the difference between MO and age.

CRF was assessed using the 20-meter shuttle run test (20-MST), a multistage-progressive aerobic capacity test used globally in schools to evaluate CRF in children and adolescents. Participants ran back and forth between two lines set 20 meters apart, following an audio signal from a pre-recorded compact disc. The initial running speed was 8.5 km/hour, increasing by 0.5 km/hour every minute (level). The test is considered an accurate predictor of peak oxygen uptake in children and adolescents[24]. Participants who failed to complete two successive shuttles were withdrawn from the test. The number of completed laps or shuttles was used to estimate CRF[25]. Procedures for administering the test and classifying participants as high or low fitness have been documented[22].

Resting systolic blood pressure (SBP) and diastolic blood pressure were measured using an automated device (HEM-705 CP; Omron, Tokyo, Japan) after participants had rested for 10 minutes. Details of the protocol have been published elsewhere[14]. Hypertension was determined based on standard benchmarks[26].

FPG, HDL-C, and TG were collected after a 12-hour overnight fast between 9: 00 and 11: 00 a.m. using a Cardio-Check Plus Analyzer (CCPA) (PTS Diagnostics, Indianapolis, IN, United States). The tests were administered by two certified nurses and a laboratory technologist. Participants rested for 10 minutes before taking the tests. Test administration procedure details have been previously described[14]. The CCPA is a validated and reliable instrument for analyzing blood glucose and lipids[27].

VAI was calculated using the gender-specific equations provided by Amato and Giordano[7]:

$$\text{VAI (Girls)}: \left(\frac{\text{WC}}{39.58 + (1.89 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{0.81}\right) \times \left(\frac{1.52}{\text{HDL-C}}\right)$$

$$\text{VAI (Boys)}: \left(\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{1.03}\right) \times \left(\frac{1.31}{\text{HDL-C}}\right)$$

In these formulas, WC is in centimeters, BMI in kg/m², and HDL-C and TG in mmol/L.

VAI has been used in earlier studies in both adults[8,10] and youths[12,13].

T2DM and cardiometabolic risk abnormalities were assessed using the International Diabetes Federation (IDF) standards[28]: FPG (≥ 5.6 mmol/L), TG (≥ 1.7 mmol/L), and HDL-C (≤ 1.04 mmol/L). Participants were classified as "healthy FPG" or "unhealthy FPG" based on their FPG levels. Since there is no established VAI threshold for the pediatric population, the minimum value of the highest tertile (1.1 for boys, 1.35 for girls) was used as the cut-off, following accepted methods[7,29].

A clustered metabolic risk score (MRS) was calculated by adding the z-scores of individual risk factors, including FPG, SBP, WC, HDL-C (inverted), and TG. A lower MRS indicated a more favorable metabolic risk profile[30].

Statistical analysis

Continuous variables were reported as means and standard deviations, while categorical variables were expressed as frequencies and percentages. The Kolmogorov-Smirnov test assessed the normality of variable distributions. Due to

participant dropout and incomplete data, complete datasets for all variables were available for 403 out of the 418 participants, resulting in a compliance rate of 96%. Gender differences were evaluated using independent samples *t*-tests or Mann-Whitney *U* tests as appropriate. Partial correlation analysis, adjusted for age and MO, examined the relationships between dependent and independent variables. The associations of VAI and CRF with FPG and their relative importance were explored using multivariate regression models, also adjusted for age and sexual maturation. Statistical analysis was conducted using IBM SPSS (Version 20, IBM Corporation, Armonk, NY, United States), with significance set at $P \leq 0.05$.

Ethical clearance

Ethical approval was obtained from the Ethical Review Committee of the College of Health Sciences, Kogi State University, Nigeria (No. COHS/02/25/2020). Written informed consent was obtained from parents/guardians, and participants provided assent before data collection. All test administration procedures complied with the ethical standards of the Helsinki Declaration. Data collection occurred between 9: 00 a.m. and 12: 00 p.m.

RESULTS

Table 1 outlines the demographic, anthropometric, performance, and biochemical characteristics of the participants, categorized by glycemic profile and fitness. The average prevalence of FPG abnormalities, indicating risk of T2DM, was 15.3% (girls = 7.4%; boys = 7.9%). When the high-risk or unhealthy category was further stratified by fitness status, T2DM risk prevalence was found to be 27.4% in the high fitness group and 72.6% in the low fitness group (Figure 1). Adolescents with healthy or normal FPG were significantly younger ($P < 0.001$), had lower WC ($P < 0.001$), and better run performance ($P = 0.001$) than those at risk of T2DM. Similarly, participants with higher fitness levels had more favorable health profiles across other indices compared to their low fitness peers, regardless of glycemic status.

Table 2 presents the characteristics of participants, stratified by glycemic profile and VAI. When stratified by VAI, the prevalence of T2DM risk was 71% in the elevated VAI group and 29% in the low VAI group (Figure 1). As anticipated, adolescents in the low VAI group exhibited healthier profiles than those in the high VAI group, irrespective of glycemic status. Overall, these findings suggest that participants with elevated VAI and low CRF exhibited significantly poorer glycemic profiles and other cardiometabolic health markers, particularly in boys.

The results of the partial correlations (after controlling for age and sexual maturity) between the dependent variable (FPG) and independent variables (CRF, VAI, BMI, WC, HDL-C, TG, and MRS) showed generally non-significant associations ($P > 0.05$), except for a significant correlation between MRS and FPG ($P < 0.001$) in girls. In boys, weak to moderate but mostly significant correlations were observed between FPG and CRF ($P = 0.010$), VAI ($P = 0.009$), WC ($P < 0.001$), TG ($P = 0.011$), and MRS ($P < 0.001$). The strongest independent predictor of FPG was MRS in both sexes. Detailed results are provided in Table 3.

Regression analysis revealed that in girls, neither VAI ($P = 0.679$) nor CRF ($P = 0.704$) were significantly associated with FPG. However, in boys, VAI was positively associated with FPG ($\beta = 0.190$, $P = 0.009$). This association remained significant albeit weaker ($\beta = 0.165$, $P = 0.023$) after adjusting for CRF. The full model accounted for 16.5% of the variation in FPG, with age and MO contributing 13.7%. VAI explained only 2.8% of the variation in FPG. A unit increase of VAI resulted in a mean increase of 1.0 mmol/L in FPG. CRF was negatively associated with FPG ($\beta = -0.206$, $P = 0.010$) and remained significant after adjusting for VAI, though the relationship attenuated ($\beta = -0.178$, $P = 0.025$). CRF explained 2.9% of the variance in FPG, while the confounders explained 13.6%. Each unit (lap) increase in CRF was associated with an average decrease of 1.1 mmol/L in FPG. Overall, CRF had greater explanatory power than VAI. These results are detailed in Table 4.

DISCUSSION

VAI and CRF were scrutinized alongside FPG, a key metabolic health indicator. The findings suggest that the risk of T2DM is prevalent among participants, with a higher incidence in boys than girls. The prevalence of impaired FPG (15.3%: Girls = 7.4%, boys = 7.9%) is comparable to the 14.5% (girls = 7.4%; boys = 7.1%) reported among Ivorian adolescents[31], though lower than the 18.4% (girls = 5.4%; boys = 13.0%) reported for American adolescents[32] and the rates (girls = 8.4%; boys = 12.3%) documented in Indian adolescents[33]. These results indicate a higher T2DM risk among boys compared to girls.

A modest correlation between independent variables and FPG was observed after controlling for age and sexual maturity, with the MRS showing the strongest association in both sexes. This is consistent with the understanding that metabolic syndrome is a key marker of T2DM risk in the general population[1,4]. Both VAI and CRF were significantly associated with FPG in boys but not girls, aligning with earlier studies in adolescents[12,34]. These findings suggest that VAI and CRF are important determinants of T2DM risk in boys.

VAI and CRF were independently associated with FPG in boys, with fitness having a stronger impact. This result highlights the significant impact of both independent variables on glucose metabolism in boys even during adolescence. Together, VAI and CRF explained only 3% of FPG variation, while age and sexual maturity explained 13.5%. The implication of the significant joint association of VAI and CRF is that adolescents with both elevated VAI and low fitness tended to exhibit highest FPG levels, suggesting a synergistic effect where the negative impact of high VAT is exacerbated

Table 1 General characteristics of participants stratified by type 2 diabetes risk versus cardiorespiratory fitness status (*n* = 403)

Variable	Healthy FPG (*n* = 341)			Unhealthy FPG (*n* = 62)		
	Low fit (*n* = 153)	High fit (*n* = 188)	Total (*n* = 341)	Low fit (*n* = 45)	High fit (*n* = 17)	Total (*n* = 62)
Girls	74 (21.7)	97 (28.4)	171 (50.1)	22 (35.5)	8 (12.9)	30 (48.4)
Boys	79 (23.2)	91 (26.6)	170 (49.9)	23 (37.1)	9 (14.5)	32 (51.6)
Age (year)	15.7 ± 1.9	13.8 ± 2.1	14.5 ± 2.2	15.3 ± 2.2	14.6 ± 2.4	15.5 ± 2.3
Body mass (kg)	56.0 ± 12.6	51.9 ± 11.3	53.4 ± 12.0	46.7 ± 15.1	51.5 ± 11.6	52.0 ± 14.0
Stature (cm)	160.4 ± 9.5	161.6 ± 9.1	160.7 ± 9.3	152.8 ± 10.7	158.5 ± 11.9	158.7 ± 11.2
BMI (kg/m^2)	21.7 ± 3.5	19.7 ± 3.4	20.6 ± 3.5	20.3 ± 3.9	20.2 ± 2.3	20.3 ± 3.5
Fat (%)	16.6 ± 7.9	14.7 ± 5.6	15.6 ± 6.7	16.0 ± 8.7	14.1 ± 5.8	15.1 ± 8.2
WC (cm)	71.5 ± 8.8	60.6 ± 5.2	64.9 ± 8.7	67.6 ± 8.4	64.9 ± 7.4	69.2 ± 8.3
HDL-C (mmol)	1.3 ± 0.3	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	1.1 ± 0.4	1.2 ± 0.4
TG (mmol)	1.2 ± 0.7	0.9 ± 0.6	1.0 ± 1.0	1.1 ± 0.4	0.9 ± 0.4	1.0 ± 0.4
FPG (mmol)	5.0 ± 0.4	4.7 ± 0.5	4.8 ± 0.5	6.2 ± 0.5	5.9 ± 0.8	6.1 ± 0.6
VAI	1.5 ± 0.5	1.0 ± 0.2	1.2 ± 2.2	1.4 ± 0.9	1.0 ± 0.5	1.3 ± 0.9
20-MST (lap)	20.8 ± 9.1	43.8 ± 13.6	33.6 ± 16.8	17.2 ± 7.0	50.6 ± 15.9	26.8 ± 15.0

BMI: Body mass index; WC: Waist circumference; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; FPG: Fasting plasma glucose VAI: Visceral adiposity index; 20-MST: Multistage shuttle run test.

Table 2 General characteristics of participants stratified by type 2 diabetes risk versus visceral adiposity index status (*n* = 403)

Variable	Healthy FPG (*n* = 341)			Unhealthy FPG (*n* = 62)		
	Low VAI (*n* = 157)	High VAI (*n* = 184)	Total (*n* = 341)	Low VAI (*n* = 18)	High VAI (*n* = 44)	Total (*n* = 62)
Girls	60 (18.0)	111 (32.6)	171 (50.1)	10 (16.1)	20 (32.3)	30 (48.4)
Boys	97 (28.4)	73 (21.4)	170 (49.9)	8 (12.9)	24 (38.7)	32 (51.6)
Age (year)	13.9 ± 2.2	15.3 ± 2.1	14.5 ± 2.2	14.2 ± 2.0	15.0 ± 3.0	15.5 ± 2.3
Body mass (kg)	52.5 ± 12.2	54.8 ± 11.2	53.4 ± 12.0	51.4 ± 18.1	47.0 ± 12.1	52.0 ± 14.0
Stature (cm)	160.8 ± 10.5	161.2 ± 8.2	160.7 ± 9.3	155.3 ± 13.5	154.1 ± 8.3	158.7 ± 11.2
BMI (kg/m^2)	20.1 ± 3.5	21.0 ± 3.5	20.6 ± 3.5	20.7 ± 4.4	19.4 ± 3.0	20.3 ± 3.5
Fat (%)	15.0 ± 6.6	16.0 ± 6.8	15.6 ± 6.7	17.5 ± 10.9	14.6 ± 6.4	15.1 ± 8.2
WC (cm)	61.3 ± 6.1	69.1 ± 9.2	64.9 ± 8.7	62.6 ± 7.2	68.6 ± 7.9	69.2 ± 8.3
HDL-C (mmol)	1.5 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.7 ± 0.3	1.1 ± 0.3	1.2 ± 0.4
TG (mmol)	0.7 ± 0.2	1.3 ± 0.3	1.0 ± 1.0	0.7 ± 0.4	1.2 ± 0.1	1.0 ± 0.4
FPG (mmol)	4.8 ± 0.4	4.9 ± 0.6	4.8 ± 0.5	6.1 ± 0.2	6.1 ± 0.3	6.1 ± 0.6
VAI	0.5 ± 0.1	1.8 ± 0.8	1.2 ± 2.2	0.5 ± 0.1	1.6 ± 0.9	1.3 ± 0.9
20-MST (lap)	41.0 ± 16.5	26.6 ± 13.1	33.6 ± 16.8	34.4 ± 23.1	23.0 ± 10.1	26.8 ± 16.9

BMI: Body mass index; WC: Waist circumference; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; FPG: Fasting plasma glucose VAI: Visceral adiposity index; 20-MST: Multistage shuttle run test.

by poor fitness. Conversely, low VAI combined with high CRF is associated with the lowest FPG levels, highlighting the protective effect of good fitness levels against the adverse effects of VAT. This result is supported by previous research among Iranian and Saudi Arabian adolescents[12,13] but contrasts with that of Raheem and Co-workers[35]. Regarding CRF, our findings are supported by several studies in adolescents[36,37] but at variance with results from other studies [38,39]. Inconsistencies in results might be potentially due to disparity in measurement procedures, ethnicity, and age across studies. The small effect size of VAI and CRF suggests that these factors may not be major predictors of FPG in this cohort, with age and sexual maturity playing a larger role. Obesity, dyslipidemia and ethnicity are among other

Table 3 Partial correlation coefficients assessing the relationship among visceral adiposity index, cardiorespiratory fitness and fasting plasma glucose and other health indices after controlling for age and maturity status (*n* = 403)

Gender	VAI	CRF	BMI	WC	HDL-C	TG	MRS
Girls	0.031	-0.030	0.011	0.047	0.032	0.008	0.316[b]
Boys	0.185[a]	-0.183[a]	0.028	0.341[b]	-0.065	0.180[a]	0.640[b]

[a]$P < 0.05$.
[b]$P < 0.01$. VAI: Visceral adiposity index; CRF: Cardiorespiratory fitness; BMI: Body mass index; WC: Waist circumference; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; MRS: Metabolic risk score.

Table 4 Standardized regression coefficients evaluating the relationship among visceral adiposity index, cardiorespiratory fitness and fasting plasma glucose after controlling for age and maturity status (*n* = 403)

Variable	Girls (*n* = 201)				Boys (*n* = 202)			
	Crude	*P* value	Adjusted	*P* value	Crude	*P* value	Adjusted	*P* value
VAI	0.031	0.655	0.029	0.679	0.190	0.009	0.165	0.023
CRF	-0.032	0.679	-.029	0.704	-0.206	0.010	-0.178	0.025

VAI: Visceral adiposity index; CRF: Cardiorespiratory fitness.

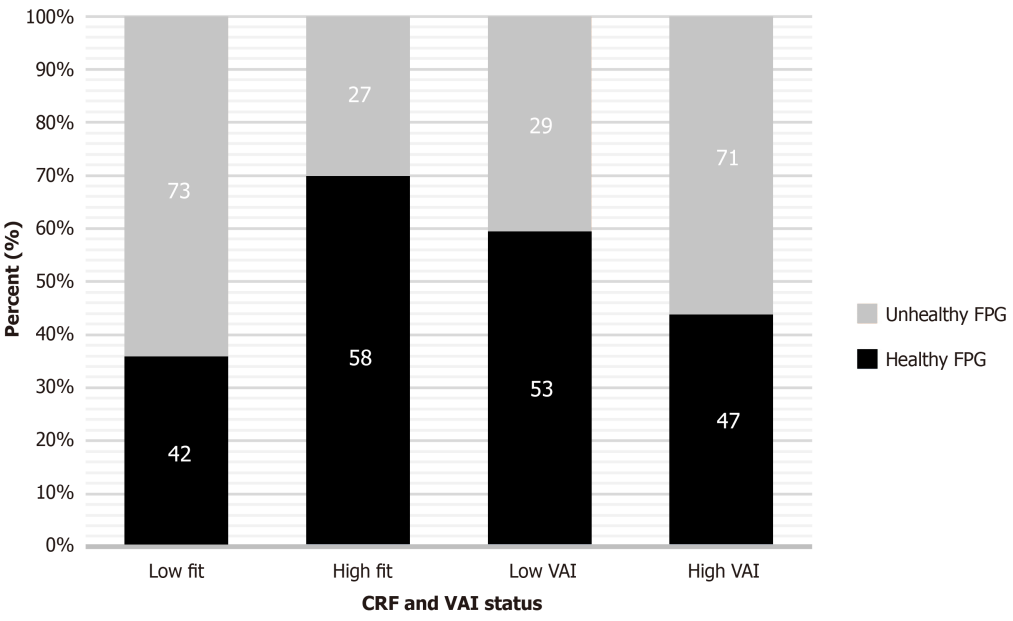

Figure 1 Glycemic profile of participants stratified by cardiorespiratory fitness and visceral adiposity index. FPG: Fasting plasma glucose; VAI: Visceral adiposity index; CRF: Cardiorespiratory fitness.

predictors of diabetes, not considered in this study[1,2]. However, longitudinal studies may better clarify the role of VAI and CRF in the development of T2DM in the pediatric population.

This study highlights that low VAI and high fitness levels are associated with better cardiometabolic health in adolescents, especially boys. Boys generally exhibited poorer glycemic profiles than girls, regardless of fitness or VAI levels (Table 1 and Table 2). VAI has been shown to be a strong correlate and independent predictor of FPG in boys[13] and in both sexes[12]. VAI serves as a surrogate for VAT, a metabolically active entity capable of secreting inflammatory cytokines and adipokines which promotes insulin resistance, dyslipidemia, impaired beta cell function and risk of diabetes[9,18]. Our findings regarding CRF are in conformity with previous studies in both youth and adults[15,39]. Regular physical activity or CRF, a well-known predictor of cardiovascular events, also plays a crucial role in insulin sensitivity, glucose metabolism, and overall metabolic health[40,41]. Prospective studies have shown that increased CRF is associated with a reduced risk of T2DM and cardiovascular disease[42]. Potential reasons for the lack of significant impact of the independent variables on risk of T2DM among girls in this study may be attributed to sexual dimorphism of fat distribution during adolescence. Boys generally accumulate more visceral fat, while girls tend to store more

subcutaneous fat[43]. Additionally, the female hormone estrogen plays a role in reducing VAT accumulation and lowering insulin resistance in girls[13]. In this study, a larger proportion of girls demonstrated higher levels of CRF (Table 1), which is linked to improved metabolic health and better glucose regulation[15]. These factors help explain why the relationship between VAI, CRF, and FPG is more pronounced in boys.

Considering the cardiometabolic benefits of fitness, promoting aerobic physical activity in children and adolescents is vital. It is essential for stakeholders in adolescent health to utilize the current physical activity guidelines for youth to encourage regular participation in activities that enhance aerobic fitness[44]. The relationship between VAI, CRF, and the risk of T2DM may be influenced by unhealthy diets and sedentary lifestyles[11]. Addressing these lifestyle factors is critical to reducing the risk of T2DM in adolescents. Health promotion initiatives should therefore focus on encouraging both healthy eating habits and regular physical activity to mitigate T2DM risk.

Public health interventions should be gender-specific. Both school- and community-based health education programs in Nigeria must be tailored to address the distinct needs of boys and girls. For girls, programs should emphasize healthy lifestyle habits, such as maintaining a balanced diet and engaging in regular physical activity, without focusing on VAT. In contrast, boys' programs should additionally highlight activities that reduce the risk of VAT, such as aerobic exercises, both continuous and interval-based. Moreover, public health policies should include provisions for routine health screenings to detect metabolic risk factors, with particular attention to glucose levels among students. This approach aims to identify adolescents at risk, enabling early interventions to prevent the onset of T2DM and other metabolic disorders.

The findings of this study should be interpreted with certain limitations in mind. First, the cross-sectional design limits the ability to establish causality. Second, the study focused solely on school-going adolescents, excluding those without formal education. This sampling bias restricts the generalizability of the results to all adolescents in the study area. Third, CRF was estimated using a field method, which may be less precise than laboratory-based measurements of maximal oxygen consumption. Similarly, VAI is an indirect estimate of VAT, which may be less accurate than laboratory techniques such as magnetic resonance imaging or computed tomography. Despite these limitations, the study has several strengths. The direct measurement of participants provided more accurate data than relying on self-reported measures. Additionally, the use of the VAI as a surrogate for VAT offered a more detailed assessment compared to WC alone. Lastly, employing health-related CRF cut-points revealed that participants meeting health standards had a better glycemic profile.

CONCLUSION

The risk of T2DM exists among Nigerian adolescents, with both VAI and CRF independently associated with T2DM risk in boys. The combined contribution of VAI and CRF is small, but age and maturity status are stronger predictors of T2DM risk. Health-promoting strategies that focus on healthy glucose levels through diet and physical activity are crucial. Future longitudinal studies will provide deeper insights into the roles of VAI and CRF, and establish their predictive value in managing T2DM risk in adolescents.

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FOOTNOTES

Author contributions: Musa DI conceived the study, analyzed the data and wrote the draft of the manuscript; Okuneye RO participated in data analysis, literature search and preparation of the manuscript; Momoh JI and Darma MH participated in data collection, literature search and proofread the manuscript; Onoja-Alexander MO and Mwangi FM participated in literature search and revised the manuscript critically for intellectual content; All authors have read and approved the final draft of the manuscript.

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REFERENCES

1 **Temneanu OR**, Trandafir LM, Purcarea MR. Type 2 diabetes mellitus in children and adolescents: a relatively new clinical problem within pediatric practice. *J Med Life* 2016; **9**: 235-239 [PMID: 27974926]
2 **Zheng Y**, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018; **14**: 88-98 [PMID: 29219149 DOI: 10.1038/nrendo.2017.151]
3 **Nadeau KJ**, Anderson BJ, Berg EG, Chiang JL, Chou H, Copeland KC, Hannon TS, Huang TT, Lynch JL, Powell J, Sellers E, Tamborlane WV, Zeitler P. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. *Diabetes Care* 2016; **39**: 1635-1642 [PMID: 27486237 DOI: 10.2337/dc16-1066]
4 **World Health Organization**. What are the risks of diabetes in children? Diabetes fact sheet 2016. [cited 15 May 2024]. Available from: https://wwww.who.int/news-room/fact-sheet/detail/diabetes
5 **Reinehr T**. Type 2 diabetes mellitus in children and adolescents. *World J Diabetes* 2013; **4**: 270-281 [PMID: 24379917 DOI: 10.4239/wjd.v4.i6.270]
6 **World Health Organization**. Screening for T2DM.Report of the WHO and IDF meeting. WHO/NMH/MNC/03.1. World Health Department of Non communicable Disease management, 2004, Geneva. [cited 15 May 2024]. Available from: https://www.who.int/mega-menu/health-topic/resources/fact-sheets
7 **Amato MC**, Giordano C. Visceral adiposity index: an indicator of adipose tissue dysfunction. *Int J Endocrinol* 2014; **2014**: 730827 [PMID: 24829577 DOI: 10.1155/2014/730827]
8 **Bozorgmanesh M**, Hadaegh F, Azizi F. Predictive performance of the visceral adiposity index for a visceral adiposity-related risk: type 2 diabetes. *Lipids Health Dis* 2011; **10**: 88 [PMID: 21619588 DOI: 10.1186/1476-511X-10-88]
9 **Amato MC**, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A; AlkaMeSy Study Group. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* 2010; **33**: 920-922 [PMID: 20067971 DOI: 10.2337/dc09-1825]
10 **Alkhalaqi A**, Al-Naimi F, Qassmi R, Shi Z, Ganji V, Salih R, Bawadi H. Visceral adiposity index is a better predictor of type 2 diabetes than body mass index in Qatari population. *Medicine (Baltimore)* 2020; **99**: e21327 [PMID: 32871862 DOI: 10.1097/MD.0000000000021327]
11 **Qin Y**, Qiao Y, Wang D, Li M, Yang Z, Li L, Yan G, Tang C. Visceral adiposity index is positively associated with fasting plasma glucose: a cross-sectional study from National Health and Nutrition Examination Survey 2017-2020. *BMC Public Health* 2023; **23**: 313 [PMID: 36774500 DOI: 10.1186/s12889-023-15231-8]
12 **Ejtahed HS**, Kelishadi R, Hasani-Ranjbar S, Angoorani P, Motlagh ME, Shafiee G, Ziaodini H, Taheri M, Qorbani M, Heshmat R. Discriminatory ability of visceral adiposity index as an indicator for modeling cardio-metabolic risk factors in pediatric population: the CASPIAN-V study. *J Cardiovasc Thorac Res* 2019; **11**: 280-286 [PMID: 31824609 DOI: 10.15171/jcvtr.2019.46]
13 **Al-Daghri NM**, Al-Attas OS, Alokail M, Alkharfy K, Wani K, Amer OE, Ul Haq S, Rahman S, Alnaami AM, Livadas S, Kollias A, Charalampidis P, Sabico S. Does visceral adiposity index signify early metabolic risk in children and adolescents?: association with insulin resistance, adipokines, and subclinical inflammation. *Pediatr Res* 2014; **75**: 459-463 [PMID: 24296798 DOI: 10.1038/pr.2013.229]
14 **Musa DI**, Toriola AL, Abubakar NO, Omachi S, Olowoleni VB, Ayodele KB. Association of adiposity and fitness with triglyceride-to-high-density lipoprotein cholesterol ratio in youth. *Ann Pediatr Cardiol* 2023; **16**: 194-200 [PMID: 37876951 DOI: 10.4103/apc.apc_1_23]
15 **Gaesser GA**. Type 2 Diabetes Incidence and Mortality: Associations with Physical Activity, Fitness, Weight Loss, and Weight Cycling. *Rev Cardiovasc Med* 2022; **23**: 364 [PMID: 39076198 DOI: 10.31083/j.rcm2311364]
16 **Musa DI**, Omachi S. Exercise as medicine in the management of type 2 diabetes mellitus: An overview. *Int J Epidemiol Public Health Res* 2021; **1**: 2021
17 **Ormerod P**, Wiltshire G. Behavioral changes. The Fifth Conference of the European Social Simulation Association Conference; 2008 Sep 1-5; Brescia, Italy. University of Brescia, 2008: 1-5
18 **Buchan DS**, Young JD, Boddy LM, Malina RM, Baker JS. Fitness and adiposity are independently associated with cardiometabolic risk in youth. *Biomed Res Int* 2013; **2013**: 261698 [PMID: 23984329 DOI: 10.1155/2013/261698]
19 **Herman KM**, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. *Int J Pediatr Obes* 2009; **4**: 281-288 [PMID: 19922043 DOI: 10.3109/17477160802596171]
20 **Adam AM**. Sample Size Determination in Survey Research. *JSRR* 2020; **26**: 90-97 [DOI: 10.9734/jsrr/2020/v26i530263]
21 **Marfell-Jones M**, Stweart AD, de Ridder JH. International standards for anthropometric assessment. International Society for the Advancement of Kinantropometry; 2012; Wellington, New Zealand. ISAK, 2012: 32-89
22 **The Cooper Institute**. FITNESSGRAM Test Administration Manual. 5th ed. Champaign, IL, United States: Human Kinetics, 2017: 39-64
23 **Moore SA**, McKay HA, Macdonald H, Nettlefold L, Baxter-Jones AD, Cameron N, Brasher PM. Enhancing a Somatic Maturity Prediction

Model. *Med Sci Sports Exerc* 2015; **47**: 1755-1764 [PMID: 25423445 DOI: 10.1249/MSS.0000000000000588]
24 **Cureton KJ**, Plowman SA, Mahar MT. Aerobic capacity assessment. In: Plowman SA, Meredith MD. In FitnessGram/ActivityGram reference Guide. Dallas, TX, United States: The Cooper Institute, 2013: 6-1-6-22
25 **Léger LA**, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. *J Sports Sci* 1988; **6**: 93-101 [PMID: 3184250 DOI: 10.1080/02640418808729800]
26 **National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents**. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *PEDIATRICS* 2004; **114**: 555-576 [DOI: 10.1542/peds.114.2.s2.555]
27 **Gao Y**, Zhu CG, Wu NQ, Guo YL, Liu G, Dong Q, Li JJ. [Study on the reliability of CardioChek PA for measuring lipid profile]. *Beijing Da Xue Xue Bao Yi Xue Ban* 2016; **48**: 523-528 [PMID: 27318918]
28 **Zimmet P**, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr Diabetes* 2007; **8**: 299-306 [PMID: 17850473 DOI: 10.1111/j.1399-5448.2007.00271.x]
29 **Bagyura Z**, Kiss L, Lux Á, Csobay-Novák C, Jermendy ÁL, Polgár L, Szelid Z, Soós P, Merkely B. Association between coronary atherosclerosis and visceral adiposity index. *Nutr Metab Cardiovasc Dis* 2020; **30**: 796-803 [PMID: 32127334 DOI: 10.1016/j.numecd.2020.01.013]
30 **Sasayama K**, Ochi E, Adachi M. Importance of both fatness and aerobic fitness on metabolic syndrome risk in Japanese children. *PLoS One* 2015; **10**: e0127400 [PMID: 25993528 DOI: 10.1371/journal.pone.0127400]
31 **Agbre-Yace ML**, Oyenusi EE, Oduwole AO, Ake MD, Abodo JR. Prevalence of diabetes mellitus among children and adolescents in the district of Abidjan in Cote d'Ivoire: a population-based study. *J Diabetes Metab Disord* 2015; **15**: 38 [PMID: 27679783 DOI: 10.1186/s40200-016-0261-7]
32 **Andes LJ**, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. *JAMA Pediatr* 2020; **174**: e194498 [PMID: 31790544 DOI: 10.1001/jamapediatrics.2019.4498]
33 **Kumar P**, Srivastava S, Mishra PS, Mooss ETK. Prevalence of pre-diabetes/type 2 diabetes among adolescents (10-19 years) and its association with different measures of overweight/obesity in India: a gendered perspective. *BMC Endocr Disord* 2021; **21**: 146 [PMID: 34233661 DOI: 10.1186/s12902-021-00802-w]
34 **Thomas NE**, Cooper SM, Williams SP, Baker JS, Davies B. Relationship of fitness, fatness, and coronary-heart-disease risk factors in 12- to 13-year-olds. *Pediatr Exerc Sci* 2007; **19**: 93-101 [PMID: 17554161 DOI: 10.1123/pes.19.1.93]
35 **Raheem J**, Sliz E, Shin J, Holmes MV, Pike GB, Richer L, Gaudet D, Paus T, Pausova Z. Visceral adiposity is associated with metabolic profiles predictive of type 2 diabetes and myocardial infarction. *Commun Med (Lond)* 2022; **2**: 81 [PMID: 35789567 DOI: 10.1038/s43856-022-00140-5]
36 **Grøntved A**, Ried-Larsen M, Ekelund U, Froberg K, Brage S, Andersen LB. Independent and combined association of muscle strength and cardiorespiratory fitness in youth with insulin resistance and β-cell function in young adulthood: the European Youth Heart Study. *Diabetes Care* 2013; **36**: 2575-2581 [PMID: 23579180 DOI: 10.2337/dc12-2252]
37 **Lätt E**, Mäestu J, Rääsk T, Jürimäe T, Jürimäe J. Cardiovascular fitness, physical activity, and metabolic syndrome risk factors among adolescent estonian boys: A longitudinal study. *Am J Hum Biol* 2016; **28**: 782-788 [PMID: 27166594 DOI: 10.1002/ajhb.22866]
38 **Henderson M**, Benedetti A, Barnett TA, Mathieu ME, Deladoëy J, Gray-Donald K. Influence of Adiposity, Physical Activity, Fitness, and Screen Time on Insulin Dynamics Over 2 Years in Children. *JAMA Pediatr* 2016; **170**: 227-235 [PMID: 26857733 DOI: 10.1001/jamapediatrics.2015.3909]
39 **Shaibi GQ**, Ball GD, Cruz ML, Weigensberg MJ, Salem GJ, Goran MI. Cardiovascular fitness and physical activity in children with and without impaired glucose tolerance. *Int J Obes (Lond)* 2006; **30**: 45-49 [PMID: 16344846 DOI: 10.1038/sj.ijo.0803171]
40 **Myers J**, Vainshelboim B, Kamil-Rosenberg S, Chan K, Kokkinos P. Physical Activity, Cardiorespiratory Fitness, and Population-Attributable Risk. *Mayo Clin Proc* 2021; **96**: 342-349 [PMID: 33549255 DOI: 10.1016/j.mayocp.2020.04.049]
41 **Ross R**, Blair SN, Arena R, Church TS, Després JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisløff U; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* 2016; **134**: e653-e699 [PMID: 27881567 DOI: 10.1161/CIR.0000000000000461]
42 **Lee DC**, Sui X, Church TS, Lavie CJ, Jackson AS, Blair SN. Changes in fitness and fatness on the development of cardiovascular disease risk factors hypertension, metabolic syndrome, and hypercholesterolemia. *J Am Coll Cardiol* 2012; **59**: 665-672 [PMID: 22322083 DOI: 10.1016/j.jacc.2011.11.013]
43 **Żegleń M**, Kryst Ł, Kowal M, Woronkowicz A. Sexual dimorphism of adiposity and fat distribution among children and adolescents (8-18 year olds) from Poland. *Am J Hum Biol* 2024; **36**: e24046 [PMID: 38308179 DOI: 10.1002/ajhb.24046]
44 **U.S. Department of Health and Human Services**. Physical activity guidelines for Americans (2nd Ed.). [cited 15 May 2024]. Available from: https://www.hhs.gov

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SYSTEMATIC REVIEWS

Indian perspective on childhood malnutrition: Prevalence, pathophysiology, risk factors, and prevention

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Abstract

BACKGROUND

Childhood malnutrition contributes over half of the childhood mortality around the world, predominantly in South-Asian and sub-Saharan countries.

AIM

To summarize the childhood malnutrition epidemiology along with the comorbid factors associated with it and its management within the community.

METHODS

The data collection process involved conducting a comprehensive search using specific keywords such as child nutrition disorders and India with Boolean operators. The search was conducted in the Scopus and PubMed electronic databases.

RESULTS

Inadequate energy consumption initiates pathological alterations in the form of growth retardation, fat, visceral, and muscle loss, a reduction in basal metabolic rate, and a significant reduction in total energy expenditure. It has become evident that malnutrition shows an increased prevalence and incidence rate, despite available guidelines for the management of malnutrition.

CONCLUSION

Malnutrition can be a major player in the establishment of severe infections that

result in significant post discharge mortalities in children. Future trials are required to fill the prime gaps in knowledge regarding the identification of other contributory factors in the pathogenesis of malnutrition and post-discharge infection. New biomarkers for early detection of malnutrition should be the priority of the scientific community for the early management of malnutrition.

Key Words: Malnutrition; Severe acute malnutrition; Management; Pathophysiology; Childhood

Core Tip: Childhood malnutrition, a leading cause of global childhood mortality, especially in South-Asian and sub-Saharan countries, demands urgent attention. This review consolidates malnutrition epidemiology, its associated factors, and community-based management. Despite available guidelines, inadequate energy intake leads to severe complications. Addressing knowledge gaps and identifying new biomarkers are pivotal for effective early detection and management of malnutrition-induced severe infections in children.

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INTRODUCTION

Acute malnutrition is prevalent among children aged below 5 years and affects 47 million children, along with 1 million deaths annually worldwide. According to the United Nations Children's Fund (UNICEF) 2024 report, in East Asia and the Pacific, 59 million (45%) young children are not getting the nutrition and variety they need to grow and develop to their full potential because of a lack of a balanced diet[1,2]. Nutrition has been a global priority for children for many years. For decades, affected children with acute malnutrition were managed by supplementation of fortified milk products. The breakthrough introduction of ready-to-use therapeutic foods (RUTF) and ready-to-use supplementary foods (RUSF) changed the scenario of acute malnutrition management completely after endorsement from the World Health Organization (WHO) and the United Nations through the Community Management of Acute Malnutrition (CMAM) Programme[3]. In many countries, only a few nutrition indicators are regularly tracked, and even fewer pay attention to the diversity of symptoms of malnutrition. Over the past ten years, India has seen considerable improvements in several health metrics. Inequality and uneven development have increased during the past ten years, especially in the fields of child nutrition, education, and health (Figure 1).

In low- and middle-income countries, malnutrition is a significant public health issue. Around 165 million under-five children are stunted, 52 million are wasted, and 17 million are severely wasted worldwide[4]. Asia is home to more than two-thirds of the wasted children and more than half of the stunted children.

A wide range of clinical disorders, including wasting or stunting, marasmus, kwashiorkor, and micronutrient deficiencies, fall under the umbrella term of malnutrition. A weight-for-height Z-score (WHZ) that is more than three SDs below the mean, a mid-upper arm circumference (MUAC) that is less than 115 mm, or the development of nutritional oedema are all considered signs of severe acute malnutrition (SAM). Marasmus is the medical term for moderate acute malnutrition (MAM) or SAM without bilateral pitting oedema. The term "kwashiorkor" is used when there is bilateral pitting oedema. Despite enormous efforts and progress in maternal and child malnutrition, a significant burden of SAM persists. In a recent study, it was reported that a slight decrease in wasting is seen in countries with low income (from 15.9% to 14.2%) while a slight increase in wasting was found in countries with middle income (from 3.3% to 4.7%). In total, 50 million children aged under 5 years remain wasted worldwide[5,6]. In a recent report, it was seen that the disease burden of SAM is likely to aggravate during the pandemic of coronavirus disease 2019, showing 6.7 million additional children at risk of wasting in the year 2020[7]. The present review assessed the prevalence and pathophysiology of malnutrition and focused on current management approaches for such affected children.

MATERIALS AND METHODS

A comprehensive search was conducted using PubMed and Scopus, applying keywords such as "child nutrition disorders," "India," "malnutrition," and "risk factors," with Boolean operators to refine results. The inclusion criteria focused on peer-reviewed articles, clinical studies, and reports published between relevant years, addressing malnutrition's prevalence, risk factors, pathophysiology, and management. Data were synthesized under key themes, including prevalence, management strategies, and developmental consequences.

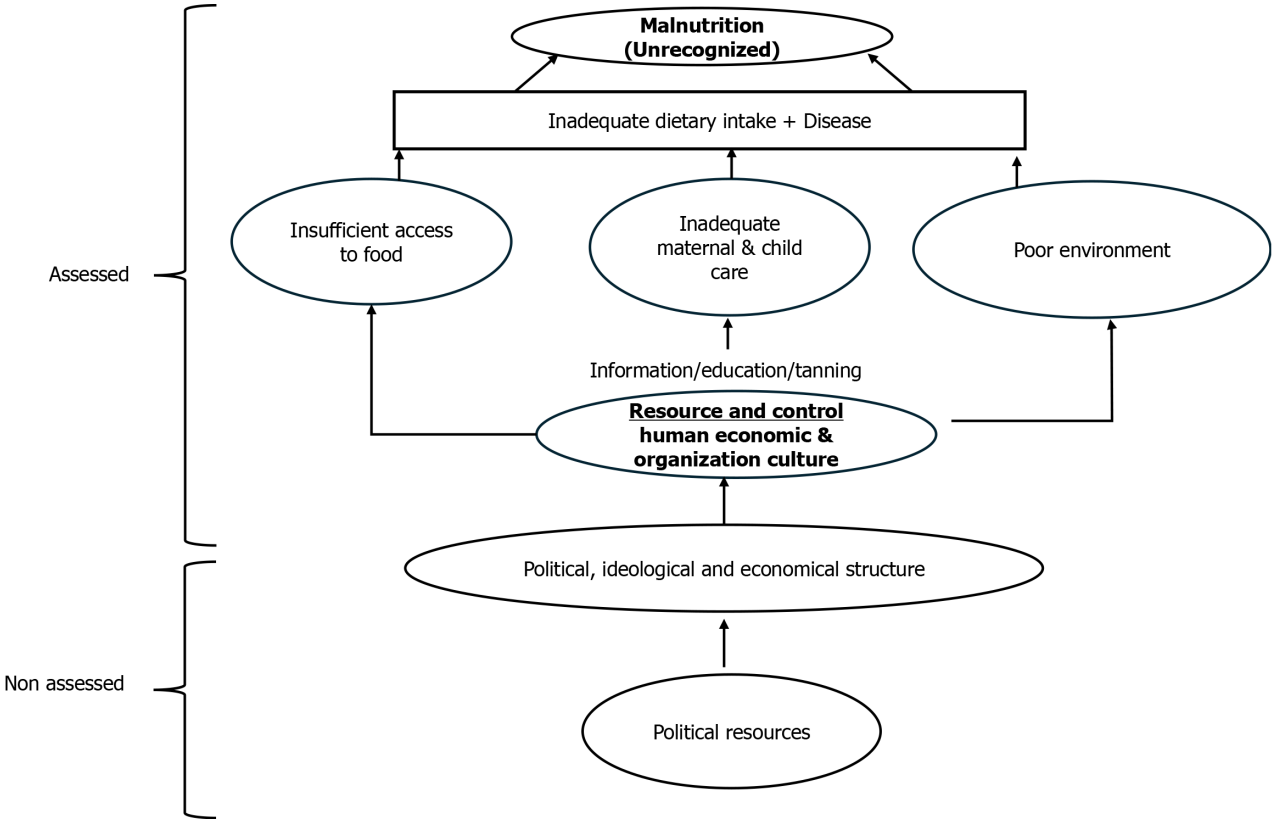

Figure 1 Conceptual framework of child malnutrition.

RESULTS

Prevalence of malnutrition in children- in Indian scenario

For several previous years, the malnutrition prevalence has decreased, however, it is around 155 million stunted children and 52 million wasted children worldwide[8].

Currently, India is on the way to reducing to target for impaired growth and development of children although approximate 34.7% of < 5 years of children are still under the phase of stunning which is much greater than the Asia region (21.8%) In the case of wasting, nothing has achieved by India, In India 17.3% of children under 5 years of age affected, which is higher than the average for the Asia region (8.9%)[9]. According to the fifth in the series of surveys, the National Family Health Survey (NFHS) 2019-2021, In India neither the population's neither health nor nutritional status have appreciably improved. The most recent statistics show that 19.3 percent of children are wasted, 7.7 percent are highly wasted, and 35.5 percent are stunted. In addition, 3.4% of children are overweight, which is higher than the NFHS-4 average of 2.1%[10]. According to NFHS-4, the prevalence of anemia in children under the age of five has dramatically increased, going from 58.6 percent to 67.1 percent. In India, it has been seen that 57% of women are anemic at childbearing age[11]. The double burden of malnutrition has been studied in numerous ways, including underweight and obesity in mothers, obesity and thinness in children[12]. SAM is a major death factor and increases the case fatality rate in children who already have complications of common illnesses like diarrhea and pneumonia[13]. For the management of SAM, WHO and UNICEF recommend two major approaches: (1) Hospital-based approach - for clinical management as per WHO criteria; and (2) Home-based approach - the use of RUTF or medical nutrition therapy as part of integrated public health response to acute malnutrition without medical complications[14].

Criteria for the assessment or diagnosis of malnutrition include specific measures such as the WHZ, MUAC, and the presence of bilateral pitting edema. Children with a WHZ below -2 or -3 standard deviations from the WHO child growth standards are considered wasted or severely wasted, respectively. Additionally, a MUAC of less than 115 mm in children aged 6–59 months is a key indicator of SAM.

Pathophysiology

General physiological changes: SAM induces a series of adaptive responses in the body. Growth restriction occurs as the body prioritizes essential functions over growth. There's a significant loss of fat, muscle, and visceral mass as the body catabolizes these tissues for energy. The basal metabolic rate decreases as a survival mechanism to conserve energy, leading to an overall reduction in energy expenditure[15,16].

Hormonal and metabolic alterations: Malnutrition causes substantial alterations in the endocrine system. It leads to reduced production of several crucial hormones, including insulin, triiodothyronine, and insulin-like growth factor-1. These hormonal changes subsequently impact the body's ability to regulate blood sugar and ultimately affect cell growth.

Conversely, growth hormone and cortisol levels rise, promoting the breakdown of tissues for energy and maintaining blood glucose levels. These hormonal shifts contribute to the catabolic state characteristic of malnutrition[17,18].

Electrolyte imbalances: Malnutrition disrupts the body's electrolyte balance. Sodium retention occurs, while intracellular potassium is depleted. In kwashiorkor, a form of severe malnutrition, cell membrane permeability increases, exacerbating these imbalances. The activity of the glycoside-sensitive, energy-dependent sodium pump is reduced, further compromising cellular homeostasis[19].

Immune system effects: The immune system is severely impacted by malnutrition. Atrophy of the thymus, lymph nodes, and tonsils impairs cellular immunity. There's a reduction in CD4 clusters of differentiation, although CD8-T cells remain relatively normal. The loss of delayed hypersensitivity, poor phagocytic activity, and lower levels of secretory IgA collectively weaken the body's defense against pathogens, increasing susceptibility to infections[20].

Neurological effects: Malnutrition has profound effects on the developing brain. It leads to a decrease in the number of neurons, synapses, dendritic arborization, and myelination, resulting in an overall reduction in brain size and thinning of the cerebral cortex. These structural changes translate into functional deficits, including delays in cognitive and motor development. Critically, if malnutrition occurs after 3-4 years of age, some of these neurological impacts may become permanent, underscoring the importance of early intervention[21-23].

Management of children with SAM

Facility based management of children with SAM: Currently, SAM-affected children in India are cared for by Nutrition Rehabilitation Centers (NRCs); however, due to the dearth of NRCs, most SAM children never receive any treatment[23]. Most SAM children admitted to NRCs do not have any medical conditions. There is already a way to help and enhance more SAM kids in India[24]. To ensure that children with SAM receive quick and high quality care, efforts are being made at the national level to identify the procedures that need to be followed. The facility-based care is implemented through a network of 262 NRCs[25]. Admission requires either edema, MUAC 115 mm, or a W/H score of less than -3Z. The appetite test is administered to all children, for 14-21 days, the children are housed in the facility, and they are given locally produced F-75 and F100[26]. The youngsters are freed after recovering a normal appetite and weight. A child is registered under the ICDS program after being released, and home visits are utilized to monitor the kid's well-being[27].

Community based management of children with SAM: Except for those experiencing complications, no SAM child needs to be admitted to the hospital. It has been discovered that home based management with RUTF is linked to better outcomes than traditional hospital therapy[28]. There is sufficient evidence that such SAM children can be successfully managed at the home level, and it has been noted that between 60% and 90% of SAM cases, identified by active case finding in the community, are without medical issues[29]. Since children experience fewer hospital-acquired infections and obtain continuity of care after discharge, home-based management of SAM children using medical nutrition therapy provides many more benefits[30]. It also benefits mother by giving them more time to spend with their families and lowering the possibility of siblings being neglected. Additionally, mothers can receive guidance on better feeding and care techniques in their local environments while also managing other family obligations[31].

Possible risk factors for SAM: Factors like low birth weight, sociodemographic traits, inadequate nutrition, improper feeding techniques, incomplete immunization, political and environmental instability, emergency situations, and a high prevalence of infectious diseases are considered risk factors for SAM (Figure 2)[32,33].

Research indicates that children suffering from SAM face a higher risk of developmental issues compared to those who receive adequate breast milk and additional nutritional supplements[34]. The risk factors such as feeding practices, water availability, sanitation, and hygiene conditions plays a critical roles in occurrence of SAM in infant and young child[35]. Islam *et al*[36] have established that when caregiver's education level is low, child stands a higher risk of becoming wasted[36,37]. Children of illiterate parents have a higher risk of SAM especially when it has to do with the caregiver[38].

Developmental consequences of childhood malnutrition

Beginning at conception, disease and insufficient food intake are major contributors to early childhood malnutrition, with the first 24 months of life having the highest risk of a fall in length-for-weight[39]. More than 200 million children under the age of five are thought to be living below their full developmental potential on a global scale[40]. A child who is malnourished starts a "vicious cycle" in which she/he becomes more prone to illness and infection, which can subsequently cause malnutrition to increase[41]. Illness can temporarily reduce infants' appetite and nutrient absorption, while increasing catabolism, which diverts nutrients from growth to the immune response, potentially hindering psychomotor and cognitive development[42].

Prevention of SAM

Giving adequate nutrition and disease prevention: Due to its importance to the early childhood developmental phase, exclusive breastfeeding should not be compromised in the fight against SAM[32]. However, preventative intervention is propelled by nutrition education. Encouragement of supplementing programs and treatment of micronutrient deficiencies by dietary approaches such as dietary diversity through home gardens or other techniques like micronutrient fortification[43].

Therapeutic foods for SAM prevention: F75 and F100 are exclusive dairy products that are typically utilized in inpatient settings to treat SAM. Inpatient treatment facilities administer the F75 to children who need to be stabilized. Children receiving inpatient care typically get 80 to 100 kcal/kg/day across eight to twelve meals per day for three to seven days [44]. The F100, which is administered during the recovery stage of inpatient therapy for SAM, provides children with

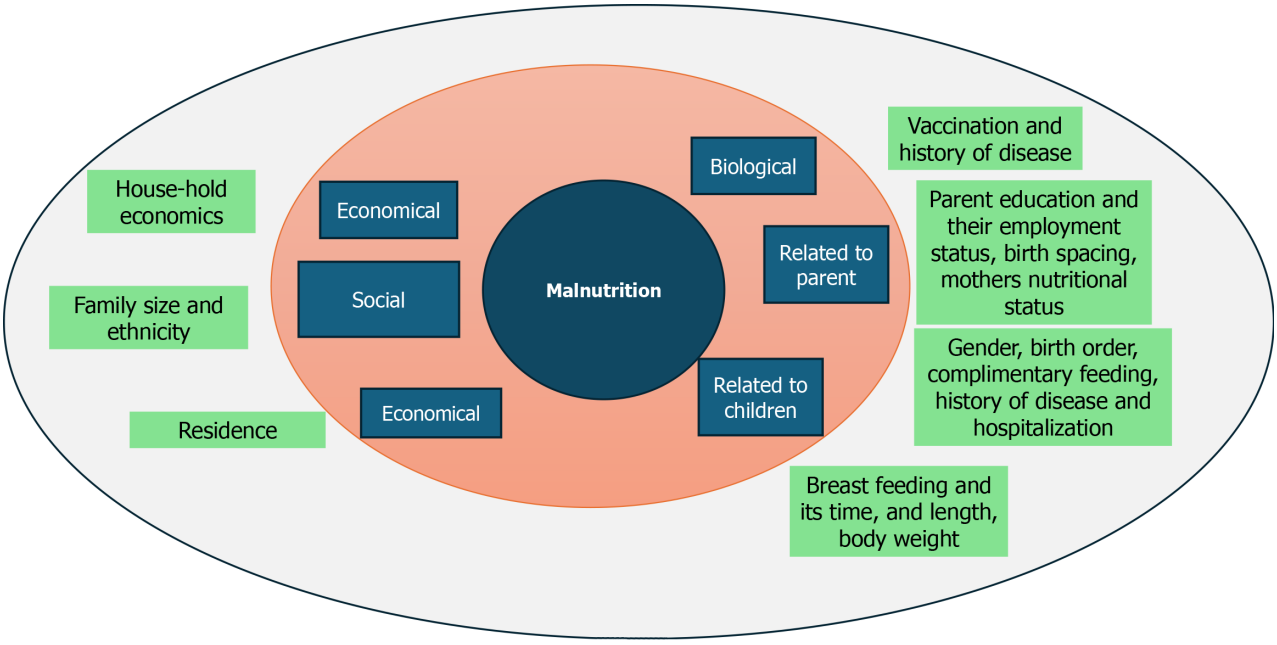

Figure 2 Contributory risk factors of malnutrition in children.

around 100-200 kcal/kg/day for three-four weeks[45]. F75s and F100s are not kept at a temperature of 25 °C for very long since they need some preparation, as well as because of their high moisture content[44].

In addition, these foods are not distributed to caretakers for home preparation (UNICEF catalog). Community-based treatment methods have benefited enormously from the creation of ready-to-use foods (RUFs)[46]. Unlike F75s and F100s, RUTFs are ready to eat without preparation and are more nutrient-dense than typical household foods, with a very low moisture content that makes them resistant to microbial growth[47].

To treat MAM and SAM, treatment centers provide a variety of items, including formulated biscuits, bars, and pastes like RUTFs, RUSFs, LNS (Lipid-based nutritional supplements and specialized products like Plumpy Sup, Plumpy'Nut, and Plumpy'Doz. Specifically, Plumpy'Doz and Plumpy Sup aimed at treating MAM, and Plumpy'Nut intended for treating both MAM and SAM in infants. Children receive one to two 92 g sachets daily for MAM and two to three sachets per day for SAM treatment. Plumpy'Nut is formulated to meet all a child's daily nutritional needs for SAM treatment (Nutriset), while families may also receive Super Cereal Plus (formerly Corn Soy Blend Plus Plus or CSB++) as part of their food rations to help prevent MAM (Table 1)[48].

Moderate malnutrition is treated with RUTF: Due to strong evidence supporting their effectiveness in treating SAM, RUFs are now being considered for use in supplemental feeding programs aimed at managing moderate malnutrition [48]. Given its success in expanding coverage through decentralized community-based care, the CMAM model may find wider application in supplemental feeding programs. RUTF was initially created as a therapeutic meal for severe malnutrition, but it has also been used to treat moderate and mild malnutrition. More recently, it has been extensively disseminated to at-risk groups in order to prevent malnutrition[46]. The nutritional content and micronutrient profile of RUTF and RUSF are quite similar. For treating SAM, RUTF must meet the full daily nutritional requirements of the child, with the dosage adjusted based on weight. In cases of moderate malnutrition, RUTF is administered as a standard 500 kcal/day ration, regardless of the child's weight, to supplement their daily diet[46].

DISCUSSION

SAM is a life-threatening condition requiring immediate attention, affecting millions of children worldwide. Understanding its impact is crucial for early action and prevention. Factors such as infant feeding practices, hygiene, and caregiver education significantly influence the risk of SAM. Childhood malnutrition starts a detrimental cycle leading to heightened vulnerability to illnesses, impairing physical and cognitive development. It's evident that over 200 million children globally aren't reaching their developmental potential, with malnutrition significantly hindering learning capabilities[49].

Preventative strategies against SAM encompass a multi-pronged approach involving adequate nutrition, disease prevention, and educational interventions. Exclusive breastfeeding, coupled with nutritional education, plays a pivotal role. Therapeutic foods like F75 and F100, administered in inpatient settings, aid stabilization and recovery, respectively, but face challenges in distribution and preparation. RUFs, such as RUTFs, exhibit promise in community-based therapy due to their ease of use and high nutrient density. These RUFs, including Plumpy'Nut and others, are proving effective in preventing and treating various degrees of malnutrition, contributing to children's nutritional needs[50]. Furthermore,

Table 1 List of items given at the treatment centers

List of items
RUTFs like formulated bars, pastes, or biscuits
RUSFs
LNS
Plumpy'Doz, Plumpy Sup, and Plumpy'Nut, which are common RUFs used to prevent or treat MAM and SAM, are given to supplement children's diets:
Plumpy'Doz, designed to prevent or treat MAM in infants
Plumpy Sup, designed to treat MAM in infants
Plumpy'Nut, designed to treat MAM or SAM in infants

RUTFs: Ready-to-use therapeutic foods; RUSFs: Ready-to-use supplementary foods; LNS: Lipid-based nutritional supplements; MAM: Moderate acute malnutrition; SAM: Severe acute malnutrition.

RUTFs have shown potential in treating moderate malnutrition, expanding their role beyond severe cases. The success of the CMAM approach indicates the possibility of broader applications in supplemental feeding programs. The nutritional equivalence of RUTFs and RUSFs is highlighted, offering insight into dosage and application, thereby broadening their usage in addressing varying degrees of malnutrition[51].

CONCLUSION

SAM remains a critical issue in low- and middle-income countries, despite ongoing efforts. Innovative management strategies and reliable biomarkers for early detection and treatment are urgently needed. Addressing the dual burden of malnutrition-undernutrition and overnutrition-among vulnerable populations, especially women and children, is crucial. The review emphasizes the importance of enhanced public health policies, targeted nutrition programs, and community-based interventions to mitigate malnutrition's impact and improve health outcomes. A comprehensive approach is essential to reduce malnutrition's prevalence and its long-term effects on global health.

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FOOTNOTES

Author contributions: Singh DD and Rao YK conceived and designed the study; Mishra M retrieved the articles, wrote, and drafted the manuscript; Shrivastav D assisted in information retrieval and inclusion of findings; Tripathi P provided intellectual inputs and proofread the manuscript; All authors approved the final version and contributed to the article and approved the submitted version.

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REFERENCES

1 **Govender I**, Rangiah S, Kaswa R, Nzaumvila D. Malnutrition in children under the age of 5 years in a primary health care setting. *S Afr Fam Pract (2004)* 2021; **63**: e1-e6 [PMID: 34677078 DOI: 10.4102/safp.v63i1.5337]

2 **Stevens GA**, Beal T, Mbuya MNN, Luo H, Neufeld LM; Global Micronutrient Deficiencies Research Group. Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys. *Lancet Glob Health* 2022; **10**: e1590-e1599 [PMID: 36240826 DOI: 10.1016/S2214-109X(22)00367-9]

3 **Duke T**. Levels and trends in child mortality estimation. *Arch Dis Child* 2024; **109**: 620-621 [PMID: 38631885 DOI: 10.1136/archdischild-2024-327211]

4 **Sigh S**, Roos N, Chhoun C, Laillou A, Wieringa FT. Ready-to-Use Therapeutic Foods Fail to Improve Vitamin A and Iron Status Meaningfully during Treatment for Severe Acute Malnutrition in 6-59-Month-old Cambodian Children. *Nutrients* 2023; **15**: 905 [PMID: 36839263 DOI: 10.3390/nu15040905]

5 **Bassaganya-Riera J**, Berry EM, Blaak EE, Burlingame B, le Coutre J, van Eden W, El-Sohemy A, German JB, Knorr D, Lacroix C, Muscaritoli M, Nieman DC, Rychlik M, Scholey A, Serafini M. Goals in Nutrition Science 2020-2025. *Front Nutr* 2020; **7**: 606378 [PMID: 33665201 DOI: 10.3389/fnut.2020.606378]

6 **Hitchings MDT**, Berthé F, Aruna P, Shehu I, Hamza MA, Nanama S, Steve-Edemba C, Grais RF, Isanaka S. Effectiveness of a monthly schedule of follow-up for the treatment of uncomplicated severe acute malnutrition in Sokoto, Nigeria: A cluster randomized crossover trial. *PLoS Med* 2022; **19**: e1003923 [PMID: 35231024 DOI: 10.1371/journal.pmed.1003923]

7 **Victora CG**, Christian P, Vidaletti LP, Gatica-Domínguez G, Menon P, Black RE. Revisiting maternal and child undernutrition in low-income and middle-income countries: variable progress towards an unfinished agenda. *Lancet* 2021; **397**: 1388-1399 [PMID: 33691094 DOI: 10.1016/S0140-6736(21)00394-9]

8 **Headey D**, Heidkamp R, Osendarp S, Ruel M, Scott N, Black R, Shekar M, Bouis H, Flory A, Haddad L, Walker N; Standing Together for Nutrition consortium. Impacts of COVID-19 on childhood malnutrition and nutrition-related mortality. *Lancet* 2020; **396**: 519-521 [PMID: 32730743 DOI: 10.1016/S0140-6736(20)31647-0]

9 **India State-Level Disease Burden Initiative Malnutrition Collaborators**. The burden of child and maternal malnutrition and trends in its indicators in the states of India: the Global Burden of Disease Study 1990-2017. *Lancet Child Adolesc Health* 2019; **3**: 855-870 [PMID: 31542357 DOI: 10.1016/S2352-4642(19)30273-1]

10 **Sahu SK**, Kumar SG, Bhat BV, Premarajan KC, Sarkar S, Roy G, Joseph N. Malnutrition among under-five children in India and strategies for control. *J Nat Sci Biol Med* 2015; **6**: 18-23 [PMID: 25810629 DOI: 10.4103/0976-9668.149072]

11 **Jha A**, Chandrakar A. A Comparative Study of National Family Health Survey-4 and National Family Health Survey-5 of Nutritional Indicators in Chhattisgarh. *Cureus* 2024; **16**: e55524 [PMID: 38576647 DOI: 10.7759/cureus.55524]

12 **Kinyoki D**, Osgood-Zimmerman AE, Bhattacharjee NV; Local Burden of Disease Anaemia Collaborators, Kassebaum NJ, Hay SI. Anemia prevalence in women of reproductive age in low- and middle-income countries between 2000 and 2018. *Nat Med* 2021; **27**: 1761-1782 [PMID: 34642490 DOI: 10.1038/s41591-021-01498-0]

13 **Popkin BM**, Corvalan C, Grummer-Strawn LM. Dynamics of the double burden of malnutrition and the changing nutrition reality. *Lancet* 2020; **395**: 65-74 [PMID: 31852602 DOI: 10.1016/S0140-6736(19)32497-3]

14 **Rodríguez L**, Cervantes E, Ortiz R. Malnutrition and gastrointestinal and respiratory infections in children: a public health problem. *Int J Environ Res Public Health* 2011; **8**: 1174-1205 [PMID: 21695035 DOI: 10.3390/ijerph8041174]

15 **Fischer M**, JeVenn A, Hipskind P. Evaluation of muscle and fat loss as diagnostic criteria for malnutrition. *Nutr Clin Pract* 2015; **30**: 239-248 [PMID: 25753808 DOI: 10.1177/0884533615573053]

16 **Keller U**. Nutritional Laboratory Markers in Malnutrition. *J Clin Med* 2019; **8**: 775 [PMID: 31159248 DOI: 10.3390/jcm8060775]

17 **Kasprzak A**. Insulin-Like Growth Factor 1 (IGF-1) Signaling in Glucose Metabolism in Colorectal Cancer. *Int J Mol Sci* 2021; **22**: 6434 [PMID: 34208601 DOI: 10.3390/ijms22126434]

18 **Martins VJB**, de Albuquerque MP, Sawaya AL. Endocrine Changes in Undernutrition, Metabolic Programming, and Nutritional Recovery. In: Preedy V, Patel V, editors. Handbook of Famine, Starvation, and Nutrient Deprivation. Cham: Springer, 2017 [DOI: 10.1007/978-3-319-40007-5_41-1]

19 **Raza M**, Kumar S, Ejaz M, Azim D, Azizullah S, Hussain A. Electrolyte Imbalance in Children With Severe Acute Malnutrition at a Tertiary Care Hospital in Pakistan: A Cross-Sectional Study. *Cureus* 2020; **12**: e10541 [PMID: 33094080 DOI: 10.7759/cureus.10541]

20 **Morales F**, Montserrat-de la Paz S, Leon MJ, Rivero-Pino F. Effects of Malnutrition on the Immune System and Infection and the Role of Nutritional Strategies Regarding Improvements in Children's Health Status: A Literature Review. *Nutrients* 2023; **16**: 1 [PMID: 38201831 DOI: 10.3390/nu16010001]

21 **Cakir M**, Senyuva S, Kul S, Sag E, Cansu A, Yucesan FB, Yaman SO, Orem A. Neurocognitive Functions in Infants with Malnutrition; Relation with Long-chain Polyunsaturated Fatty Acids, Micronutrients Levels and Magnetic Resonance Spectroscopy. *Pediatr Gastroenterol Hepatol Nutr* 2019; **22**: 171-180 [PMID: 30899693 DOI: 10.5223/pghn.2019.22.2.171]

22 **Cusick SE**, Georgieff MK. The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days". *J Pediatr* 2016; **175**: 16-21 [PMID: 27266965 DOI: 10.1016/j.jpeds.2016.05.013]

23 **Tandon M**, Quereishi J, Prasanna R, Tamboli AF, Panda B. Performance of Nutrition Rehabilitation Centers: A Case Study from Chhattisgarh, India. *Int J Prev Med* 2019; **10**: 66 [PMID: 31198501 DOI: 10.4103/ijpvm.IJPVM_194_17]

24 **Kumar B**, Shrivastava J, Satyanarayana S, Reid AJ, Ali E, Zodpey S, Agnani M. How effective is the integration of facility and community-based management of severe acute malnutrition in India? *Public Health Action* 2013; **3**: 265-270 [PMID: 26393044 DOI: 10.5588/pha.13.0058]

25 **Kumar P**, Sinha RK, Daniel A, Shah H, Sriswan R, Kokane A, Mohapatra A, Kashyap V, Goel AK, Kumar V, Kiran A, Arlappa N, Joshi A, Nayak RR, Singh M, Salasibew M, Ghosh S, Pawar SM, Mishra P, Tiwari K, Bhattacharjee S, Saiyed F, Patel TS, Nayak PK, Sahoo SK, Prajapati M, Sinha S, de Wagt A. Effectiveness of community-based treatment programs for treatment of uncomplicated severe acute malnourished children aged 6-59 months using locally produced nutrient dense foods: protocol for a multicentric longitudinal quasi-experimental study. *BMC Nutr* 2021; **7**: 85 [PMID: 34906257 DOI: 10.1186/s40795-021-00489-1]

26 **Grellety E**, Golden MH. Severely malnourished children with a low weight-for-height have a higher mortality than those with a low mid-upper-arm-circumference: I. Empirical data demonstrates Simpson's paradox. *Nutr J* 2018; **17**: 79 [PMID: 30217205 DOI: 10.1186/s12937-018-0384-4]

27 **Chakraborty R**, Joe W, ShankarMishra U, Rajpal S. Integrated child development service (ICDS) coverage among severe acute malnourished (SAM) children in India: A multilevel analysis based on national family health survey-5. *PLoS One* 2024; **19**: e0294706 [PMID: 38330040 DOI: 10.1371/journal.pone.0294706]

28 **Schoonees A**, Lombard MJ, Musekiwa A, Nel E, Volmink J. Ready-to-use therapeutic food (RUTF) for home-based nutritional rehabilitation of severe acute malnutrition in children from six months to five years of age. *Cochrane Database Syst Rev* 2019; **5**: CD009000 [PMID: 31090070 DOI: 10.1002/14651858.CD009000.pub3]

29 **Jones KD**, Berkley JA. Severe acute malnutrition and infection. *Paediatr Int Child Health* 2014; **34** Suppl 1: S1-S29 [PMID: 25475887 DOI: 10.1179/2046904714Z.000000000218]

30 **Williams PCM**, Berkley JA. Guidelines for the treatment of severe acute malnutrition: a systematic review of the evidence for antimicrobial therapy. *Paediatr Int Child Health* 2018; **38**: S32-S49 [PMID: 29790840 DOI: 10.1080/20469047.2017.1409453]

31 **Poduval J**, Poduval M. Working mothers: how much working, how much mothers, and where is the womanhood? *Mens Sana Monogr* 2009; **7**: 63-79 [PMID: 21836780 DOI: 10.4103/0973-1229.41799]

32 **Mukuku O**, Mutombo AM, Kamona LK, Lubala TK, Mawaw PM, Aloni MN, Wembonyama SO, Luboya ON. Predictive Model for the Risk of Severe Acute Malnutrition in Children. *J Nutr Metab* 2019; **2019**: 4740825 [PMID: 31354989 DOI: 10.1155/2019/4740825]

33 **David SM**, Pricilla RA, Paul SS, George K, Bose A, Prasad JH. Risk factors for severe acute malnutrition among children aged 6-59 months: A community-based case-control study from Vellore, Southern India. *J Family Med Prim Care* 2020; **9**: 2237-2243 [PMID: 32754480 DOI: 10.4103/jfmpc.jfmpc_211_20]

34 **Abeshu MA**, Lelisa A, Geleta B. Complementary Feeding: Review of Recommendations, Feeding Practices, and Adequacy of Homemade Complementary Food Preparations in Developing Countries - Lessons from Ethiopia. *Front Nutr* 2016; **3**: 41 [PMID: 27800479 DOI: 10.3389/fnut.2016.00041]

35 **Sachdeva S**, Vijayaran M. Nutritional rehabilitation using energy dense local food as ready to use therapeutic food in hospitalized malnourished children: Case for primary prevention at grass root levels. *J Med Trop* 2014; **16**: 22 [DOI: 10.4103/2276-7096.132573]

36 **Islam MM**, Alam M, Tariquzaman M, Kabir MA, Pervin R, Begum M, Khan MM. Predictors of the number of under-five malnourished children in Bangladesh: application of the generalized poisson regression model. *BMC Public Health* 2013; **13**: 11 [PMID: 23297699 DOI: 10.1186/1471-2458-13-11]

37 **Patel MP**, Sandige HL, Ndekha MJ, Briend A, Ashorn P, Manary MJ. Supplemental feeding with ready-to-use therapeutic food in Malawian children at risk of malnutrition. *J Health Popul Nutr* 2005; **23**: 351-357 [PMID: 16599106]

38 **Sanghvi J**, Mehta S, Kumar R. Predicators for weight gain in children treated for severe acute malnutrition: a prospective study at nutritional rehabilitation center. *ISRN Pediatr* 2014; **2014**: 808756 [PMID: 25006491 DOI: 10.1155/2014/808756]

39 **Reinhardt K**, Fanzo J. Addressing Chronic Malnutrition through Multi-Sectoral, Sustainable Approaches: A Review of the Causes and Consequences. *Front Nutr* 2014; **1**: 13 [PMID: 25988116 DOI: 10.3389/fnut.2014.00013]

40 **Grantham-McGregor S**, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B; International Child Development Steering Group. Developmental potential in the first 5 years for children in developing countries. *Lancet* 2007; **369**: 60-70 [PMID: 17208643 DOI: 10.1016/S0140-6736(07)60032-4]

41 **Schaible UE**, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. *PLoS Med* 2007; **4**: e115 [PMID: 17472433 DOI: 10.1371/journal.pmed.0040115]

42 **Dewey KG**, Mayers DR. Early child growth: how do nutrition and infection interact? *Matern Child Nutr* 2011; **7** Suppl 3: 129-142 [PMID: 21929641 DOI: 10.1111/j.1740-8709.2011.00357.x]

43 **Nair MK**, Augustine LF, Konapur A. Food-Based Interventions to Modify Diet Quality and Diversity to Address Multiple Micronutrient Deficiency. *Front Public Health* 2015; **3**: 277 [PMID: 26779472 DOI: 10.3389/fpubh.2015.00277]

44 **Lanyero B**, Namusoke H, Nabukeera-Barungi N, Grenov B, Mupere E, Michaelsen KF, Mølgaard C, Christensen VB, Friis H, Briend A. Transition from F-75 to ready-to-use therapeutic food in children with severe acute malnutrition, an observational study in Uganda. *Nutr J* 2017; **16**: 52 [PMID: 28854929 DOI: 10.1186/s12937-017-0276-z]

45 **Das JK**, Salam RA, Saeed M, Kazmi FA, Bhutta ZA. Effectiveness of Interventions for Managing Acute Malnutrition in Children under Five Years of Age in Low-Income and Middle-Income Countries: A Systematic Review and Meta-Analysis. *Nutrients* 2020; **12** [PMID: 31906272 DOI: 10.3390/nu12010116]

46 **Brixi G**. Innovative optimization of ready to use food for treatment of acute malnutrition. *Matern Child Nutr* 2018; **14**: e12599 [PMID: 29536665 DOI: 10.1111/mcn.12599]

47 **Bitew ZW**, Ayele EG, Worku T, Alebel A, Alemu A, Worku F, Yesuf A. Determinants of mortality among under-five children admitted with severe acute malnutrition in Addis Ababa, Ethiopia. *Nutr J* 2021; **20**: 94 [PMID: 34930311 DOI: 10.1186/s12937-021-00750-0]

48 **Medoua GN**, Ntsama PM, Ndzana AC, Essa'a VJ, Tsafack JJ, Dimodi HT. Recovery rate of children with moderate acute malnutrition treated with ready-to-use supplementary food (RUSF) or improved corn-soya blend (CSB+): a randomized controlled trial. *Public Health Nutr* 2016; **19**: 363-370 [PMID: 25939394 DOI: 10.1017/S1368980015001238]

49 **Sokhela H**, Govender L, Siwela M. Complementary Feeding Practices and Childhood Malnutrition in South Africa: The Potential of Moringa Oleifera Leaf Powder as a Fortificant: A Narrative Review. *Nutrients* 2023; **15**: 2011 [PMID: 37111230 DOI: 10.3390/nu15082011]

50 **Akinmoladun OF**, Bamidele OP, Jideani VA, Nesamvuni CN. Severe Acute Malnutrition: The Potential of Non-Peanut, Non-Milk Ready-to-Use Therapeutic Foods. *Curr Nutr Rep* 2023; **12**: 603-616 [PMID: 37897619 DOI: 10.1007/s13668-023-00505-9]

51 **Fetriyuna F**, Purwestri RC, Jati IRAP, Setiawan B, Huda S, Wirawan NN, Andoyo R. Ready-to-use therapeutic/supplementary foods from local food resources: Technology accessibility, program effectiveness, and sustainability, a review. *Heliyon* 2023; **9**: e22478 [PMID: 38046154 DOI: 10.1016/j.heliyon.2023.e22478]

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SYSTEMATIC REVIEWS

Nutritional management and autism spectrum disorder: A systematic review

Mohammed Al-Beltagi

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Abstract

BACKGROUND

Autism spectrum disorder (ASD) presents unique challenges related to feeding and nutritional management. Children with ASD often experience feeding difficulties, including food selectivity, refusal, and gastrointestinal issues. Various interventions have been explored to address these challenges, including dietary modifications, vitamin supplementation, feeding therapy, and behavioral interventions.

AIM

To provide a comprehensive overview of the current evidence on nutritional management in ASD. We examine the effectiveness of dietary interventions, vitamin supplements, feeding therapy, behavioral interventions, and mealtime practices in addressing the feeding challenges and nutritional needs of children with ASD.

METHODS

We systematically searched relevant literature up to June 2024, using databases such as PubMed, PsycINFO, and Scopus. Studies were included if they investigated dietary interventions, nutritional supplements, or behavioral strategies to improve feeding behaviors in children with ASD. We assessed the quality of the studies and synthesized findings on the impact of various interventions on feeding difficulties and nutritional outcomes. Data extraction focused on intervention types, study designs, participant characteristics, outcomes measured, and intervention effectiveness.

RESULTS

The review identified 316 studies that met the inclusion criteria. The evidence indicates that while dietary interventions and nutritional supplements may offer

benefits in managing specific symptoms or deficiencies, the effectiveness of these approaches varies. Feeding therapy and behavioral interventions, including gradual exposure and positive reinforcement, promise to improve food acceptance and mealtime behaviors. The findings also highlight the importance of creating supportive mealtime environments tailored to the sensory and behavioral needs of children with ASD.

CONCLUSION

Nutritional management for children with ASD requires a multifaceted approach that includes dietary modifications, supplementation, feeding therapy, and behavioral strategies. The review underscores the need for personalized interventions and further research to refine treatment protocols and improve outcomes. Collaborative efforts among healthcare providers, educators, and families are essential to optimize this population's nutritional health and feeding practices. Enhancing our understanding of intervention sustainability and long-term outcomes is essential for optimizing care and improving the quality of life for children with ASD and their families.

Key Words: Feeding therapy; Behavioral interventions; Mealtime practices; Autism spectrum disorder; Children; High-dose methyl cobalamine

Core Tip: Effective management of feeding challenges in children with autism spectrum disorder (ASD) requires a comprehensive approach integrating feeding therapy and behavioral interventions. Addressing oral motor skills and sensory sensitivities and establishing structured mealtime routines are crucial. Behavioral strategies like gradual exposure, positive reinforcement, and modeling can significantly improve food acceptance and mealtime behaviors. Creating a sensory-friendly environment and involving parents in meal planning are essential. This systematic review highlights the importance of multidisciplinary collaboration and tailored interventions to enhance nutritional intake and overall health outcomes for children with ASD.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by challenges in social interaction, communication, and repetitive behaviors. The term "spectrum" reflects the wide variability in challenges and strengths among individuals with autism. Typically diagnosed in early childhood, ASD is identified based on persistent deficits in social communication and interaction, restricted and repetitive patterns of behavior, and significant impairment in daily functioning[1]. According to the Centers for Disease Control and Prevention, approximately 1 in 36 children in the United States is diagnosed with ASD. This prevalence has increased over the past few decades due to improved awareness and diagnostic practices[2].

The etiology of ASD is not fully understood but is believed to result from a complex interplay of genetic and environmental factors. Genetic research has identified numerous genes associated with increased risk, and family studies show that having a sibling with ASD raises the risk for others[3]. Environmental factors, such as advanced parental age, low birth weight, and prenatal exposure to certain drugs, have also been linked to ASD, though no single factor has been definitively proven. Neurologically, individuals with ASD may exhibit differences in brain structure and function, affecting neuronal communication and information processing[4].

Clinically, ASD manifests in a variety of ways. Social communication challenges include difficulty understanding and using verbal and nonverbal communication, maintaining relationships, and sharing interests or emotions. Repetitive behaviors may involve movements like hand-flapping, strict adherence to routines, intense interests, and sensory sensitivities[5]. Many individuals with ASD also experience comorbid conditions such as intellectual disability, attention deficit hyperactivity disorder (ADHD), anxiety disorders, epilepsy, gastrointestinal (GI) issues, and sleep disturbances[6].

Diagnosis of ASD involves a comprehensive evaluation by a multidisciplinary team using developmental history, direct observation, and standardized tools like the autism diagnostic observation schedule and the autism diagnostic interview-revised. While there is no cure for ASD, various interventions can significantly improve the quality of life[7]. Behavioral interventions, such as applied behavior analysis (ABA), social skills training, and cognitive behavioral therapy, are common. Educational interventions include individualized education programs, speech and language therapy, and occupational therapy. Medical interventions often address co-occurring conditions; family support and training are crucial for empowering families to support their loved ones[8].

Understanding the dietary influences on ASD is crucial due to the significant impact diet can have on the health and well-being of individuals with autism. Many people with ASD experience sensory sensitivities that affect their food preferences, leading to limited and repetitive eating patterns, which can result in nutritional deficiencies[9]. Additionally, GI issues, which are common in individuals with ASD, can be influenced by dietary habits and may exacerbate behavioral symptoms[10]. Exploring the relationship between diet and ASD can help identify effective nutritional interventions that may alleviate some of these challenges, improve overall health, and enhance quality of life[11]. This understanding can guide caregivers and healthcare professionals in developing personalized nutrition plans that cater to the unique needs of individuals with ASD, ultimately supporting their physical health, cognitive development, and behavioral regulation. Research into dietary influences also holds the potential to uncover new insights into the underlying mechanisms of ASD, further contributing to the development of comprehensive treatment strategies.

This review seeks to provide an extensive overview of the current literature on nutritional challenges and management in ASD, including GI problems, dietary interventions, vitamins, nutrients, mineral supplements, feeding therapy, and behavioral strategies. By synthesizing evidence from recent studies, this review aims to offer insights into the effectiveness of these approaches and guide clinicians and caregivers in optimizing feeding and nutritional outcomes for children with ASD.

MATERIALS AND METHODS

Study design and literature search strategy

This study employed a systematic approach to synthesize existing literature on feeding therapy, behavioral interventions, and mealtime practices for children with ASD. The review focused on identifying effective strategies and techniques used in clinical settings and research studies to improve feeding behaviors and expand food preferences in this population. A systematic search of electronic databases, including PubMed, Scopus, and PsycINFO, was conducted to identify relevant studies published up to July 2024. The search terms included combinations of keywords such as "autism spectrum disorder," "ASD," "feeding therapy," "behavioral interventions," "mealtime practices," "sensory integration," "oral motor skills," "food selectivity," and "nutritional intake." Only studies published in English and involving children diagnosed with ASD were included.

Selection criteria

Studies were included if they examined feeding therapy interventions, behavioral strategies, or mealtime practices for children diagnosed with ASD, reported outcomes related to improving oral motor skills, sensory integration, food acceptance, or nutritional intake, were peer-reviewed articles, systematic reviews, meta-analyses, clinical trials, or observational studies. Studies were excluded if they focused solely on adults with ASD or other developmental disorders, lacked clear methodology or reported relevant outcomes, and were published in a non-English language.

Data extraction and synthesis and quality assessment

Two independent reviewers screened the titles and abstracts of identified articles based on the selection criteria. Full-text articles were retrieved to assess eligibility further. Data extraction included study design, participant characteristics (age, gender), intervention details (feeding therapy techniques, behavioral strategies), outcomes measured (changes in feeding behaviors, food acceptance, nutritional status), and key findings relevant to the study objectives. The quality of included studies was assessed using appropriate tools such as the Cochrane Collaboration's tool for assessing risk of bias in randomized trials or the Newcastle-Ottawa Scale for observational studies. Studies were evaluated based on criteria including study design, sample size, blinding, outcome measures, and statistical analysis.

Data synthesis and analysis and ethical considerations

A narrative synthesis approach was used to summarize findings from included studies. Key themes and patterns across interventions and outcomes were identified, focusing on effective strategies for improving feeding behaviors and mealtime practices in children with ASD. Quantitative data, when available, were synthesized descriptively or meta-analyzed if studies were homogeneous in methodology and outcomes. Ethical approval was not required since this study involved a review of existing literature. All data were obtained from published studies with proper ethical standards adhered to by the original researchers.

RESULTS

The systematic review identified 316 relevant studies meeting the inclusion criteria. Figure 1 shows the article's flow chart (96 research articles, 177 reviews, 24 systematic reviews, 10 meta-analyses, 6 case reports, and 3 guidelines). The included studies encompassed a variety of study designs, including randomized controlled trials (RCTs), observational studies, and systematic reviews. Participants across studies were primarily children diagnosed with ASD, with ages ranging from early childhood to adolescence. Some studies included specific subgroups based on age, severity of ASD symptoms, or comorbid conditions.

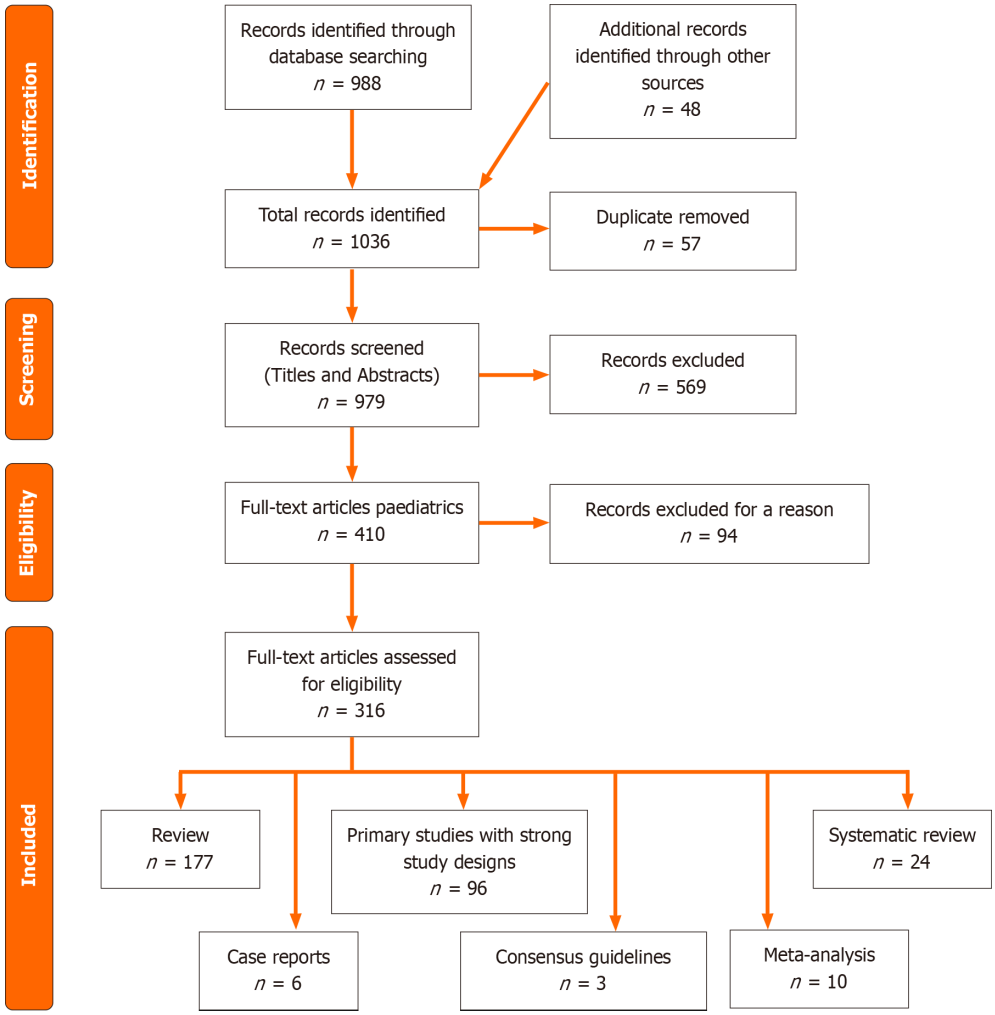

Figure 1 The flow chart of the study.

Several studies focused on improving oral motor skills through structured exercises and sensory-motor activities. Techniques included facial massages, chewing exercises, and tongue stimulation to enhance swallowing and chewing abilities. Feeding therapists utilized sensory integration techniques to address sensory sensitivities related to food textures, tastes, and smells. Gradual exposure and desensitization strategies were commonly employed to increase tolerance to new foods. Behavioral interventions based on ABA principles were widely utilized to modify feeding behaviors. Techniques included reinforcement strategies, task analysis, and shaping to encourage positive eating behaviors and reduce food selectivity. Some studies employed modeling techniques where children observed peers or adults demonstrating appropriate eating behaviors. Social stories were used to prepare children for mealtime routines and promote understanding of expected behaviors.

Establishing consistent meal and snack times was emphasized across studies to provide predictability and reduce anxiety during meals. Visual schedules and timers were used to help children understand mealtime expectations and transitions. Modifications such as soft lighting, non-patterned tableware, and comfortable seating arrangements were implemented to minimize sensory distractions and enhance focus on eating. Many studies reported significant improvements in food acceptance and willingness to try new foods following intervention. Techniques like food chaining and gradual exposure were effective in expanding food preferences. Interventions targeting oral motor skills improved chewing, swallowing, and overall oral coordination among children with ASD. Several studies indicated that effective feeding therapy and mealtime practices improved nutritional outcomes, including increased dietary diversity and nutrient intake. Variability in intervention protocols and outcome measures across studies made direct comparisons challenging. The diversity in participant characteristics and settings also influenced the interpretation of findings.

There was a tendency for studies to report positive outcomes, potentially leading to publication bias. Negative or null findings may be underrepresented in the literature. Studies were assessed for quality using criteria appropriate to their study design, such as the Cochrane Collaboration's risk of bias tool for RCTs or the Newcastle-Ottawa Scale for observational studies. High-quality studies with rigorous methodologies provided more robust evidence of intervention effectiveness. The synthesis of findings highlighted common themes and effective strategies across studies, including the importance of multidisciplinary approaches involving dietitians, speech-language pathologists, occupational therapists, and psychologists. Effective interventions focused on improving oral motor skills, addressing sensory sensitivities, and establishing structured mealtime routines.

DISCUSSION

Sensory sensitivities and food preferences

Individuals with ASD often experience heightened or diminished sensitivity to sensory stimuli, significantly influencing their food choices and eating behaviors. These sensory sensitivities can manifest in various ways. For instance, many individuals with ASD have strong preferences or aversions to specific food textures, leading them to prefer crunchy foods and avoid soft or mushy textures, or vice versa[12]. Sensitivity to smells can cause rejection of foods with strong odors, with even the smell of food being prepared or served nearby becoming overwhelming. Taste sensitivities might make certain flavors intolerable, causing individuals to avoid bitter, sour, or spicy foods and gravitate towards bland or sweet items, resulting in a limited diet lacking variety and essential nutrients[13]. Additionally, the visual appearance of food can influence acceptance, as some individuals are particular about how food is presented, preferring visually appealing foods and avoiding unfamiliar ones. Preferences for food temperature and sensitivity to the sounds associated with eating can also affect what individuals with ASD are willing to consume. These sensory sensitivities often lead to selective eating habits, posing challenges for maintaining a balanced diet and adequate nutrition[14]. Understanding these sensory influences is crucial for developing effective strategies to broaden food acceptance and ensure nutritional adequacy in individuals with ASD.

Individuals with ASD often exhibit distinct food preferences and aversions influenced by their sensory sensitivities, significantly impacting their dietary intake and nutritional status. Commonly, they prefer bland foods with mild flavors, such as plain pasta, rice, bread, and crackers, as well as crunchy or crispy textures found in chips, crackers, and raw vegetables. Sweet and salty foods, including candies, cookies, and snack foods, are also frequently favored[14]. Familiar and predictable foods, particularly specific brands or types of packaged foods, and carbohydrate-rich items like bread, pasta, and potatoes, are often preferred due to their consistency and simplicity. Conversely, individuals with ASD often avoid foods with strong, bitter, spicy, or sour flavors, including spicy dishes, citrus fruits, and certain vegetables[9]. Soft or slimy textures, such as those found in mashed potatoes, bananas, and some cooked vegetables, are frequently rejected, as are mixed textures in dishes like casseroles, stews, or sandwiches due to their sensory complexity[15]. New or unfamiliar foods are commonly resisted, leading to a very limited diet, and foods with potent odors, such as certain cheeses, fish, and cooked cabbage, are typically avoided. These preferences and aversions result in restricted diets that may lack nutritional balance, highlighting the need for caregivers and healthcare professionals to develop strategies to gradually introduce new foods and ensure adequate nutrition for individuals with ASD[11].

The impact of sensory-based food selectivity on nutrition and health in individuals with ASD is profound and multifaceted. Many individuals with ASD exhibit selective eating patterns driven by sensory sensitivities, which often result in a limited variety of accepted foods[16]. This can lead to significant nutritional deficiencies, as essential vitamins, minerals, and dietary fiber may be lacking due to avoidance of certain textures or flavors. Such imbalanced diets, often skewed towards carbohydrates and processed foods that meet sensory preferences, can contribute to weight management issues and increase the risk of chronic diseases like diabetes and cardiovascular conditions[17]. Moreover, inadequate nutrition can impair physical growth and development, particularly concerning bone health and cognitive function in younger individuals. GI problems, such as constipation and diarrhea, are also common and exacerbated by limited dietary variety and fiber intake. Behavioral challenges and emotional well-being may also be affected, with inadequate nutrition potentially contributing to increased anxiety, irritability, and difficulties in mood regulation[10]. Addressing these challenges requires tailored interventions that gradually introduce new foods, modify textures, and incorporate sensory integration techniques to broaden food acceptance and ensure optimal nutrition and overall health for individuals with ASD[18].

GI issues and autism

Prevalence of GI problems in individuals with ASD: The prevalence of GI problems in individuals with ASD is notably higher compared to the general population. Studies and clinical observations indicate that a significant proportion of individuals with ASD experience various GI issues, which can impact their overall health and quality of life[10]. Research suggests that up to 70% of individuals with ASD may have GI symptoms, such as abdominal pain, constipation, diarrhea, bloating, and gastroesophageal reflux disease (GERD). These symptoms are often reported to occur at higher rates and with greater severity in individuals with ASD compared to neurotypical peers[19]. The exact reasons for this elevated prevalence are still under investigation. Still, they may involve factors such as altered gut microbiota, immune system dysregulation, dietary factors, and sensory sensitivities influencing food choices[20].

The presence of GI problems in individuals with ASD can complicate behavioral management and may exacerbate core symptoms of autism, such as communication difficulties and repetitive behaviors[21]. Addressing GI issues is crucial for improving the overall well-being and quality of life of individuals with ASD. This often involves a multidisciplinary approach that includes healthcare providers specializing in both autism and gastroenterology, along with dietary interventions and behavioral strategies tailored to the unique needs of each individual[10]. Continued research into the underlying mechanisms and effective treatments for GI problems in ASD is essential for developing targeted interventions and improving outcomes for this population.

Types of GI issues commonly observed: Several GI issues are commonly observed in individuals with ASD, significantly impacting their overall health and well-being. Constipation is a prevalent concern, characterized by infrequent bowel movements and discomfort, often leading to abdominal pain and changes in appetite[10]. Conversely, diarrhea, marked by loose or watery stools, can also occur, potentially causing dehydration and nutrient malabsorption if persistent[10]. GERD is another common problem in patients with autism, where stomach acid or bile refluxes into the esophagus, causing heartburn, regurgitation, and difficulty swallowing[22]. Abdominal pain is frequently reported and may stem

from constipation, food intolerances, or inflammation. Bloating, characterized by abdominal discomfort and distension, is also common and may be related to dietary factors or impaired digestion[23]. Many individuals with ASD experience food intolerances or sensitivities, often to gluten or dairy, which can exacerbate GI symptoms. Feeding difficulties, such as selective eating patterns or swallowing issues, further complicate nutritional intake and digestive health management [11]. Inflammatory bowel diseases (IBD) like Crohn's disease or ulcerative colitis, though less common, can also occur in individuals with ASD, necessitating careful monitoring and treatment by healthcare professionals specializing in both autism and gastroenterology[24]. Understanding and addressing these GI issues are crucial for improving the quality of life and health outcomes of individuals with ASD, often requiring tailored interventions that consider their unique sensory and dietary needs.

Constipation: Constipation is a prevalent GI issue among individuals with ASD, affecting a significant number of those diagnosed. It is characterized by infrequent bowel movements and difficulty passing stools, often resulting in abdominal discomfort or pain[25]. Several factors contribute to constipation in individuals with ASD, including sensory sensitivities that affect food choices and dietary habits. Many individuals with ASD have selective eating patterns, preferring certain textures or avoiding foods high in fiber, such as fruits, vegetables, and whole grains, which are essential for regular bowel movements[10]. Additionally, factors like reduced physical activity, inadequate fluid intake, and side effects from medications commonly used to manage symptoms associated with ASD can further exacerbate constipation[26]. Addressing constipation in individuals with ASD requires a multidisciplinary approach involving healthcare providers, including gastroenterologists and dietitians, who specialize in understanding the unique needs and challenges of individuals on the autism spectrum. Management typically includes dietary adjustments to increase fiber intake, hydration strategies, promoting physical activity, and, when necessary, medications to alleviate symptoms and improve bowel function. Regular monitoring and proactive management of constipation are essential to minimize discomfort, promote GI health, and enhance overall well-being in individuals with ASD[10].

Diarrhea: Diarrhea, though less frequently discussed compared to constipation, is a GI issue that can affect individuals with ASD. Characterized by loose, watery stools, diarrhea can lead to dehydration and electrolyte imbalances if not managed promptly[10]. Several factors contribute to diarrhea in individuals with ASD, including sensory sensitivities that influence dietary preferences and aversions, potentially affecting digestive health[27]. Food sensitivities or intolerances, such as reactions to gluten or dairy products, are also common triggers for GI symptoms like diarrhea. Additionally, medications prescribed to manage symptoms associated with ASD may have side effects that include GI disturbances. Anxiety or stress, which can be heightened in individuals with ASD, may further impact gut function and contribute to diarrhea episodes[10]. Managing diarrhea involves identifying and addressing these underlying factors, including dietary adjustments, hydration strategies, and potentially modifying medications under the guidance of healthcare providers. Monitoring and proactive management are essential to minimize discomfort, promote GI health, and improve overall well-being in individuals with ASD affected by diarrhea[10].

Abdominal pain: Abdominal pain is a significant issue affecting many individuals with ASD, impacting their daily lives and overall well-being. Commonly experienced as recurrent or chronic discomfort, abdominal pain in individuals with ASD can stem from various factors. These include GI issues such as constipation, diarrhea, bloating, and GERD, often exacerbated by dietary preferences and sensory sensitivities[10]. Sensitivities to certain foods, like gluten or dairy, can also contribute to abdominal discomfort. Additionally, heightened levels of anxiety or stress, frequently observed in individuals with ASD, may manifest physically as abdominal pain[25]. Sensory sensitivities can further intensify the experience of pain, making individuals more sensitive to discomfort in the abdominal region. Communication challenges can complicate diagnosis and treatment, requiring caregivers and healthcare providers to rely on behavioral cues and careful observation to address underlying issues effectively[28]. Managing abdominal pain in individuals with ASD involves a holistic approach that includes addressing GI health, managing dietary sensitivities, promoting strategies to reduce anxiety, and ensuring effective communication to improve overall quality of life. Regular monitoring and collaboration with healthcare professionals specializing in ASD and gastroenterology are essential for developing personalized management plans that address the unique needs of individuals affected by abdominal pain[10].

Potential links between GI issues and dietary habits: There are several potential links between GI issues and dietary habits in individuals with ASD, underscoring the intricate relationship between diet and digestive health. Many individuals with ASD have sensory sensitivities that influence their food preferences and aversions. These preferences often lead to selective eating habits, where individuals may avoid foods with certain textures, flavors, or appearances that trigger discomfort or sensory overload[14]. This selective eating can limit dietary variety and potentially lead to nutritional deficiencies or imbalances contributing to GI issues. Individuals with ASD commonly experience food sensitivities or allergies, particularly to gluten, dairy, and artificial additives. These sensitivities can provoke GI symptoms such as abdominal pain, bloating, diarrhea, or constipation[29]. Managing these sensitivities through dietary modifications is crucial for alleviating GI discomfort and improving overall digestive health.

Emerging research suggests that individuals with ASD may have alterations in gut microbiota composition compared to neurotypical individuals. These microbial imbalances can influence digestion, immune function, and inflammation levels, potentially contributing to GI symptoms such as irritable bowel syndrome or IBD[30]. Diet plays a significant role in shaping gut microbiota composition, with dietary habits affecting microbial diversity and function. Selective eating habits and restricted diets common in individuals with ASD can result in nutritional deficiencies, such as insufficient fiber intake, vitamins, and minerals. These deficiencies may exacerbate GI issues like constipation or affect overall digestive function and health[31].

Medications commonly prescribed to manage symptoms associated with ASD, such as antipsychotics or stimulants, can have side effects that impact GI function. These may include constipation, diarrhea, or changes in appetite, necessitating dietary adjustments or additional interventions to mitigate these effects[10]. Understanding these potential links between dietary habits and GI issues is essential for developing effective management strategies tailored to the unique needs of individuals with ASD. Integrating nutritional counseling, monitoring dietary intake, addressing food sensitivities, and promoting a balanced diet are critical components of supporting digestive health and overall well-being in this population[32].

Effects of GI problems on behavior and overall well-being: GI problems can have significant effects on behavior and overall well-being in patients with ASD, influencing various aspects of their daily lives. GI issues can exacerbate behavioral symptoms commonly associated with ASD, such as irritability, agitation, and increased repetitive behaviors [33]. Discomfort or pain from GI symptoms may lead to heightened levels of distress and difficulty in self-regulation, contributing to behavioral outbursts or withdrawal. Individuals with ASD often face challenges in communicating their discomfort or pain verbally, making it difficult for caregivers and healthcare providers to identify and address underlying GI issues promptly, potentially prolonging distress and behavioral difficulties[34]. Persistent GI symptoms, such as abdominal pain, bloating, constipation, or diarrhea, can significantly impact the overall quality of life for individuals with ASD. These symptoms may affect sleep patterns, appetite, social interactions, and participation in daily activities, leading to decreased enjoyment and engagement in their surroundings[35]. Severe or chronic GI problems can interfere with daily functioning, including disruptions in eating habits, difficulty attending school or work, and reduced participation in recreational activities. Managing GI symptoms effectively is crucial for optimizing daily functioning and promoting independence in individuals with ASD[23].

The discomfort and unpredictability of GI symptoms can contribute to heightened anxiety, stress, or mood disturbances in individuals with ASD. Addressing GI issues improves physical health and supports emotional well-being and overall mental health resilience[36]. GI symptoms may affect social interactions and participation in community settings, as individuals with ASD may experience discomfort or embarrassment related to their symptoms. Managing GI health can enhance social engagement and improve overall social functioning[37]. Recognizing and addressing the impact of GI problems on behavior and well-being in individuals with ASD requires a comprehensive approach that includes regular monitoring, proactive management of symptoms, and collaboration among caregivers, healthcare providers, and specialists in autism and gastroenterology. Tailored interventions, such as dietary modifications, behavioral therapies, and medications, when necessary, can help alleviate GI symptoms, improve overall comfort, and enhance the quality of life for individuals with ASD affected by GI issues[38].

Nutritional deficiencies and ASD

Common nutritional deficiencies in individuals with ASD: Individuals with ASD often experience nutritional deficiencies that can impact their overall health and well-being. Here's a comprehensive review focusing on common deficiencies in vitamins, minerals, and essential fatty acids (EFAs) observed in individuals with ASD. Vitamin D deficiency is prevalent among individuals with ASD due to several factors. Many individuals with ASD may have limited outdoor activities or sunlight exposure, reducing their body's ability to synthesize Vitamin D[39]. Selective eating habits and aversions to certain foods, such as dairy products or fortified cereals, can further limit Vitamin D intake. Some individuals with ASD may have altered metabolism or absorption patterns that affect Vitamin D levels. Vitamin D deficiency can impact bone health and immune function and may exacerbate behavioral symptoms associated with ASD [16].

B vitamins are critical in neurological function, energy metabolism, and overall health. Deficiencies in B vitamins, particularly B6 (pyridoxine), B12 (cobalamin), and folate (B9), are commonly observed in individuals with ASD. Limited intake of sources rich in B vitamins, such as meats, leafy greens, and fortified grains, due to selective eating patterns or food sensitivities[40]. Increased metabolic demands or altered metabolism in individuals with ASD may contribute to B vitamin deficiencies. B vitamin deficiencies can affect neurotransmitter synthesis and function, potentially influencing mood, behavior, and cognitive abilities in individuals with ASD. Additional vitamin deficiencies in individuals with ASD include vitamins A, E, and C. Vitamin A is essential for vision, immune function, and cellular growth[6]. Dietary restrictions or selective eating habits may contribute to Vitamin A deficiency. Vitamin E Acts as an antioxidant and supports immune function. Individuals with ASD may have a limited intake of sources like nuts, seeds, and vegetable oils. Vitamin C is important for immune function and collagen synthesis. Limited intake of fruits and vegetables rich in Vitamin C may contribute to deficiencies[41].

Mineral disorders, especially for zinc, iron, and calcium, in patients with ASD are commonly observed and can significantly impact their health and well-being. Zinc is crucial in immune function, protein synthesis, and wound healing. Zinc deficiency is prevalent among individuals with ASD due to several factors[42]. Dietary restrictions and selective eating patterns or food aversions may lead to inadequate intake of zinc-rich foods such as meats, shellfish, nuts, and seeds. Individuals with ASD may experience GI problems that impair zinc absorption, exacerbating deficiency. Some individuals with ASD may have increased metabolic demands or higher losses of zinc due to medications or other factors [43].

Iron is essential for oxygen transport in the blood, energy metabolism, and cognitive development. Iron deficiency anemia is commonly reported in individuals with ASD. Limited consumption of iron-rich foods like red meat, poultry, beans, and fortified cereals can contribute to iron deficiency[44]. Digestive problems such as constipation or diarrhea may affect iron absorption and contribute to deficiency. In addition, preferences for certain textures or flavors may restrict dietary diversity and lead to insufficient iron intake. Magnesium is involved in hundreds of biochemical reactions in the body, including muscle and nerve function, energy production, and bone health. Imbalances in magnesium levels,

including both deficiency and excess, have been observed in individuals with ASD[45]. Inadequate intake of magnesium-rich foods such as nuts, seeds, whole grains, and leafy greens due to dietary restrictions or preferences. Similar to zinc and iron, GI problems may affect magnesium absorption and contribute to imbalances. Magnesium deficiency or imbalance can impact neurological function and may exacerbate behavioral symptoms in individuals with ASD[46]. Calcium is crucial for bone health, muscle function, and nerve transmission. Individuals with ASD may have insufficient calcium intake. They avoid dairy products, a primary source of calcium, due to lactose intolerance or sensory issues. Calcium deficiency can affect bone density and increase the risk of osteoporosis or fractures, especially as individuals with ASD age[47].

EFA, particularly omega-3 and omega-6 fatty acids, play crucial roles in brain function, inflammation regulation, and overall health. Disorders related to EFAs are often observed in patients with ASD, impacting their cognitive, behavioral, and physical well-being[48]. Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential for brain development, cognitive function, and reducing inflammation[49]. They are primarily found in fatty fish, flaxseeds, walnuts, and chia seeds. Individuals with ASD often have lower levels of omega-3 fatty acids due to selective eating habits that exclude omega-3-rich foods or metabolic differences affecting the synthesis and utilization of these fatty acids[50]. Omega-3 deficiencies are associated with various cognitive and behavioral issues in individuals with ASD, including difficulties with attention, hyperactivity, and social interactions. These fatty acids are crucial for synaptic function and neuronal communication, and deficiencies can exacerbate symptoms of ASD[51].

Omega-6 fatty acids, such as linoleic acid (LA) and arachidonic acid (AA), are important for immune function and inflammation regulation and are found in vegetable oils, nuts, and seeds. While necessary for health, an imbalance between omega-6 and omega-3 fatty acids is common in individuals with ASD[52]. A diet high in omega-6 but low in omega-3 can promote inflammation and negatively affect brain function and behavior. Addressing EFA disorders involves increasing the intake of omega-3-rich foods and reducing the consumption of omega-6-rich processed foods and vegetable oils to balance the ratio of omega-6 to omega-3 fatty acids[53]. Omega-3 supplements, such as fish oil or algae-based supplements, can effectively increase EPA and DHA levels in individuals with ASD. It is important to choose high-quality supplements and follow recommended dosages under the guidance of healthcare providers[54]. Regular monitoring of fatty acid levels through blood tests can track the effectiveness of dietary and supplementation interventions, with adjustments made based on individual responses and progress.

Consequences of nutritional deficiencies on physical and cognitive health: Nutritional deficiencies can have profound consequences on the physical and cognitive health of patients with ASD. These deficiencies, often stemming from selective eating habits, sensory sensitivities, and GI issues, can exacerbate the core symptoms of ASD and lead to additional health complications.

Physical health consequences: Nutritional deficiencies can impair physical growth and development. For example, deficiencies in essential vitamins and minerals like Vitamin D, calcium, and zinc can lead to poor bone health, increasing the risk of fractures and osteoporosis[55]. Inadequate intake of essential nutrients can also hinder muscle development and overall physical growth. Deficiencies in vitamins such as A, C, D, and E and minerals like zinc and iron can weaken the immune system. This can make individuals with ASD more susceptible to infections and illnesses, potentially leading to frequent health complications and extended recovery times[56]. Nutritional deficiencies can exacerbate existing GI problems, such as constipation, diarrhea, and abdominal pain. These issues are common in individuals with ASD and can be both a cause and consequence of poor nutrition, creating a challenging cycle to break[10]. Iron deficiency anemia, common in individuals with ASD, can lead to fatigue and low energy levels. This can affect their ability to engage in daily activities, participate in physical exercise, and maintain overall vitality[57].

Cognitive health consequences: Essential nutrients like omega-3 fatty acids, B vitamins, and iron play crucial roles in brain function. Deficiencies in these nutrients can impair cognitive processes such as attention, memory, and executive function. For example, omega-3 fatty acids are vital for synaptic function and neuronal communication, and their deficiency can affect cognitive performance and developmental outcomes[58]. Nutritional deficiencies can exacerbate behavioral symptoms associated with ASD. Deficiencies in omega-3 fatty acids and B vitamins have been linked to increased hyperactivity, irritability, and aggression. Iron deficiency can lead to cognitive and behavioral disturbances, impacting mood and increasing the severity of ASD symptoms[59]. Nutritional deficiencies can contribute to mental health issues such as anxiety and depression. For instance, deficiencies in B vitamins, particularly B6, B12, and folate, can affect neurotransmitter synthesis and regulation, influencing mood and emotional stability. A well-balanced diet with adequate nutrients is essential for maintaining mental health and emotional well-being[60].

Strategies to address and prevent nutritional deficiencies in individuals with autism: Nutritional deficiencies are common among individuals with ASD, so addressing and preventing them requires a comprehensive, multidisciplinary approach that involves healthcare providers, dietitians, caregivers, and behavioral therapists[11]. Various strategies could effectively address these nutritional deficiencies. First, we should do a comprehensive nutritional assessment. These deficiencies could be initially assessed through dietary assessments to identify nutrient gaps and eating patterns[61]. Physicians could utilize food diaries, questionnaires, and interviews with caregivers to gather detailed information on dietary intake. Some laboratory tests could help check for deficiencies in essential vitamins and minerals such as vitamin D, B vitamins, iron, zinc, and fatty acids and monitor biomarkers of nutritional status to adjust interventions accordingly [62].

Secondly, physicians should tailor the dietary interventions according to the initial assessment and initiate personalized meal plans. They can develop individualized meal plans that address specific nutritional needs while considering food preferences and sensory sensitivities[63]. They may introduce nutrient-dense foods gradually to increase acceptance

and encourage a diverse diet that includes a range of fruits, vegetables, whole grains, lean proteins, and healthy fats. The caregivers are advised to use creative presentations and recipes to make foods more appealing. Thirdly, behavioral and sensory-based strategies could help support nutritional management[12]. New foods and textures can be slowly introduced new foods to reduce sensory aversions. Parents can pair preferred foods with new or less preferred items to increase acceptance[64]. They can use rewards and praise to encourage them to try and consume new foods. Parents should try their best to create a positive mealtime environment to reduce anxiety and stress related to eating. Sensory integration therapy can help desensitize individuals and become more comfortable with different textures, tastes, and smells. In addition, occupational therapists can provide specialized support to address sensory processing issues[65].

Targeted nutritional supplementation is another crucial step in the management. The patients should be supplemented with vitamins and minerals that are difficult to obtain through diet alone, such as Vitamin D, B vitamins, iron, zinc, and omega-3 fatty acids[66]. Supplements should also be in forms that are easy to ingest and well-tolerated (*e.g.*, liquids, chewable). Supplements should be provided in the appropriate dosages and monitored for potential interactions or side effects, with regular review and adjustment of the supplementation plans based on ongoing assessments[67]. Addressing, identifying, and managing GI problems such as constipation, diarrhea, and abdominal pain that can affect nutrient absorption is paramount. Patients can use probiotics, fiber supplements, or medications as healthcare providers recommend to improve digestive health[68]. Diets should be adjusted to include high-fiber foods to support healthy digestion. In addition, patients should avoid foods that exacerbate GI symptoms and consider elimination diets if food intolerances or allergies are suspected[69].

Nutritional education is another essential corner of proper dietary management. Caregivers should receive information on balanced nutrition, portion sizes, and healthy eating habits. They should be educated on the importance of consistency and patience in implementing dietary changes[70]. Caregivers should be provided with practical tips for meal planning, grocery shopping, and preparing meals that meet the nutritional needs of individuals with ASD. They also need to share strategies for managing mealtime behaviors and reducing the stress around eating. Other pillars of management are ongoing monitoring and follow-up. Regular follow-up appointments should be scheduled to monitor nutritional status, growth, and overall health[71]. Dietary and supplementation plans can be adjusted based on changes in nutritional needs and intervention responses. Addressing and preventing nutritional deficiencies in individuals with ASD requires a comprehensive, individualized approach that combines dietary interventions, behavioral strategies, supplementation, and ongoing support[72]. By leveraging a multidisciplinary team and continuously monitoring and adjusting plans, healthcare providers and caregivers can significantly improve the nutritional status, overall health, and quality of life of individuals with ASD.

Nutrition assessment of individuals diagnosed with autism

A thorough nutritional assessment is crucial for individuals with ASD due to the high prevalence of feeding difficulties, dietary restrictions, and GI issues in this population. Proper nutritional assessment can help identify deficiencies, guide dietary interventions, and improve overall health outcomes. Tailored dietary interventions, regular monitoring, and interdisciplinary collaboration can significantly enhance nutritional status and overall quality of life[73]. The initial step is dietary history, followed by anthropometric assessment, complete clinical examination, evaluation of GI function, and biochemical assessment. A comprehensive nutritional assessment is essential for individuals with ASD to address the unique challenges and optimize their health and development. Tailored dietary interventions, regular monitoring, and interdisciplinary collaboration can significantly enhance nutritional status and overall quality of life[74].

Dietary and medical history: Many individuals with ASD exhibit strong preferences and aversions for certain textures, colors, and types of food, often leading to a limited diet. Physicians can assess dietary records using a 3-day food record to analyze dietary intake and guide recommendations. Assessment of mealtime and feeding behaviors, such as refusal to eat certain foods, prolonged mealtimes, or disruptive behaviors, is a crucial step in nutritional assessment[75]. To assess nutrient adequacy, physicians should also obtain a detailed record of daily food and beverage intake, including portion sizes. They should also get information on any special diets, such as gluten-free, casein-free, or other therapeutic diets. Generally, carbohydrate and fat requirements are met, but fiber intake is often suboptimal. Protein intake may be sufficient if dairy is included; otherwise, non-dairy proteins are assessed. Common deficiencies include vitamin A, calcium, D, E, pantothenic acid, vitamin K, and zinc. Special attention is needed for children on gluten-free, casein-free diets, as many gluten-free foods are not fortified[76].

GI issues like constipation, diarrhea, abdominal pain, and reflux should be documented when present. Assessment of gut microbiota and potential dysbiosis helps address the defects that open the door for better treatment[23]. Medication history is also of paramount importance, as many medications used by individuals with autism could induce nutritional assessment. For example, ADHD medications can affect appetite negatively, anticonvulsants can cause nausea, vomiting, diarrhea, and decreased levels of vitamin D and calcium due to osteoclastic activity, and atypical antipsychotics may lead to increased appetite, weight gain, and glucose intolerance[77].

Laboratory values from the primary care physician are essential when assessing a child being evaluated for or already diagnosed with ASD. Lead levels are frequently measured when a developmental disability is suspected, as high serum levels are associated with mental retardation[78]. Iron deficiency anemia is a common risk factor in children with developmental disabilities, necessitating baseline ferritin level checks and ongoing monitoring if iron therapy is initiated [79]. Serum cholesterol levels are also of interest due to the correlation between low cholesterol and a positive ASD diagnosis. This correlation is related to the physiological milieu of autism rather than nutrition[80]. Biochemical assessment includes blood tests for nutrient levels such as vitamins D, B12, folate, minerals like iron and zinc, and EFAs. Urine tests evaluate metabolic markers and nutrient excretion[81].

Anthropometric assessment: Anthropometric assessment is the second step in nutritional assessment. Regular monitoring is crucial to tracking growth patterns and identifying potential undernutrition or obesity. Body mass index is calculated and interpreted according to age-specific percentiles to help identify underweight and malnutrition[82]. Measuring head circumference in younger children helps to monitor brain development and growth. Triceps and subscapular skinfolds and arm circumference are other important anthropometric measures that help identify malnutrition. Recumbent measurements should be taken for younger children (0-36 months). In older children (6-10 years), metacarpal morphometry or dual-energy X-ray absorptiometry may be used to assess bone health[83].

Clinical assessment: Recording the patient's medical history helps review medical conditions, including GI disorders, allergies, and metabolic issues. Then, a thorough physical examination can help detect signs of nutrient deficiencies or excesses, such as skin changes, hair loss, or dental problems. Signs of vitamin D deficiency may include rickets, bone pain, and muscle weakness. Iron deficiency may be manifested in anemia, fatigue, and poor concentration[84]. Zinc deficiency may induce growth retardation, impaired immune function, and skin rashes. Furthermore, omega-3 deficiency may initiate cognitive and behavioral issues, dry skin, and cardiovascular problems[84].

Feeding skills: Evaluation of oral-motor deficits such as weak suck, tongue thrust, poor lip closure, and oral tactile sensitivity is of paramount importance. Feeding skills may be assessed by a multidisciplinary team, including a dietitian, occupational therapist, speech pathologist, pediatric psychologist, and pediatrician[85]. Table 1 compares the feeding developmental milestones in children with typical development *vs* those with autism[86-88].

Dietary interventions and therapies

Specific dietary intervention may be beneficial in some individuals with autism, particularly in managing GI symptoms and certain behavioral issues. Dietary interventions and therapies play a crucial role in managing and improving the health and well-being of individuals with ASD[89]. These interventions aim to address common nutritional deficiencies, GI issues, and selective eating habits often observed in patients with autism. By tailoring dietary plans to meet the unique needs of individuals with ASD, healthcare providers can help alleviate some of the core symptoms and associated health problems[10]. Figure 2 shows the general effects of dietary therapy in children with ASD. Nutritional therapies may include specialized diets, such as gluten- or casein-free diets, ketogenic diets (KD), and specific carbohydrate diets (SCD), which some believe can reduce behavioral symptoms and GI distress[90]. Supplementation with essential nutrients like vitamins, minerals, and omega-3 fatty acids can address specific deficiencies and support overall health. Additionally, incorporating behavioral strategies, such as gradual exposure to new foods and positive reinforcement, can improve food acceptance and mealtime behaviors[91]. Other dietary management approaches might include elimination diets to identify and remove potential allergens or irritants and probiotics to enhance gut health. Through a comprehensive and personalized approach, nutritional interventions can support better physical health, cognitive function, and overall quality of life for individuals with autism[92].

Gluten-free diet: Gluten-free diet (GFD) is a popular but controversial intervention for individuals with autism. While some parents and practitioners report positive outcomes, the scientific community calls for more rigorous research to substantiate these claims. This diet eliminates gluten, wheat, barley, and rye protein from the patient's diet[93]. While some parents and practitioners report positive outcomes, others deny any noticeable effect. Proponents of the GFD for autism believe it can alleviate certain symptoms associated with the disorder, particularly GI issues and behavioral symptoms[94].

The rationale for a GFD in autism: Some researchers and clinicians propose that individuals with autism may have an increased sensitivity to gluten, which could exacerbate their symptoms (Theory of Gluten Sensitivity). This sensitivity may be due to an abnormal immune response or an inability to digest gluten properly. The gut-brain axis theory suggests that GI dysfunctions can influence brain function and behavior[93]. Gluten, as a potential irritant to the gut lining, could contribute to inflammation and increased intestinal permeability (often referred to as "leaky gut"), leading to the release of peptides that affect brain function and behavior in individuals with ASD[95]. Additionally, the opioid excess theory posits that incomplete digestion of gluten can produce peptides with opioid-like activity, which can cross the blood-brain barrier and affect neurotransmission, potentially leading to the exacerbation of autistic symptoms[96].

Implementation of a GFD: Before starting a GFD, it is essential to conduct a thorough assessment to determine if there is a potential gluten sensitivity or celiac disease[97]. This may involve blood tests, endoscopic evaluations, and consultations with a gastroenterologist. Transitioning to a GFD requires careful planning to ensure nutritional adequacy. This involves identifying and eliminating all sources of gluten from the diet, including obvious sources like bread, pasta, and cereals, as well as hidden sources in processed foods, sauces, and condiments[98]. To maintain a balanced diet, the patients can use gluten-free substitutes such as rice, quinoa, gluten-free oats, and specially formulated gluten-free products. It is important to choose nutrient-dense options to avoid potential nutrient deficiencies. Regular monitoring by a healthcare provider or dietitian is crucial to assess the diet's impact on symptoms and overall health. Support from caregivers and educators can also help ensure diet adherence[99].

Benefits of a GFD: Some individuals with ASD who follow a GFD report improvements in GI symptoms such as diarrhea, constipation, and abdominal pain. Improved gut health can contribute to overall well-being and comfort[10]. Anecdotal reports and some preliminary studies suggest that a GFD may improve behavior, attention, and social interactions. Parents and caregivers have observed reduced hyperactivity, irritability, and repetitive behaviors. For some individuals with ASD, adhering to a GFD can lead to enhanced quality of life due to better health and symptom

Table 1 Feeding development in children with normal development vs. those with autism

Age range	Normal feeding development	Feeding development in children with autism
0-6 months	Suck-swallow reflexes are well-developed; begins to coordinate sucking, swallowing, and breathing during feeding	May exhibit weak suck, poor coordination of sucking and swallowing, or difficulties breastfeeding
6-12 months	Introduced to pureed foods; begins to develop pincer grasp for self-feeding; starts to handle a variety of textures	It may show oral tactile sensitivity or gagging, a preference for smooth, pureed foods, and delays in self-feeding skills
12-18 months	Progresses to more textured foods; begins to use utensils; starts to drink from a cup	Persistent preference for purees; resistance to textured foods; may continue using a bottle; difficulty using utensils
18-24 months	Eats a variety of foods; able to chew a wide range of textures; uses a spoon and fork more efficiently	Limited food variety; preference for specific textures or types of food; may have incomplete mastication and occasional choking
2-3 years	Further develops chewing skills; eats most family foods; drinks from an open cup; uses utensils independently	Continued rigidity with food choices; may insist on specific foods or avoid entire food groups; ongoing issues with chewing and swallowing
3-4 years	Expands diet to include more complex textures; shows improved self-feeding skills; less picky eating	Persistent selective eating; might insist on using a bottle or refuse sippy cup; difficulty with mixed textures
4-5 years	Eats a wide range of foods; improved social eating behaviors; uses utensils proficiently	Ongoing rigidity with food variety and textures; may still prefer smooth or specific-textured foods; potential social eating challenges
5+ years	Generally eats a varied diet, participates in family meals, fewer food-related issues	Continues to display selective eating patterns; may require feeding therapy; potential need for specialized diets to meet nutritional needs

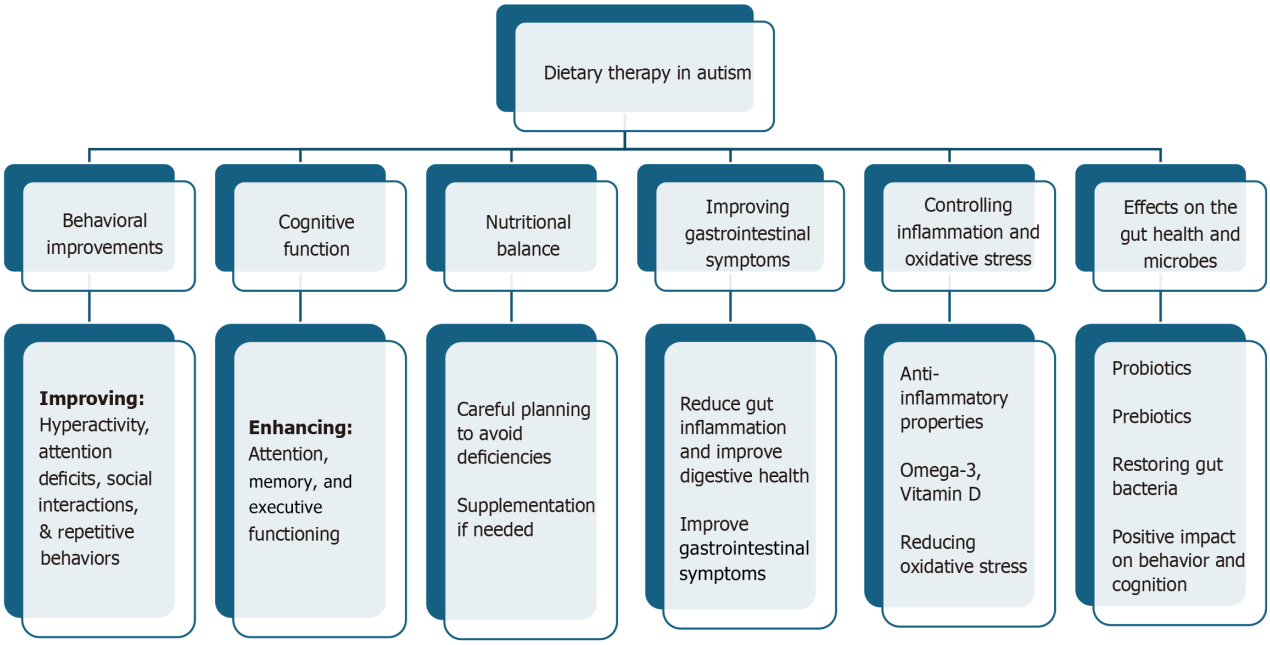

Figure 2 The general effects of dietary therapy in children with autism spectrum disorders.

management. This can translate to improved daily functioning and engagement in activities[100].

Challenges and considerations: The evidence supporting the efficacy of a GFD for autism is mixed. While some studies and anecdotal reports suggest benefits, it's crucial to note that large-scale, RCTs are needed to establish clear clinical guidelines. A GFD can lead to potential nutritional deficiencies, especially if not well-planned. Individuals on this diet may lack essential nutrients such as fiber, iron, calcium, and B vitamins, commonly found in gluten-containing grains [101]. Strict adherence to a GFD can be challenging, particularly in social settings like schools, parties, and restaurants. This can lead to social isolation or difficulty maintaining a long-term diet[97]. Gluten-free products can be more expensive and less accessible than their gluten-containing counterparts. This can create financial and logistical challenges for families and individuals trying to adhere to the diet[102]. Therefore, being well-informed about a GFD's potential challenges and benefits is essential.

Casein-free diet

The casein-free diet is a dietary intervention that some individuals with autism may find beneficial, particularly in

managing GI symptoms and specific behavioral issues. It involves eliminating casein, a protein found in dairy products [94]. However, the scientific evidence supporting its efficacy is inconclusive, and the diet may not suit everyone. Like the GFD, the casein-free diet is based on theories that suggest a link between dietary proteins and autism symptoms[103].

Rationale for casein-free diet in autism: Some individuals with autism may have an increased sensitivity or allergy to casein. This can lead to GI issues and inflammation, which might exacerbate autism symptoms[35]. Similar to gluten, casein can break down into peptides with opioid-like activity (casomorphins) during digestion. These peptides can potentially cross the blood-brain barrier, influencing brain function and behavior in individuals with ASD[104]. The gut-brain axis theory also suggests that gut health that significantly impacts brain function could be affected by casein. Casein, as a potential irritant to the gut, may contribute to increased intestinal permeability ("leaky gut"), releasing harmful substances that affect the brain and behavior[105].

Implementation of a casein-free diet: Before starting a casein-free diet, it is essential to conduct a thorough assessment to identify potential casein sensitivity or allergy. This may involve skin prick tests, blood tests for IgE antibodies, and consultations with an allergist or gastroenterologist. Transitioning to a casein-free diet requires careful planning to ensure nutritional adequacy. It eliminates all casein sources, including milk, cheese, yogurt, butter, and other dairy products, and hidden sources in processed foods[106]. The caregivers can use casein-free substitutes such as almond milk, soy milk, rice milk, coconut milk, and casein-free cheese alternatives to maintain a balanced diet. It is crucial to choose fortified options to ensure adequate intake of nutrients typically provided by dairy[107]. Regular monitoring by a healthcare provider or dietitian is vital to assess the diet's impact on symptoms and overall health. Support from caregivers and educators is also essential to ensure adherence to the diet.

Benefits of casein-free diet: Some individuals with ASD who follow a casein-free diet report improvements in GI symptoms such as diarrhea, constipation, and abdominal pain. Improved gut health can contribute to overall well-being and comfort[10]. Anecdotal reports and preliminary studies suggest that a casein-free diet may improve behavior, attention, and social interactions. Parents and caregivers have observed reduced hyperactivity, irritability, and repetitive behaviors[100]. For some individuals with ASD, adhering to a casein-free diet can lead to enhanced quality of life due to better health and symptom management. This can translate to improved daily functioning and activity engagement[108].

Challenges and considerations: The evidence supporting the efficacy of a casein-free diet for autism is mixed. While some studies and anecdotal reports suggest benefits, large-scale, RCTs are needed to establish clear clinical guidelines. A casein-free diet can lead to potential nutritional deficiencies, especially if not well-planned. Individuals on this diet may lack essential nutrients such as calcium, vitamin D, and protein, commonly found in dairy products[109]. Strict adherence to a casein-free diet can be challenging, particularly in social settings like schools, parties, and restaurants. This can lead to social isolation or difficulties in maintaining the diet long-term. Casein-free products can be more expensive and less accessible than their dairy-containing counterparts. This can create financial and logistical challenges for families and individuals trying to adhere to the diet[110].

Current state of scientific evidence: Studies on the casein-free diet for autism have produced mixed results. Some research suggests improvements in GI health and behavioral symptoms, while other studies find no significant benefits [94,111]. The variability in individual responses highlights the need for personalized approaches[110]. More rigorous, large-scale, RCTs are needed to establish the effectiveness of the casein-free diet in managing autism symptoms. Future research should also explore the underlying mechanisms that might explain why some individuals with ASD benefit from this diet. Given the mixed evidence, the casein-free diet should be considered case-by-case. Healthcare providers should work closely with families to assess potential benefits and risks, ensuring that dietary changes are safe and nutritionally adequate. As scientific evidence supporting its efficacy is inconclusive, consulting with healthcare professionals before starting a casein-free diet is crucial to ensure it is implemented safely and effectively, considering both potential benefits and challenges.

KD

The KD is a promising but still experimental intervention for individuals with autism. The KD is a high-fat, low-carbohydrate, and moderate-protein diet. It has been used for nearly a century primarily to treat refractory epilepsy[112]. Recently, it has gained attention as a potential intervention for various neurological and neurodevelopmental disorders, including ASD. While some individuals may experience significant improvements in behavior, cognitive function, and overall health, others may not see substantial benefits[113].

Rationale for KD in autism: The KD produces ketones, which serve as an alternative energy source for the brain. Ketones have neuroprotective properties, including reducing oxidative stress and inflammation and improving mitochondrial function, which may benefit individuals with ASD[114]. The diet may also help restore the balance between excitatory (glutamate) and inhibitory gamma-aminobutyric acid (GABA) neurotransmitters in the brain. This balance is often disrupted in individuals with ASD, leading to symptoms such as hyperactivity and seizures[115]. The KD may positively influence the gut microbiota, reducing GI issues and improving gut health. Since the gut-brain axis plays a significant role in ASD, these improvements can potentially impact behavior and cognitive function. Abnormal energy metabolism has been observed in individuals with ASD. The KD enhances mitochondrial function and energy production, which could alleviate some metabolic dysfunctions associated with autism[116].

Implementation of a KD: A thorough medical evaluation is necessary before starting the KD. This includes assessing baseline nutritional status, metabolic health, and potential contraindications such as metabolic disorders or pancreatitis

[112]. The KD typically involves a macronutrient ratio of approximately 70%-80% fat, 10%-20% protein, and 5%-10% carbohydrates. Meals must be planned carefully to meet these ratios while ensuring nutritional adequacy. Common foods include meats, fatty fish, eggs, high-fat dairy products, nuts, seeds, avocados, and low-carb vegetables[117]. Regular monitoring by healthcare professionals is crucial to track the diet's impact on health and symptoms. Blood tests, urine tests for ketone levels, and dietary logs are often used to ensure adherence and effectiveness. Adjustments to the diet may be necessary based on individual responses and goals. Providing education and support to caregivers and individuals is vital for successful implementation. This includes guidance on meal preparation, understanding macronutrient ratios, and managing potential side effects[118].

Benefits of the KD: Some studies and anecdotal reports suggest that the KD can improve behavior, social skills, and communication in individuals with ASD. In some cases, reductions in hyperactivity, irritability, and repetitive behaviors have been observed[116]. Given its established efficacy in treating epilepsy, the KD may benefit individuals with ASD who also experience seizures or epilepsy. Improved seizure control can significantly enhance the quality of life. The diet's impact on brain metabolism and neurotransmitter balance may lead to cognitive improvements, including better attention, memory, and learning capabilities[119]. The KD may also improve GI symptoms commonly seen in individuals with ASD, such as constipation, diarrhea, and abdominal pain. These improvements can contribute to overall well-being and comfort[120].

Challenges and considerations: While there are promising anecdotal and preliminary evidence, the scientific data on the KD's effectiveness for autism is still limited. More rigorous, large-scale studies are needed to establish clear clinical guidelines. Ensuring that the KD meets all nutritional requirements can be challenging. If necessary, potential deficiencies in vitamins, minerals, and fiber must be addressed through careful planning and supplementation[121]. Strict adherence to the KD can be difficult, especially in social settings like schools, parties, and restaurants. This can lead to social isolation or challenges in long-term maintaining the diet[122]. Potential side effects of the KD include GI discomfort, nutrient deficiencies, kidney stones, and increased cholesterol levels. Regular monitoring and adjustments are essential to manage these risks[123]. The KD can be more expensive and less accessible than a typical diet. Access to high-quality fats, specific supplements, and specialized food products can create financial and logistical challenges[124].

Current state of scientific evidence: The evidence supporting the KD for autism is mixed. Some studies and case reports show significant improvements in behavior and cognitive function, while others find no substantial benefits. Individual responses can vary widely[90]. More rigorous, large-scale, RCTs are needed to establish the KD's efficacy and safety in managing autism symptoms. Research should focus on understanding the underlying mechanisms and identifying which individuals are most likely to benefit. Given the variability in individual responses, a personalized approach to the KD is essential[125]. Healthcare providers should work closely with families to assess potential benefits and risks, ensuring that dietary changes are safe and nutritionally adequate. Through careful planning, monitoring, and support, the KD may be a valuable tool in managing symptoms and improving the quality of life for some individuals with ASD[126].

SCD

The SCD has garnered attention within the autism community as a potential way to address some of the GI and behavioral concerns associated with ASD. United States pediatrician Dr. Sidney Haas originally developed it in the 1920s to treat children suffering from celiac disease, who experienced symptoms like diarrhea, bloating, gas, and weight loss [11]. The diet became later popularized due to its positive effects on symptoms of IBD, leading to its increased use among those with similar GI issues. The SCD revolves around eliminating specific carbohydrates not well absorbed by the body and may promote the growth of harmful bacteria in the intestines[127]. By removing complex carbohydrates, lactose, and sucrose from the diet and increasing the intake of nutrient-dense foods, SCD aims to reduce gut dysbiosis and GI inflammation[128]. The diet strictly excludes grains, sugars, and starches that are considered difficult to digest. Doing so aims to restore balance to the intestinal flora and allow the gut to heal, potentially leading to improved behavior and social interactions in individuals with ASD[129]. However, according to the University of Virginia School of Medicine, SCD does not reduce symptoms of autism.

Rationale for the SCD in autism: The gut-brain axis theory suggests a bidirectional relationship between gut health and brain function. Individuals with ASD often experience GI issues, which may contribute to or exacerbate behavioral and cognitive symptoms[10]. The SCD aims to restore gut health, potentially improving overall well-being and behavior. Some individuals with ASD may have difficulties digesting and absorbing complex carbohydrates, leading to fermentation by gut bacteria, production of harmful byproducts, and GI symptoms[130]. The SCD restricts these carbohydrates to prevent such issues. An imbalance in gut microbiota, or dysbiosis, is commonly observed in individuals with ASD. The SCD aims to reduce gut inflammation and dysbiosis by eliminating fermentable carbohydrates that feed pathogenic bacteria and yeasts[127].

Implementation of the SCD: Before starting the SCD, a thorough medical evaluation is necessary to assess baseline GI health, nutritional status, and potential contraindications. Consultation with a healthcare provider or dietitian experienced with SCD is recommended. The SCD involves eliminating complex carbohydrates, disaccharides, and polysaccharides. Allowed foods include meats, fish, eggs, aged cheeses, certain vegetables and fruits, nuts, and seeds. Prohibited foods include grains, most dairy products, starchy vegetables, and processed foods[131]. Transitioning to SCD can be gradual to allow the body to adapt and to monitor for any adverse reactions. Starting with easily digestible foods and gradually incorporating a wider variety of permitted foods is recommended. Regular monitoring by healthcare

professionals is crucial to tracking the diet's impact on symptoms and overall health. Blood tests, stool tests, and dietary logs can be used to ensure adherence and effectiveness[132]. Based on individual responses, adjustments to the diet may be necessary. Providing education and support to caregivers and individuals is vital for successful implementation. This includes guidance on meal preparation, understanding allowed and prohibited foods, and managing potential challenges [130]. For those considering this dietary approach, it is crucial to consult with healthcare professionals to ensure it is implemented safely and effectively, considering both potential benefits and challenges. Through careful planning, monitoring, and support, SCD may be a valuable tool in managing symptoms and improving the quality of life for some individuals with ASD.

Benefits of the SCD: Many individuals with ASD who follow the SCD report significant improvements in GI symptoms such as diarrhea, constipation, bloating, and abdominal pain. Improved gut health can contribute to overall well-being and comfort. Some studies and anecdotal reports suggest that SCD can lead to improvements in behavior, social skills, and communication in individuals with ASD. In some cases, reductions in hyperactivity, irritability, and repetitive behaviors have been observed[131]. The diet's impact on gut health and the reduction of inflammation may lead to cognitive improvements, including better attention, memory, and learning capabilities[133]. For some individuals with ASD, adhering to the SCD can lead to enhanced quality of life due to better health and symptom management. This can translate to improved daily functioning and engagement in activities[134].

Challenges and considerations: The SCD is known for being restrictive, often leading to concerns about potential nutritional deficiencies due to the elimination of various food groups. Ensuring that the diet meets all nutritional requirements can be challenging. If necessary, potential deficiencies in vitamins, minerals, and fiber must be addressed through careful planning and supplementation[129]. Strict adherence to the SCD can be difficult, especially in social settings like schools, parties, and restaurants. This can lead to social isolation or long-term challenges in maintaining the diet[135]. Potential side effects of SCD include GI discomfort during the initial transition period, nutrient deficiencies, and potential challenges in maintaining weight, especially in growing children[136]. Regular monitoring and adjustments are essential to manage these risks. The SCD can be more expensive and less accessible than a typical diet. Access to high-quality, specific foods and supplements can create financial and logistical challenges for families and individuals trying to adhere to the diet[137]. While there is promising anecdotal and preliminary evidence, the scientific data on SCD's effectiveness for autism is still limited. More rigorous, large-scale studies are needed to establish clear clinical guidelines.

Current state of scientific evidence: The evidence supporting the SCD for autism is mixed. Some studies and case reports show significant improvements in GI health and behavioral symptoms, while others find no substantial benefits. Individual responses can vary widely[129,131,134]. There is a need for more rigorous, large-scale, RCTs to establish the SCD's efficacy and safety in managing autism symptoms. Research should focus on understanding the underlying mechanisms and identifying which individuals are most likely to benefit. Given the variability in individual responses, a personalized approach to SCD is essential. Healthcare providers should work closely with families to assess potential benefits and risks, ensuring that dietary changes are safe and nutritionally adequate.

Gut and psychology syndrome protocol

Gut and psychology syndrome protocol (GAPS diet) protocol is a therapeutic diet developed by Dr. Natasha Campbell-McBride, aimed at addressing various psychological and physiological conditions through dietary intervention. This diet is based on the premise that many health issues, including ASD, are linked to gut health[138]. The GAPS diet focuses on healing the gut lining, restoring healthy gut flora, and reducing inflammation to improve overall health and prevent potentially harmful substances from seeping into the bloodstream, affecting brain function and development[139]. Dr. Natasha created the GAPS diet after observing a strong correlation between gut health and brain function. She developed the diet based on her clinical experience and the dietary principles of the SCD by Dr. Sidney Haas (Table 2).

Principles of the GAPS diet: The GAPS diet is structured in phases, starting with an introductory phase and gradually progressing to a full GAPS diet. Each phase includes specific foods to heal the gut and support the body's detoxification processes. The main principles of the diet include eliminating processed foods, including healing foods, and gradually reintroducing them[138]. The diet excludes processed foods, refined sugars, grains, and starchy vegetables, which can contribute to gut dysbiosis and inflammation. Then, the diet emphasizes the consumption of nutrient-dense, easily digestible foods such as bone broths, fermented foods, and healthy fats to support gut healing. Then, foods are reintroduced gradually to monitor tolerance and ensure the gut can handle them without adverse reactions[140].

Phases of the GAPS diet: The introduction phase is the most restrictive phase, focusing on easily digestible foods to initiate gut healing and restore leaky guts. Foods include homemade meat or fish stocks, probiotic foods, and boiled vegetables. After completing the introduction phase, individuals transition to the full GAPS diet, which allows a wider variety of foods but still excludes grains, processed sugars, and certain starchy vegetables[141].

Core components of the GAPS diet: Bone broth and meat stock, rich in amino acids, collagen, and minerals, are central to the diet for their gut-healing properties. In addition, fermented foods, including homemade yogurt, kefir, sauerkraut, and other fermented vegetables, are consumed to introduce beneficial bacteria to the gut. The food should be organic, unprocessed, natural, and free from additives and chemicals to support overall health. Healthy fats are incorporated from meat, fish, avocados, and coconut oil, which are essential for cell repair and energy. The diet also emphasizes including non-starchy vegetables and low-sugar fruits, preferably cooked to aid digestion[133,142].

Table 2 The differences between the specific carbohydrate diet and the gut and psychology syndrome diet

Aspect	Specific carbohydrate diet	Gut and psychology syndrome diet
Origins and development	Developed by Dr. Sidney V. Haas in the 1920s	Developed by Dr. Natasha Campbell-McBride in 2004
Original purpose	Treatment of celiac disease and gastrointestinal disorders	Addressing neurological and psychological conditions
Popularized by	Elaine Gottschall, through "Breaking the Vicious Cycle"	Dr. Campbell-McBride, through "Gut and Psychology Syndrome"
Focus	Elimination of specific carbohydrates to reduce gut dysbiosis	Healing gut lining, restoring healthy gut flora, reducing inflammation
Principles	Excludes complex carbohydrates, lactose, and sucrose	Focuses on healing the gut lining, restoring gut flora
	Includes easily digestible foods	Eliminates processed foods, refined sugars, starchy vegetables
	Emphasizes nutrient-dense foods	Structured in distinct phases
Main foods	Meat, fish, eggs, vegetables, fruits, nuts, certain dairy products	Similar to SCD, with greater emphasis on bone broth, fermented foods, healthy fats
Foods excluded	All grains, starchy vegetables, lactose (initially), sucrose, processed foods	All grains, starchy vegetables, refined sugars, processed foods, certain dairy products
Diet structure	More flexible, with less emphasis on phases	Structured in phases: Introductory phase to full GAPS diet
Emphasis on healing	Eliminating specific carbohydrates to reduce gut dysbiosis	Healing the gut lining and restoring healthy gut flora
Food focus	Eliminating specific carbohydrates	Healing foods like bone broth and fermented foods
Underlying philosophy	Specific carbohydrates promote gut dysbiosis	Gut health linked to psychological and neurological health
Target conditions	Celiac disease, gastrointestinal disorders, IBD, ASD	ASD, ADHD, depression, psychological and neurological conditions
Overall approach	Straightforward food elimination	Phased approach with emphasis on gut healing

This table summarizes the key differences between the specific carbohydrate diet and the gut and psychology syndrome diet, highlighting their distinct origins, principles, and implementation strategies. IBD: Inflammatory bowel disease; ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder; GAPS: Gut and psychology syndrome; SCD: Specific carbohydrate diet.

Mechanisms of action: Nutrient-dense foods like bone broth and fermented foods help repair the gut lining, reducing permeability and inflammation. Probiotic-rich foods and supplements help balance gut microbiota, which is crucial for digestion and immune function. Eliminating processed and toxic foods reduces the burden on the liver and other detoxification pathways[143]. Improved gut health leads to better immune system regulation, potentially reducing autoimmunity and systemic inflammation[144].

Research and evidence: Scientific evidence supporting the GAPS diet is primarily anecdotal, with limited peer-reviewed research specifically on the diet, with the risk that the early introductory phases may not maintain adequate nutrition. However, studies on the principles underlying the GAPS diet, such as the impact of gut microbiota on brain function and the benefits of nutrient-dense, anti-inflammatory foods, provide indirect support. Research has established a strong link between gut health and brain function, supporting the diet's focus on healing the gut to improve psychological symptoms [145-147]. In addition, studies have shown the benefits of probiotics in restoring gut flora and reducing GI symptoms, aligning with the diet's emphasis on fermented foods[148].

Practical considerations: The GAPS diet can be challenging to implement due to its restrictive nature, requiring careful meal planning and preparation. To avoid deficiencies, it is essential to ensure that all nutritional needs are met, particularly in children[149]. Responses to the diet can vary widely; some individuals may experience significant improvements, while others may see minimal changes[150]. Consulting with healthcare providers, particularly those experienced with the GAPS diet, can help tailor the diet to individual needs and monitor progress.

Camel milk

Camel milk has been used for centuries in Middle Eastern and African cultures as a promising complementary approach, valued for its nutritional and medicinal properties. In recent years, interest in camel milk has extended to the management of ASD, where anecdotal reports and emerging research suggest potential benefits arising from its anti-inflammatory, antioxidant, immune-modulating, and gut health-supporting properties[151].

Nutritional profile of camel milk: Camel milk is distinct from cow's milk and other types of milk in several nutritional aspects. It contains unique proteins, such as lactoferrin and immunoglobulins, with antimicrobial and immune-modulating properties. Unlike cow milk, which contains beta-lactoglobulin and beta-casein, camel milk does not have these components[152]. It has less lactose, lower fat, and a different fatty acid profile than cow's milk, including less cholesterol and higher levels of unsaturated fatty acids. Camel milk is also rich in vitamins (A, B, C, D, and E) and minerals (calcium, magnesium, zinc, and iron) essential for overall health. In addition, it contains enzymes such as lysozyme, which has antibacterial properties. Furthermore, camel milk is generally considered hypoallergenic and may be suitable for individuals with cow's milk allergies[153,154]. Figure 3 summarizes the nutritional benefits of camel milk.

Proposed mechanisms of action: The potential benefits of camel milk for individuals with ASD are thought to arise from several mechanisms. Camel milk contains bioactive compounds that have anti-inflammatory properties, which may help reduce systemic and neural inflammation associated with ASD[155]. It is also rich in antioxidants and can help combat oxidative stress, often elevated in individuals with ASD. Camel milk boosts the levels of superoxide dismutase, myeloperoxidase, and plasma GSH, which helps mitigate oxidative stress-a significant factor in the development of autism. Additionally, camel milk alleviates oxidative stress by downregulating MAPK signaling pathways[156]. In addition, the immunoglobulins and lactoferrin in camel milk can modulate immune responses, potentially improving immune function and reducing autoimmunity[157]. Camel milk may also support gut health by promoting a balanced microbiota and reducing GI inflammation, which is common in individuals with ASD. Furthermore, the high vitamin and mineral content can help address nutritional deficiencies often seen in children with ASD[158].

Current research findings: Research on the effects of camel milk on ASD is still in its infancy, but several studies and anecdotal reports have provided promising results. Some studies have reported significant behavioral improvements after camel milk consumption, including reduced hyperactivity, lethargy, and irritability[159]. Improvements in cognitive functions, such as attention and communication skills, have been observed in some children with ASD. Several reports suggest that camel milk may also alleviate GI symptoms such as constipation, diarrhea, and bloating, which are common in ASD[10,156,159]. Numerous anecdotal accounts from parents and caregivers describe noticeable improvements in behavior, social interaction, and digestive health in children with ASD who consume camel milk[160,161]. As with many interventions, responses to camel milk can vary widely among individuals, with some experiencing significant benefits and others showing no noticeable changes.

Practical considerations: Several practical aspects should be considered when considering camel milk for individuals with ASD. Obtaining camel milk of good quality and from reputable sources is crucial to ensure it is free from contaminants and produced under hygienic conditions[162]. Caregivers should gradually introduce camel milk into the diet to monitor for adverse reactions. They should consult a healthcare provider to determine an appropriate dosage[163]. While camel milk is generally hypoallergenic, it is crucial to observe for any allergic reactions, especially in individuals with a history of food allergies. Camel milk should be integrated into a balanced diet, meeting all nutritional needs[164]. The individual's response to camel milk should be regularly monitored, including behavioral, cognitive, and GI changes, and the intervention should be adjusted as needed[165]. Caregivers and healthcare providers should consider camel milk supplementation carefully, ensuring choices are evidence-based, personalized, and integrated into a broader therapeutic strategy.

Probiotics supplements

Probiotics are live microorganisms that confer health benefits on the host when administered in adequate amounts. Recently, their potential role in managing ASD has gained considerable interest due to the increasing recognition of the gut-brain axis and its influence on neurological and behavioral health[166]. The use of probiotics in managing ASD offers a promising avenue for alleviating GI issues and potentially improving behavioral symptoms through the modulation of the gut-brain axis[167].

Scientific rationale: The gut-brain axis is a bidirectional communication system between the GI tract and the brain, involving neural, hormonal, and immune pathways. This connection suggests that gut health can significantly impact neurological function and behavior[168]. Children with ASD often present with GI issues, such as constipation, diarrhea, and abdominal pain, which can exacerbate behavioral symptoms[10]. Dysbiosis, an imbalance in the gut microbiota, has been observed in many individuals with ASD, leading researchers to explore the potential benefits of probiotics in restoring a healthy gut microbiome and mitigating ASD symptoms[30].

Mechanisms of action: Probiotics may benefit individuals with ASD through several mechanisms. Probiotics can help reestablish a healthy balance of gut bacteria, which may reduce gut dysbiosis commonly observed in ASD[167]. By modulating the immune system and producing anti-inflammatory compounds, probiotics can help reduce inflammation in the gut, potentially alleviating GI symptoms[169]. Probiotics can also strengthen the gut barrier, preventing the translocation of harmful substances from the gut into the bloodstream, which might affect the brain and behavior[170]. Some probiotic strains produce neurotransmitters and other neuroactive compounds that can influence brain function and behavior. Probiotics can modulate immune responses, potentially reducing systemic inflammation that may affect neurological health[171].

Current research findings: Research on probiotics use in ASD is still in its early stages, but several studies and clinical trials have shown promising results. Studies have consistently found differences in the gut microbiota composition of individuals with ASD compared to neurotypical controls. These differences often include reduced diversity and an

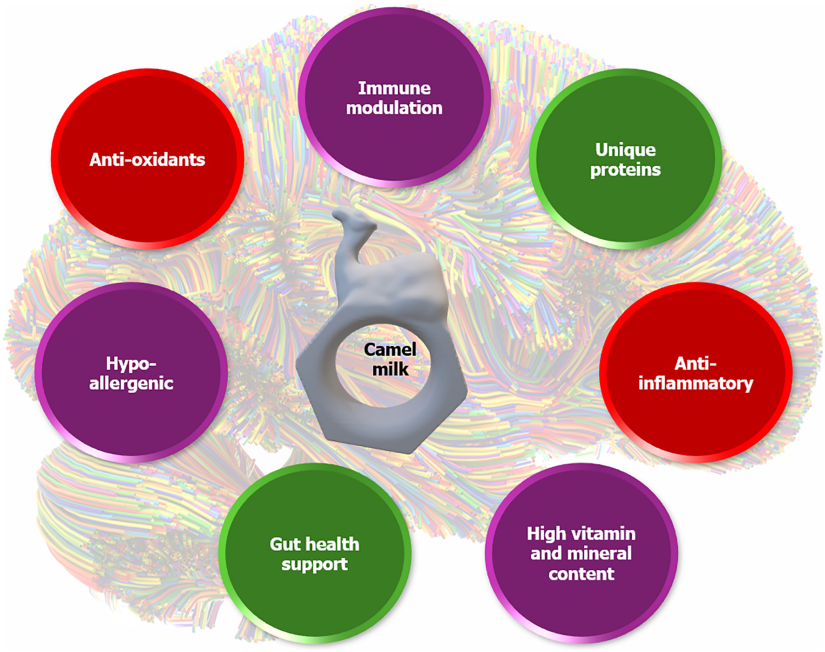

Figure 3 The nutritional benefits of camel milk.

overrepresentation of specific bacterial groups associated with inflammation and GI distress[105]. Some clinical trials have reported improved GI and behavioral symptoms following probiotic supplementation. For example, Lactobacillus and Bifidobacterium strains improve bowel habits and reduce stereotypical behaviors and hyperactivity[172]. Despite promising findings, results have been mixed, with some studies showing no significant improvements. This variability may be due to differences in study design, probiotic strains, dosages, and individual responses[173]. Animal models of autism have shown that probiotics can reduce anxiety-like behaviors, improve social interactions, and normalize gut microbiota composition[174]. Animal studies have provided insights into how probiotics may exert their effects, such as modulation of the gut-brain axis and reducing systemic inflammation[175].

Practical considerations: When considering probiotics for individuals with ASD, several practical aspects should be considered. Different probiotic strains have different effects. It is essential to choose strains that have been studied and shown to be effective in ASD[176]. The optimal dosage and duration of probiotic treatment can vary. Clinical guidance should be sought to determine appropriate regimens[177]. Probiotics should be sourced from reputable manufacturers to ensure quality, purity, and safety. Products should be free from contaminants and accurately labeled regarding strain composition and potency. Responses to probiotics can vary widely among individuals with ASD[178]. Monitoring and adjusting the intervention based on individual responses and any adverse effects is crucial. Probiotics can be used alongside other dietary and therapeutic interventions[179]. Coordination with healthcare providers ensures a comprehensive approach to managing ASD symptoms. Healthcare providers and caregivers should carefully consider probiotic interventions, ensuring that choices are evidence-based, personalized, and integrated into a broader therapeutic strategy.

Prebiotics supplementation

Prebiotics, non-digestible food ingredients that promote the growth of beneficial microorganisms in the intestines, hold promise as a therapeutic option for managing GI and potentially behavioral symptoms in individuals with autism[180]. Prebiotics are compounds in food that induce the growth or activity of beneficial microorganisms such as bacteria and fungi. The most common types of prebiotics are fructooligosaccharides, found in foods like onions, garlic, and bananas; galactooligosaccharides, found in legumes and certain root vegetables; inulin, found in chicory root, asparagus, and leeks, and lactulose, a synthetic sugar used as a prebiotic and laxative[181].

Mechanisms of action: Prebiotics promote gut health by serving as a food source for beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli*[182]. These bacteria ferment prebiotics to produce short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, which have several beneficial effects. SCFAs help maintain the integrity of the gut lining, preventing the translocation of harmful substances into the bloodstream[183]. SCFAs reduce inflammation by modulating immune responses in the gut. Some SCFAs are involved in synthesizing neurotransmitters, which can influence brain function and behavior. Prebiotics can also affect the gut-brain axis, potentially impacting mood and cognitive function[184].

Prebiotics and autism: Many individuals with ASD suffer from GI issues such as constipation, diarrhea, and abdominal pain. Prebiotics can improve gut health by increasing the population of beneficial bacteria, enhancing stool consistency, and reducing inflammation[185]. Emerging research suggests that improving gut health with prebiotics can positively

affect behavior and cognitive function in individuals with ASD. This is thought to be mediated through the gut-brain axis [186]. Individuals with ASD often have immune dysregulation. Prebiotics can modulate the immune system, reducing systemic inflammation that might contribute to neurodevelopmental issues[187]. Figure 4 shows the role of probiotics and prebiotics in ASD.

Current research findings: Preclinical studies have shown that prebiotics can alter gut microbiota composition, reduce inflammation, and improve social behaviors in animal models of autism. Human trials are limited but promising. Some studies have reported improved GI symptoms and better behavior in children with ASD following prebiotic supplementation[188,189].

Practical considerations: The optimal dosage of prebiotics for individuals with ASD is not well established and may vary depending on individual needs and responses[190]. It is crucial to start with a low dose and gradually increase it to avoid adverse effects such as bloating and gas. Including prebiotic-rich foods in the diet can be a natural way to promote gut health[191]. Garlic, onions, bananas, and asparagus are good sources of prebiotics. Prebiotic supplements are available and can be used under the guidance of a healthcare professional. It is essential to choose high-quality products and monitor for any adverse reactions[192]. Prebiotics are often used in conjunction with probiotics (beneficial bacteria) to create a synergistic effect, known as synbiotics. This combination can enhance the growth and activity of beneficial gut bacteria more effectively than prebiotics or probiotics alone[193]. Healthcare providers should consider prebiotics as part of a comprehensive approach to managing ASD, tailored to each patient's individual needs. Integrating prebiotics through diet or supplements, along with other interventions, may offer a valuable strategy for improving the quality of life for those with autism[194].

High-dose methyl cobalamin in autism

ASD is a neurodevelopmental disorder characterized by deficits in social communication, repetitive behaviors, and restricted interests. While the exact etiology of ASD remains unclear, emerging research has explored various biomedical interventions, including the use of high-dose methylcobalamin (vitamin B12)[195]. Methylcobalamin is one of the active forms of vitamin B12, a water-soluble vitamin essential for brain function, nerve tissue health, and the production of red blood cells. Unlike cyanocobalamin, another common form of vitamin B12, methylcobalamin is directly utilized by the body without needing conversion. It plays a critical role in methylation, a biochemical process vital for DNA synthesis, detoxification, and neurotransmitter production[196].

Potential mechanisms of action: The therapeutic potential of high-dose methylcobalamin in autism may be attributed to several mechanisms. Methylcobalamin is crucial for the methylation cycle, which involves transferring methyl groups to DNA, proteins, and other molecules. Proper methylation is necessary for gene regulation, detoxification, and neurotransmitter production[197]. Methylcobalamin is involved in glutathione synthesis, a powerful antioxidant that helps protect cells from oxidative stress. Many individuals with ASD have been found to have low glutathione levels[198]. Vitamin B12 is essential for maintaining myelin, the protective sheath around nerves. Methylcobalamin's neuroprotective properties may help improve nerve function and cognitive abilities[199]. Methylcobalamin supports the detoxification process by aiding in the removal of heavy metals and other toxins from the body, which may be particularly beneficial for individuals with ASD who exhibit detoxification impairments[200].

Benefits in autism: Studies have suggested that high-dose methylcobalamin may improve behaviors such as social interaction, communication, and repetitive behaviors in individuals with autism[201]. Some research indicates that methylcobalamin can enhance cognitive functions, including attention, focus, and learning abilities, potentially contributing to better academic and social outcomes[202]. By boosting glutathione levels, high-dose methylcobalamin may reduce oxidative stress, which is often elevated in individuals with autism and associated with various neurological and behavioral symptoms[203]. Enhanced methylation and glutathione production can improve the body's ability to detoxify harmful substances, potentially reducing the toxic burden and impacting neurological health[143].

Current research findings: Some clinical trials have shown promising results with high-dose methylcobalamin in autism. For instance, a study by Hendren *et al*[204] reported that methylcobalamin injections significantly improved methylation capacity, reduced oxidative stress markers, and improved clinician-rated ASD symptoms that were correlated with improvements in measures of methionine metabolism and cellular methylation capacity in children with ASD. Various case reports and small-scale studies have noted behavioral improvements, including better communication, increased social engagement, and reduced stereotypical behaviors following high-dose methylcobalamin treatment[201,205]. Research has demonstrated that high-dose methylcobalamin can normalize specific autism-associated biomarkers, such as increased levels of homocysteine and improved glutathione status[206]. The treatment response to methylcobalamin is expected when the treatment is associated with increased glutathione redox status[195].

Practical considerations: High-dose methylcobalamin is typically administered *via* subcutaneous or intramuscular injections. The exact dosage varies, but common protocols involve 75-150 mcg/kg body weight doses administered every 1-3 days[200]. Regular monitoring of vitamin B12 Levels, methylation markers, and clinical response is essential to ensure safety and efficacy. Side effects are generally rare but can include mild irritability or hyperactivity[207]. Methylcobalamin is often used in conjunction with other biomedical interventions, such as folinic acid, to enhance its therapeutic effects. Tailoring the treatment plan to each patient's needs is important[208]. Healthcare providers should consider high-dose methylcobalamin as part of a comprehensive, individualized treatment plan for individuals with autism, ensuring careful monitoring and adjustment as needed.

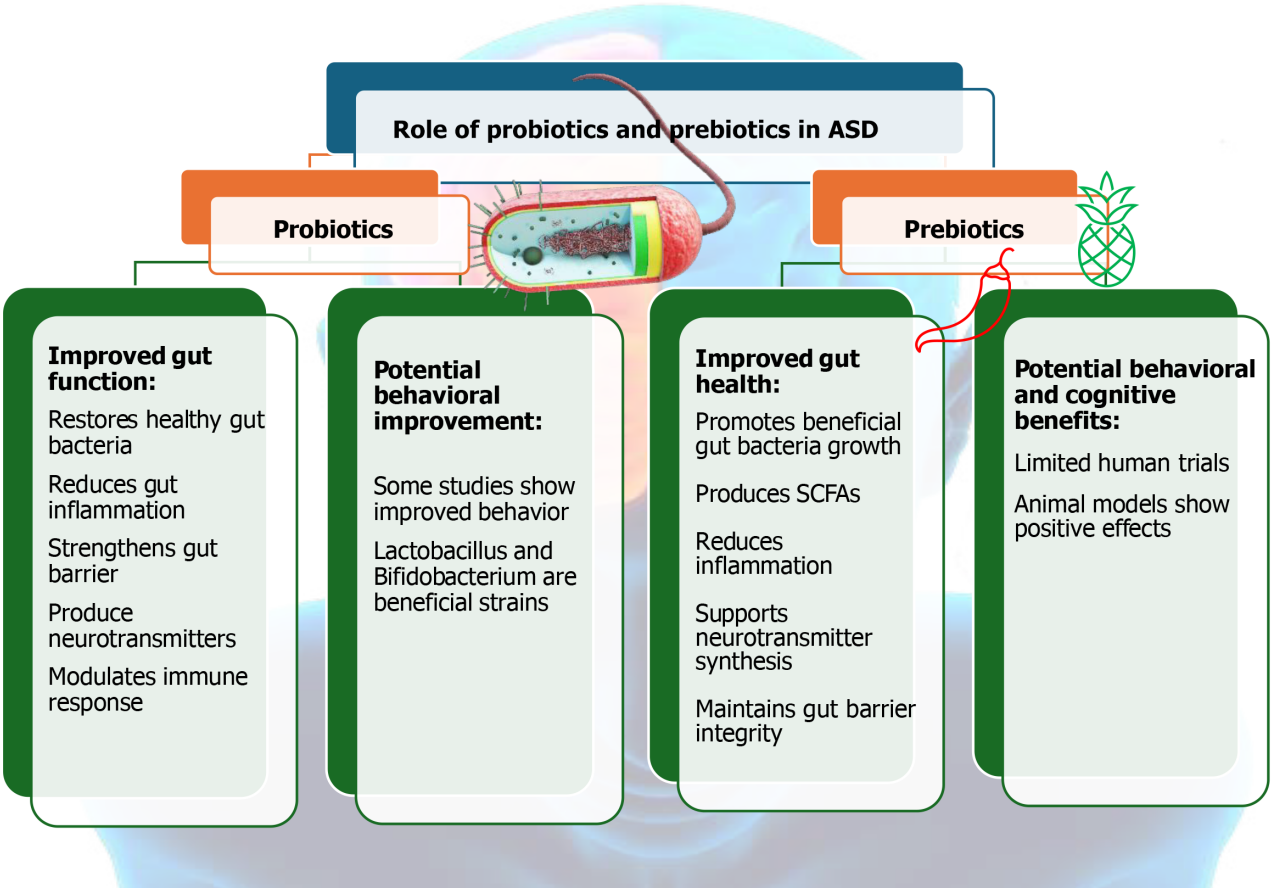

Figure 4 The role of probiotics and prebiotics in autism spectrum disorder. ASD: autism spectrum disorder; SCFAs: Short-chain fatty acids.

Folic acids in autism

ASD has been linked to abnormalities in folate metabolism, prompting several mechanistic hypotheses regarding its causes and potential symptomatic treatments[209]. Folic acid, a synthetic form of the naturally occurring folate (vitamin B9), plays a critical role in various biochemical processes, including DNA synthesis, repair, and methylation[210]. Its significance during pregnancy, particularly in neural tube development, is well established. Folic acid supplementation plays a promising role in the potential reduction of ASD risk, particularly when administered prenatally. Its involvement in critical metabolic pathways that influence neurodevelopment underscores its importance[211].

Folate metabolism and ASD: Abnormalities in folate metabolism have been implicated in ASD. Key pathways affected by folate include one-carbon metabolism and the transsulfuration pathway, both essential for proper neurodevelopment. Disruptions in these pathways can lead to deficits in methylation and increased oxidative stress, factors associated with ASD[212].

Potential mechanisms: Folate is crucial for the methylation of DNA, a process essential for regulating gene expression. Abnormal methylation patterns have been observed in individuals with ASD, suggesting that proper folate levels may influence the risk of developing ASD by ensuring regular gene expression during critical periods of neurodevelopment [213,214]. Folate also reduces homocysteine levels, a byproduct of one-carbon metabolism that, in excess, can contribute to oxidative stress. Elevated oxidative stress is a common finding in individuals with ASD, and maintaining adequate folate levels may help mitigate this condition by supporting antioxidant defenses[203]. In addition, folate is involved in synthesizing neurotransmitters such as serotonin, dopamine, and norepinephrine. Imbalances in these neurotransmitters are often reported in individuals with ASD, suggesting that folate supplementation might help normalize their levels and improve related symptoms[215].

Prenatal folic acid supplementation: Research indicates that prenatal folic acid supplementation can significantly reduce the risk of ASD[216]. The critical window for folic acid supplementation appears to be before conception and during the first trimester of pregnancy. Supplementation during this period is associated with a reduced incidence of ASD, possibly due to its role in neural tube formation and early brain development[217]. Standard prenatal doses of folic acid (400-800 mcg per day) are generally recommended. High doses should be taken under medical supervision, especially considering the potential risk of masking vitamin B12 deficiency symptoms[218]. Large epidemiological studies have shown a correlation between maternal folic acid supplementation and a decreased risk of ASD in offspring. For example, a study published in the "Journal of the American Medical Association" found that children whose mothers took folic acid supplements around the time of conception had a lower risk of developing ASD compared to those whose mothers did

not[219].

Challenges and considerations: Variations in genes involved in folate metabolism (*e.g.*, MTHFR polymorphisms) can affect individual responses to folic acid supplementation. Personalized approaches considering genetic makeup may be necessary to optimize folate supplementation strategies[220]. The presence of other nutrients, such as vitamin B12 and iron can influence the effectiveness of folic acid. A balanced diet that ensures adequate intake of these nutrients is crucial for maximizing the benefits of folic acid[221]. While folic acid supplementation is generally safe, excessive intake has been associated with potential risks, including the masking of vitamin B12 deficiency and possible associations with other health conditions[222]. Therefore, it is essential to adhere to recommended doses. However, further research is needed to understand the mechanisms and fully optimize supplementation strategies. Healthcare providers should consider individual genetic and nutritional contexts when recommending folic acid to maximize its benefits and minimize potential risks.

Vitamin B6 supplement

Vitamin B6, also known as pyridoxine, is a water-soluble neurotropic vitamin that plays a crucial role in brain development and function. It is involved in synthesizing neurotransmitters, chemicals that transmit signals in the brain [223]. The potential therapeutic role of Vitamin B6 in ASD has been the subject of research for several decades.

Mechanisms of action: Vitamin B6 is a cofactor for over 140 enzymatic functions and enzymes involved in synthesizing several neurotransmitters, including serotonin, dopamine, and GABA. These neurotransmitters are critical for mood regulation, behavior, and cognitive function[224]. Elevated levels of homocysteine, an amino acid, have been associated with neurological disorders. Vitamin B6 helps convert homocysteine into cysteine, reducing its neurotoxic effects and supporting neurological health[225]. Glutamate is an excitatory neurotransmitter, and its imbalance has been implicated in autism. Vitamin B6 plays a role in converting glutamate to GABA, an inhibitory neurotransmitter, thus maintaining neurotransmitter balance[226].

Clinical evidence for role of Vitamin B6 in ASD: Initial studies in the 1960s and 1970s suggested that high doses of Vitamin B6, often combined with magnesium, improved behavior and communication in autistic children. These studies, however, were small and had methodological limitations[227,228]. Subsequent RCTs have produced mixed results. Some studies reported improvements in social interactions, communication, and behavioral problems, while others found no significant effects[229,230]. Meta-analyses of Vitamin B6 supplementation in autism have highlighted the variability in study design, dosages, and outcome measures, leading to inconclusive results. However, some analyses suggest potential benefits for specific subgroups of individuals with ASD[231].

Potential benefits of Vitamin B6 in ASD: Vitamin B6 supplementation may improve behavior, including reduced irritability and hyperactivity, in some children with autism. Reports indicate that Vitamin B6 may support language development and communication skills in some individuals with autism. Although evidence is inconsistent, vitamin B6's role in neurotransmitter synthesis and homocysteine metabolism may contribute to cognitive improvements[232].

Safety and dosage: Studies vary widely on the effective dose of Vitamin B6 for autism, ranging from moderate to high doses. One of the proposed doses is to use vitamin B6 in a dose of 5 mg/kg/day for two weeks, followed by 10 mg/kg for another two weeks[233]. Determining the appropriate dosage based on individual needs and under medical supervision is essential. High doses of Vitamin B6 can cause peripheral neuropathy, a condition characterized by nerve damage, leading to numbness and tingling in the extremities[234]. Therefore, monitoring and adjusting the dosage is crucial to avoid toxicity. Vitamin B6 is often supplemented alongside magnesium, which may enhance its effectiveness and mitigate potential side effects. Magnesium itself plays a role in neuromuscular function and has been studied for its possible benefits in autism[235]. As the evidence for the beneficial role of Vitamin B6 in ASD remains mixed, more robust, large-scale studies are needed to establish its efficacy and safety conclusively. Parents and caregivers considering Vitamin B6 supplementation for their children with autism should consult healthcare professionals to determine the appropriate dosage and monitor for adverse effects[10]. As part of a comprehensive treatment plan, Vitamin B6 may offer a valuable option for supporting neurological health and improving the quality of life for individuals with autism.

Vitamin D in autism

Vitamin D is a fat-soluble vitamin essential for maintaining bone health, immune function, and cellular processes. It has two main forms: Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is synthesized in the skin upon exposure to sunlight and can also be obtained from dietary sources such as fatty fish, egg yolks, and fortified foods. Vitamin D2 is found in some plants and fungi. Both forms are converted in the liver to 25-hydroxyvitamin D, the main circulating form[236,237]. Then, in the kidneys, in the biologically active form, 1,25-dihydroxy vitamin D. Vitamin D plays a crucial role in various physiological processes relevant to brain development and managing ASD. Emerging evidence suggests that vitamin D deficiency may contribute to the pathophysiology of autism, and supplementation may offer therapeutic benefits[238].

Functions of Vitamin D: Vitamin D facilitates the absorption of calcium and phosphorus from the gut, which is crucial for forming and maintaining healthy bones and teeth. Vitamin D also modulates the immune system, reduces inflammation, and enhances the pathogen-fighting effects of monocytes and macrophages[239,240]. Vitamin D receptors and the enzyme required to activate vitamin D are present in the brain, suggesting a role in brain development and function. It

influences neurodevelopmental processes, such as neuronal differentiation, axonal connectivity, and neurotransmission [241].

Potential links between Vitamin D deficiency and autism: Several studies have suggested that low maternal vitamin D levels during pregnancy may increase the risk of ASD in offspring. Vitamin D is crucial for fetal brain development, and deficiency during this critical period may lead to neurodevelopmental abnormalities[242]. Vitamin D deficiency is associated with immune dysregulation, which is often observed in individuals with ASD. Abnormal immune responses and chronic inflammation are thought to contribute to the pathophysiology of autism[243]. Vitamin D influences the production and release of neurotransmitters, such as serotonin and dopamine, implicated in mood regulation and cognitive functions. Deficiency in vitamin D may lead to imbalances in these neurotransmitters, affecting behavior and cognition. Individuals with autism often exhibit elevated oxidative stress levels[244]. Vitamin D has antioxidant properties that help reduce oxidative stress, potentially mitigating some neurobiological abnormalities in ASD[245].

Current research findings: Epidemiological studies have found an association between low vitamin D levels and an increased risk of autism[39]. For instance, multicentre research from Denmark, Finland, Norway, Sweden, and Western Australia indicates that children born in regions with lower sunlight exposure or during seasons with less sunlight have a higher prevalence of ASD[246]. Some clinical trials have explored the effects of vitamin D supplementation in individuals with autism. Studies measuring vitamin D levels in individuals with ASD often report lower levels compared to neurotypical controls[245]. A RCT by Song *et al*[247] showed that vitamin D3 supplementation in children with ASD significantly improved autism severity scores, social interaction, and stereotypical behaviors. These findings suggest a potential benefit of vitamin D supplementation in correcting deficiencies and improving symptoms.

Practical considerations: The appropriate vitamin D dosage for individuals with autism varies based on age, baseline vitamin D levels, and individual needs[230]. General recommendations suggest a daily intake of 600-800 IU for children and adults, but higher doses may be necessary to correct deficiencies[248]. While vitamin D supplementation is generally safe, excessive intake can lead to toxicity, characterized by hypercalcemia, nausea, and kidney problems. Regularly monitoring serum 25-hydroxyvitamin D levels is essential to ensure optimal dosing and prevent adverse effects[249]. Vitamin D supplementation is often used alongside other interventions, such as behavioral therapies and nutritional support, to maximize its potential benefits in managing autism symptoms[250]. Healthcare providers should consider evaluating and monitoring vitamin D levels as part of a comprehensive treatment plan for autism, ensuring individualized and evidence-based care.

L-Carnitine supplement

ASD is linked to abnormal synaptogenesis, neurotransmitter transformations, neurometabolism, and mitochondrial function[251]. L-carnitine, a naturally occurring amino acid derivative, has gained attention for its potential in managing autism due to its involvement in energy metabolism and mitochondrial health[252]. Synthesized in the liver and kidneys from lysine and methionine, L-carnitine is crucial for transporting long-chain fatty acids into mitochondria for oxidation and energy production. It also helps remove excess short- and medium-chain fatty acids, preventing their accumulation and potential toxicity[253]. Given its role in energy production, mitochondrial function, and antioxidant defense, L-carnitine is relevant to the pathophysiology of ASD[254]. Emerging evidence suggests that L-carnitine supplementation may benefit individuals with autism by enhancing mitochondrial function, reducing oxidative stress, and improving fatty acid metabolism[72].

Functions of L-Carnitine: L-carnitine facilitates the transport of fatty acids into the mitochondria, enabling their β-oxidation and subsequent production of ATP, the primary energy currency of cells. By promoting efficient fatty acid metabolism, L-carnitine supports mitochondrial health and function, which is crucial for maintaining cellular energy balance. L-carnitine has antioxidant properties, helping to reduce oxidative stress and protect cells from damage caused by free radicals[255].

Potential links between L-Carnitine deficiency and autism: Mitochondrial dysfunction is frequently observed in individuals with ASD. Since L-carnitine plays a pivotal role in mitochondrial energy production, deficiency in L-carnitine could exacerbate mitochondrial abnormalities, contributing to the symptoms of autism. Increased oxidative stress is a common feature in autism[256]. L-carnitine's antioxidant properties may help mitigate oxidative stress, potentially improving cellular function and reducing neuroinflammation. Impaired fatty acid metabolism has been implicated in the pathophysiology of autism. L-carnitine deficiency can lead to the accumulation of unmetabolized fatty acids, which may adversely affect brain function and development[257].

Current research findings: Research has shown that individuals with autism often have lower levels of L-carnitine and its precursors in the blood. These findings suggest that L-carnitine deficiency may be a contributing factor in the development and severity of autism symptoms[256]. Studies on the metabolic profiles of individuals with autism have highlighted abnormalities in fatty acid metabolism and mitochondrial function[6]. Several clinical trials have investigated the effects of L-carnitine supplementation in children with autism[258]. A notable study by Geier *et al*[259] found that L-carnitine supplementation by 50 mg/kg/day for 3 months improved social behavior, communication, and overall autism severity scores in children with ASD. Another study by Fahmy *et al*[260] reported significant improvements in speech, social interactions, and repetitive behaviors following L-carnitine supplementation. L-carnitine supplementation has been shown to restore normal metabolic function and improve energy production in these individuals.

Practical considerations: The appropriate L-carnitine dosage for individuals with autism varies based on age, weight, and individual needs. Typical dosages range from 50 to 100 mg/kg/day, divided into multiple doses[257]. It is crucial to consult a healthcare provider to determine the optimal dosage. L-carnitine supplementation is generally safe and well-tolerated. However, potential side effects include GI discomfort, fishy body odor, and, in rare cases, seizures. Regular monitoring of blood L-carnitine levels and overall health is recommended to ensure safe and effective supplementation [261]. L-carnitine supplementation may be used alongside other interventions, such as behavioral therapies and nutritional support, to maximize its potential benefits in managing autism symptoms[262]. Healthcare providers should consider evaluating and monitoring L-carnitine levels as part of a comprehensive treatment plan for autism, ensuring individualized and evidence-based care.

Omega 3 and 6 supplements

Omega-3 and Omega-6 fatty acids are essential polyunsaturated fats critical for various bodily functions, including brain development and function. Omega-3 is one of the most used complementary and alternative supplements in individuals with ASD[91]. Omega-3 fatty acids include alpha-linolenic acid, EPA, and DHA. They are primarily found in fish oils, flaxseeds, and walnuts. Omega-6 fatty acids, including LA and AA, are found in vegetable oils, nuts, and seeds[263]. Omega-3 and omega-6 fatty acids play critical roles in brain health and function, and their supplementation may benefit individuals with ASD. Given the unique neurological and developmental challenges faced by individuals with ASD, there has been significant interest in understanding the role these fatty acids might play in managing autism symptoms [264].

Biological functions: Omega-3 fatty acids are crucial for brain function, anti-inflammatory processes, and overall neural health. DHA, in particular, is a major structural component of the brain and retina. Omega-6 fatty acids are essential for skin health and growth and are a precursor for inflammatory and anti-inflammatory eicosanoids[265].

Potential benefits for individuals with ASD: Omega-3 fatty acids, especially DHA, are vital for brain development and cognitive function. Deficiencies in these fatty acids can impair neurodevelopment, which is particularly concerning in ASD. Omega-3s have anti-inflammatory effects that may help mitigate neuroinflammation, which has been implicated in the pathophysiology of ASD[49]. Reducing inflammation can potentially improve brain function and behavior. Some studies suggest that omega-3 supplementation can improve social interaction, communication, and repetitive behaviors in children with ASD[251]. Omega-3 fatty acids influence the production and function of neurotransmitters, such as serotonin and dopamine, which play roles in mood regulation and behavior[266,267]. These fatty acids are essential components of cell membranes, influencing their fluidity and the function of membrane-bound proteins, which are crucial for cellular signaling and function[268].

Studies and evidence: Research on omega-3 and omega-6 supplementation in ASD has shown mixed results, and more research is needed to establish definitive benefits. Some studies, such as Cheng *et al*[269] and Doaei *et al*[270], have reported improvements in hyperactivity, social skills, and cognitive development following omega-3 supplementation. Other studies have found no significant benefits, highlighting the variability in response among individuals with ASD[52, 271].

Recommended dosage and safety: There is no standardized dosage for omega-3 supplementation in ASD, and recommendations can vary[272]. It's essential to consult healthcare providers to determine appropriate dosages tailored to individual needs. Omega-3 supplements are generally considered safe with few side effects. However, high doses can lead to GI issues and an increased risk of bleeding due to their blood-thinning properties[273]. Maintaining a balanced ratio of omega-3 to omega-6 fatty acids is crucial. A high intake of omega-6 relative to omega-3 can promote inflammation, counteracting the benefits of omega-3s[274]. A typical Western diet often has a disproportionately high omega-6 to omega-3 ratio, which may necessitate omega-3 supplementation to restore balance[275].

Practical considerations: Encouraging the consumption of fatty fish, flaxseeds, chia seeds, and walnuts can naturally increase omega-3 intake. Fish oil supplements, especially DHA and EPA, are a common and effective way to ensure adequate omega-3 intake[276]. Fatty acid levels should be monitored regularly, and dietary intake or supplementation should be adjusted based on individual responses and nutritional needs[277]. While some evidence suggests potential improvements in behavior and cognitive function, the response can vary widely among individuals. Thus, omega-3 supplementation should be considered part of a comprehensive, individualized approach to managing autism, ideally under healthcare professionals' guidance. Table 3 summarizes dietary interventions, supplements, and their related details for ASD.

Role of feeding therapy and behavioral interventions in autism

Feeding problems are common in children with ASD, often manifesting as food selectivity, refusal, and limited dietary variety. These issues can lead to nutritional deficiencies and negatively impact overall health and development. Feeding therapy and behavioral interventions are crucial in addressing these challenges by promoting healthier eating habits and expanding food preferences[278].

Feeding therapy: Feeding therapy typically involves a multidisciplinary team, including dietitians, speech-language pathologists, occupational therapists, and psychologists. The primary goals are to improve oral motor skills, reduce sensory sensitivities, and establish positive mealtime behaviors[279]. Critical components of feeding therapy include oral motor skills development, sensory integration, mealtime structure, and positive reinforcement[280].

Table 3 The dietary interventions, supplements, and their related details for autism spectrum disorder

Intervention/supplement	Description	Functions	Potential links with ASD	Current research findings	Practical considerations
Gluten-free diet	Eliminates gluten (wheat, barley, rye). Requires careful planning for nutritional adequacy	Aims to improve gastrointestinal symptoms, behavior, attention, and social interactions	Increased sensitivity to gluten may affect brain function	Mixed evidence; more rigorous trials are needed.	Strict adherence is challenging; potential nutritional deficiencies; more expensive and less accessible
Casein-free diet	Eliminates casein (dairy products). Requires careful planning for nutritional adequacy	Aims to improve gastrointestinal symptoms, behavior, attention, and social interactions	Sensitivity or allergy to casein may exacerbate autism symptoms	Mixed evidence; more rigorous trials are needed	Strict adherence is challenging; potential nutritional deficiencies; more expensive and less accessible
Ketogenic diet	High-fat, low-carbohydrate, moderate-protein diet. Requires careful planning, medical evaluation, and regular monitoring	Aims to improve behavior, cognitive function, seizure control, and gastrointestinal symptoms	Ketones may have neuroprotective properties and improve brain function	Limited data; more rigorous trials are needed.	Potential nutritional deficiencies; strict adherence is challenging; potential side effects (GI discomfort, kidney stones, increased cholesterol)
Specific carbohydrate diet	Eliminates complex carbohydrates, disaccharides, and polysaccharides. Includes meats, certain vegetables, fruits, nuts, and seeds	Aims to improve gastrointestinal symptoms, behavior, and cognitive function	Addresses gut dysbiosis and gastrointestinal inflammation	Mixed results; more rigorous trials are needed	Restrictive; potential nutritional deficiencies; strict adherence is challenging; more expensive and less accessible
Gut and psychology syndrome diet	Structured in phases, includes bone broths, fermented foods, and healthy fats	Aims to improve gut health, behavior, cognitive function, and overall well-being	Focuses on healing the gut lining and restoring healthy gut flora	Limited peer-reviewed research; indirect support from studies on gut microbiota.	Restrictive; potential nutritional deficiencies; challenging to implement; anecdotal evidence
Camel milk	Rich in vitamins, minerals, and unique proteins	Anti-inflammatory, antioxidant, immune modulation, gut health promotion	Emerging research suggests behavioral improvements, cognitive functions, and GI symptom relief	Emerging research and anecdotal reports suggest significant benefits	Obtain from reputable sources, gradually introduce, consult healthcare provider for dosage, monitor response and allergic reactions
Probiotics	Restores healthy gut bacteria balance, reduces gut inflammation, strengthens gut barrier	Improves GI function, potential behavioral improvements	May improve gut health and behavior by restoring healthy gut bacteria	Mixed results; some studies show improved GI and behavioral symptoms	Choose effective strains, determine optimal dosage with clinical guidance, monitor and adjust based on individual response
Prebiotics	Promotes growth of beneficial gut bacteria, reduces inflammation, supports neurotransmitter synthesis	Improves gut health, potential behavioral and cognitive benefits	May improve gut health and behavior by promoting beneficial gut bacteria growth	Limited human trials but promising; animal models support positive effects	Start with low dose, include prebiotic-rich foods, use supplements under healthcare guidance, consider combining with probiotics, monitor for adverse reactions
High-dose methylcobalamin	Supports methylation cycle, boosts glutathione synthesis, neuroprotective properties	Enhances cognitive functions, reduces oxidative stress, improves detoxification	May improve behavioral and cognitive functions, reduce oxidative stress	Promising results; improved methylation capacity and reduced oxidative stress markers	Administer *via* injections, determine dosage with healthcare provider, regular monitoring of vitamin B12 Levels, consider combined treatment with folinic acid
Folic acid	Supports DNA methylation, reduces homocysteine levels, involved in	Potential reduction in ASD risk, improved neurodevelopment, reduced oxidative stress	Prenatal supplementation may reduce ASD risk.	Prenatal doses support reduced ASD risk; large epidemiological	Recommend 400-800 mcg/day prenatal doses, consider genetic variations, ensure

	neurotransmitter synthesis			studies support benefits	balanced diet, consult healthcare provider for high doses
Vitamin B6	Synthesizes neurotransmitters, reduces homocysteine levels, converts glutamate to GABA	Potential improvements in behavior, language development, cognitive function	May improve behavior, language, and cognitive functions	Mixed results; some studies show improvements; variability in outcomes	Determine dosage with healthcare provider, monitor for side effects (peripheral neuropathy), consider combination with magnesium.
Vitamin D	Fat-soluble vitamin; exists as vitamin D2 and D3; synthesized in skin or obtained from food sources	Facilitates calcium and phosphorus absorption, modulates immune system, reduces inflammation, supports brain development	Low vitamin D levels linked with ASD risk; deficiency associated with immune dysregulation and neurotransmitter imbalances	Benefits of vitamin D3 supplementation include improved autism severity scores and social behaviors	Dosage varies; general recommendation 600-800 IU daily; excessive intake can lead to toxicity; regular monitoring essential
L-Carnitine	Naturally occurring amino acid derivative; involved in energy metabolism and mitochondrial health	Facilitates fatty acid transport into mitochondria, supports mitochondrial health, and has antioxidant properties	Mitochondrial dysfunction and oxidative stress observed in autism; L-carnitine may improve mitochondrial function and reduce oxidative stress	Lower L-carnitine levels in autism; improvements in behavior and communication with supplementation.	Dosage ranges from 50 to 100 mg/kg/day; consult healthcare providers; generally safe but may cause gastrointestinal discomfort or fishy odor
Omega-3 and Omega-6	Essential polyunsaturated fatty acids; Omega-3 (ALA, EPA, DHA) and Omega-6 (LA, AA)	Vital for brain function, anti-inflammatory effects, and overall neural health	Omega-3 deficiencies may impair neurodevelopment; Omega-3s may improve behavior; Omega-6 imbalance can promote inflammation	Mixed results; some studies show improvements in behavior, cognitive development, and social skills	No standardized dosage; consult healthcare providers; high doses may cause GI issues and increased bleeding risk; balance omega-3 and omega-6 intake

ASD: Autism spectrum disorder; ALA: Alpha-linolenic acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; LA: Linoleic acid; AA: Arachidonic acid; GI: Gastrointestinal; GABA: gamma-aminobutyric acid.

Many children with ASD have difficulty chewing, swallowing, and oral coordination. Therapists strengthen these skills through exercises and activities to improve muscle function and coordination[281]. Sensory sensitivities to textures, tastes, and smells are common in children with ASD[282]. Feeding therapists use gradual exposure techniques to desensitize children to various sensory stimuli. This may involve introducing new foods in a non-threatening way, such as through play or gradual taste testing[65]. Establishing consistent mealtime routines can help reduce anxiety and improve eating behaviors. This includes having regular meal and snack times, creating a calm eating environment, and using visual schedules to help children understand what to expect[283]. Encouraging positive eating behaviors through rewards and praise can motivate children to try new foods and adopt healthier eating habits. This approach focuses on reinforcing desired behaviors rather than punishing undesirable ones[284].

Feeding behavioral interventions: Behavioral interventions are often used in conjunction with feeding therapy to address food selectivity and refusal. These interventions are based on principles of ABA and involve systematic techniques to modify eating behaviors[285]. Key strategies include gradual exposure and desensitization, modeling and social stories, choice, and control, reinforcement, and rewards, and task analysis and shaping[286].

Introducing new foods gradually and in small amounts can help reduce resistance. This technique involves pairing new foods with preferred ones, starting with just a touch or smell and gradually progressing to tasting and eating[287]. Children with ASD often learn through imitation. Modeling involves demonstrating appropriate eating behaviors, either by therapists, parents, or peers. Social stories are short, descriptive narratives that explain social situations and appropriate responses; helping children understand and anticipate mealtime routines and allowing children to make choices about what and how much to eat can reduce anxiety and resistance[288]. Providing a limited selection of healthy options empowers children while ensuring nutritional needs are met[289].

Positive reinforcement, such as verbal praise, stickers, or small toys, can be used to reward desired behaviors like trying a new food or sitting at the table for the duration of a meal[290]. The reinforcement should be immediate and consistently applied. Breaking down the process of eating into small, manageable steps and reinforcing each step can help children gradually build up to more complex behaviors. Shaping involves reinforcing successive approximations of the target behavior until the desired behavior is achieved[291,292].

Techniques to expand food preferences: Expanding food preferences in children with ASD involves a combination of strategies aimed at increasing acceptance and variety in their diet. Techniques include food chaining, systematic desensitization, cooking and food preparation involvement, sensory play, consistency and patience, and parental involvement and education[16].

The food chain method involves gradually introducing new foods similar in taste, texture, or appearance to foods the child already accepts[293]. For example, if a child likes chicken nuggets, therapists might introduce breaded fish sticks, then grilled chicken, and eventually other types of protein. Similar to gradual exposure, the systematic desensitization technique involves slowly introducing new foods to reduce sensory overload[294] and, for instance, starting with a visual introduction, followed by touching, smelling, and finally tasting the food[295]. Involving children in cooking and food preparation can increase their interest in and acceptance of new foods. This hands-on approach allows children to explore new foods in a fun and non-threatening way. Encouraging sensory play with food can help children become more comfortable with different textures and smells[296]. Activities like playing with food-based sensory bins or using food in art projects can reduce sensory sensitivities[297]. Consistently offering new foods and being patient with the child's progress is crucial. It may take multiple exposures before a child is willing to try a new food. Avoid pressuring the child, which can increase resistance[298]. It is essential to educate parents about the importance of variety in the diet and provide them with strategies to encourage healthy eating at home. Parents play a critical role in modeling positive eating behaviors and creating a supportive mealtime environment[299]. By combining oral-motor skill development, sensory integration, structured mealtime routines, and behavioral techniques, therapists can help expand food preferences and improve nutritional intake, contributing to better overall health and development for children with autism.

Mealtime environment and practices for children with autism

Creating a supportive and structured mealtime environment is crucial for children with ASD. The mealtime setting can significantly influence a child's eating behaviors, food acceptance, and overall nutritional intake[300]. To enhance the mealtime environment for children with autism, they need to have a consistent mealtime routine, a calm and positive atmosphere, a sensory-friendly environment, positive mealtime practices, gradual introduction of new foods, managing feeding challenges, nutritional balance, collaboration with professionals, and parental support and education[301].

Establishing regular meal and snack times is essential for a consistent mealtime routine. This can create predictability and structure, reducing anxiety and resistance[302]. Visual schedules or timers can help children understand and anticipate mealtime routines, making transitions smoother. The meals should be consistent in length, typically around 20-30 minutes, to maintain structure without overstaying the child's attention span[303]. A calm and positive atmosphere is attempted by reducing background noise and distractions such as TV, loud music, or excessive conversation to help the child focus on eating[304]. Children should engage in pleasant and encouraging conversations that promote a relaxed atmosphere while avoiding discussing stressful or negative topics during meals. Children should be comfortably seated at the table with appropriate support, using adaptive seating if necessary to help them stay seated and focused[305].

Creating a sensory-friendly environment is crucial for helping children with autism focus on their food. Opting for soft, natural lighting can prevent the overwhelming effects of harsh or flickering lights, which can be distracting and distressing[306]. Additionally, using plain, non-patterned tableware helps to avoid overstimulation and aligns with the child's sensory preferences regarding textures and materials[307]. Ensuring the room temperature is comfortable is also important, as some children with ASD are sensitive to extreme temperatures, which can significantly affect their eating behavior[308]. By addressing these sensory factors, the mealtime experience can be made more comfortable and conducive to positive eating behaviors for children with autism. Positive mealtime practices are essential for fostering healthy eating habits in children with autism. Role modeling by adults and peers is crucial, as it demonstrates appropriate eating behaviors, positive food attitudes, and table manners[309]. Consistent encouragement and praise should be provided for trying new foods, using utensils correctly, or displaying other desired behaviors. Additionally, involving the child in meal planning and preparation can increase their interest in food. Simple tasks such as washing vegetables or stirring ingredients can make children more willing to try new foods[310].

Gradually introducing new foods is essential for children with autism to minimize resistance and encourage acceptance. Introducing new foods slowly and in small quantities alongside familiar and preferred foods can significantly reduce resistance[18]. Food chaining is an effective technique that involves gradually expanding the range of accepted foods by linking new foods to those the child already likes based on similarities in taste, texture, or appearance[293]. Additionally, non-pressured exposure, where new foods are offered repeatedly in a non-coercive manner, allows the child to become familiar with the food over time without feeling forced. This approach fosters a more positive and accepting attitude towards new foods[311].

Managing feeding challenges in children with autism involves several key strategies. When a child refuses food, it is essential to remain calm and remove the food without negative comments, reintroducing it later without making it a focus. For selective eating, respecting the child's preferences while gently encouraging variety is essential; a range of foods should be offered repeatedly, even if initially rejected[312]. Addressing oral-motor difficulties with appropriate therapy and techniques is crucial to improving chewing, swallowing, and overall eating skills. These approaches help create a supportive feeding environment and promote better nutritional intake[313]. Ensuring nutritional balance in children with autism involves promoting dietary diversity and monitoring for potential deficiencies. A balanced diet with various foods is essential to ensure the child receives all necessary nutrients, particularly if they have restrictive eating habits[17]. It is advisable to consult with healthcare providers about the need for nutritional supplements if the child's diet lacks essential vitamins or minerals to support their overall health and development.

Collaboration with professionals is crucial in addressing the nutritional needs and mealtime behaviors of children with autism. Working with dietitians, speech-language pathologists, and occupational therapists allows for the development of personalized strategies to improve mealtime behaviors and ensure adequate nutrition[314]. Additionally, collaborating with behavioral specialists to implement ABA techniques can help modify eating behaviors and reduce mealtime stress, fostering a more positive and effective eating environment[315]. Parental support and education play a vital role in managing mealtime challenges for children with autism. Training parents and caregivers in effective mealtime strategies and emphasizing the importance of a structured, positive environment are essential[71]. Additionally, encouraging

participation in support groups allows parents to share experiences and strategies, providing a network of support and practical advice for addressing feeding issues[316].

Recommendations

Based on the synthesis of current literature, several recommendations can be made to optimize feeding therapy, behavioral interventions, and mealtime practices for children with ASD. Firstly, healthcare professionals should prioritize multidisciplinary approaches integrating dietitians, speech-language pathologists, occupational therapists, and psychologists in designing personalized treatment plans tailored to each child's specific needs and challenges. Emphasizing early intervention is crucial, as interventions targeting oral motor skills, sensory sensitivities, and mealtime routines have shown promising outcomes in improving food acceptance and nutritional intake. Structured feeding therapy programs should focus on individualized goals that address oral motor deficits and sensory aversions, employing techniques such as oral motor exercises, sensory integration activities, and gradual exposure to new foods. Behavioral interventions grounded in ABA principles should be utilized to reinforce positive eating behaviors, systematically desensitize sensory aversions, and promote mealtime routines that enhance predictability and reduce anxiety. Creating a supportive mealtime environment is essential. This involves establishing consistent meal schedules, sensory-friendly settings, and visual supports to aid understanding and anticipation of mealtime routines. Parents and caregivers play a pivotal role in implementing strategies learned from professionals, emphasizing positive reinforcement, modeling appropriate eating behaviors, and gradually expanding food choices through techniques like food chaining and systematic desensitization. Further research is needed to standardize intervention protocols, assess long-term outcomes, and explore the effectiveness of emerging technologies and innovative therapies in improving feeding behaviors and nutritional status among children with ASD. Collaboration among researchers, healthcare providers, educators, and families is essential to develop evidence-based practices that enhance the quality of life and nutritional health for children with ASD.

Limitations

Several limitations should be considered when interpreting the findings of this systematic review. Firstly, the variability in study designs, intervention protocols, and outcome measures across the included studies may introduce heterogeneity and limit direct comparisons. Most studies relied on small sample sizes, which may affect the generalizability of findings to broader populations of children with ASD. Moreover, many studies lacked long-term follow-up assessments, making evaluating the sustainability of intervention effects over time challenging. The quality of evidence varied among studies, with some lacking rigorous methodologies such as RCTs or blinding of assessors. This variability in study quality could impact the reliability and strength of conclusions drawn from the collective evidence. Additionally, the reliance on parent-reported outcomes in many studies may introduce bias, as subjective perceptions of improvement in feeding behaviors and mealtime practices could influence reported outcomes. Furthermore, the complexity of ASD as a heterogeneous neurodevelopmental disorder presents challenges in identifying universally effective interventions. Children with ASD often present with diverse sensory sensitivities, oral motor deficits, and behavioral patterns, necessitating personalized and adaptive approaches to treatment. The effectiveness of interventions may vary depending on individual characteristics, comorbidities, and family dynamics, highlighting the need for tailored intervention strategies. Lastly, publication bias may influence the availability of studies included in this review, as studies reporting positive outcomes may be more likely to be published than those with null or negative findings. This potential bias could impact the comprehensiveness and representativeness of the evidence base synthesized in this review.

CONCLUSION

In conclusion, this systematic review synthesizes current evidence on feeding therapy, behavioral interventions, and mealtime practices for children with ASD. The findings highlight the multifaceted nature of interventions to improve this population's feeding behaviors and mealtime practices. Feeding therapy approaches, including oral motor skills development, sensory integration techniques, and structured mealtime routines, show promise in addressing the unique challenges faced by children with ASD. Behavioral interventions based on ABA principles, such as gradual exposure, modeling, and positive reinforcement, offer effective strategies for reducing food selectivity and enhancing mealtime behaviors. Additionally, creating supportive mealtime environments that cater to sensory sensitivities and providing parental education and support are critical components of successful interventions. Despite the promising results observed across various studies, several limitations warrant cautious interpretation of findings, including study heterogeneity, small sample sizes, and methodological biases. The variability in intervention outcomes underscores the need for personalized, tailored approaches that consider individual differences in sensory profiles, oral motor skills, and behavioral patterns among children with ASD. Future research should focus on conducting well-designed RCTs with larger sample sizes and standardized outcome measures further to elucidate the effectiveness and long-term benefits of specific interventions. Longitudinal studies are needed to assess the sustainability of intervention effects over time and to understand better the complex interplay between intervention components, individual characteristics, and family dynamics. Overall, while significant strides have been made in understanding and addressing feeding difficulties and mealtime challenges in children with ASD, continued research and clinical innovation are essential to optimize interventions and improve outcomes for this vulnerable population.

FOOTNOTES

Author contributions: Al-Beltagi M wrote this review exploring the effects of diet on children with autism; Al-Beltagi M conceptualized and designed the review, conducted the search in electronic databases, and synthesized the included studies' findings.

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REFERENCES

1 **Al-Beltagi M**. Autism medical comorbidities. *World J Clin Pediatr* 2021; **10**: 15-28 [PMID: 33972922 DOI: 10.5409/wjcp.v10.i3.15]
2 **Maenner MJ**, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, Durkin MS, Fitzgerald RT, Furnier SM, Hughes MM, Ladd-Acosta CM, McArthur D, Pas ET, Salinas A, Vehorn A, Williams S, Esler A, Grzybowski A, Hall-Lande J, Nguyen RHN, Pierce K, Zahorodny W, Hudson A, Hallas L, Mancilla KC, Patrick M, Shenouda J, Sidwell K, DiRienzo M, Gutierrez J, Spivey MH, Lopez M, Pettygrove S, Schwenk YD, Washington A, Shaw KA. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. *MMWR Surveill Summ* 2023; **72**: 1-14 [PMID: 36952288 DOI: 10.15585/mmwr.ss7202a1]
3 **Havdahl A**, Niarchou M, Starnawska A, Uddin M, van der Merwe C, Warrier V. Genetic contributions to autism spectrum disorder. *Psychol Med* 2021; **51**: 2260-2273 [PMID: 33634770 DOI: 10.1017/S0033291721000192]
4 **Ha S**, Sohn IJ, Kim N, Sim HJ, Cheon KA. Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. *Exp Neurobiol* 2015; **24**: 273-284 [PMID: 26713076 DOI: 10.5607/en.2015.24.4.273]
5 **Petrolini V**, Jorba M, Vicente A. What does it take to be rigid? Reflections on the notion of rigidity in autism. *Front Psychiatry* 2023; **14**: 1072362 [PMID: 36860504 DOI: 10.3389/fpsyt.2023.1072362]
6 **Al-Beltagi M**, Saeed NK, Bediwy AS, Elbeltagi R. Metabolomic changes in children with autism. *World J Clin Pediatr* 2024; **13**: 92737 [PMID: 38947988 DOI: 10.5409/wjcp.v13.i2.92737]
7 **Brian JA**, Zwaigenbaum L, Ip A. Standards of diagnostic assessment for autism spectrum disorder. *Paediatr Child Health* 2019; **24**: 444-460 [PMID: 31660042 DOI: 10.1093/pch/pxz117]
8 **Weiss JA**, Wingsiong A, Lunsky Y. Defining crisis in families of individuals with autism spectrum disorders. *Autism* 2014; **18**: 985-995 [PMID: 24254639 DOI: 10.1177/1362361313508024]
9 **Byrska A**, Błażejczyk I, Faruga A, Potaczek M, Wilczyński KM, Janas-Kozik M. Patterns of Food Selectivity among Children with Autism Spectrum Disorder. *J Clin Med* 2023; **12** [PMID: 37685537 DOI: 10.3390/jcm12175469]
10 **Al-Beltagi M**, Saeed NK, Bediwy AS, Elbeltagi R, Alhawamdeh R. Role of gastrointestinal health in managing children with autism spectrum disorder. *World J Clin Pediatr* 2023; **12**: 171-196 [PMID: 37753490 DOI: 10.5409/wjcp.v12.i4.171]
11 **Önal S**, Sachadyn-Król M, Kostecka M. A Review of the Nutritional Approach and the Role of Dietary Components in Children with Autism Spectrum Disorders in Light of the Latest Scientific Research. *Nutrients* 2023; **15** [PMID: 38068711 DOI: 10.3390/nu15234852]
12 **Cermak SA**, Curtin C, Bandini LG. Food selectivity and sensory sensitivity in children with autism spectrum disorders. *J Am Diet Assoc* 2010; **110**: 238-246 [PMID: 20102851 DOI: 10.1016/j.jada.2009.10.032]
13 **Bennetto L**, Kuschner ES, Hyman SL. Olfaction and taste processing in autism. *Biol Psychiatry* 2007; **62**: 1015-1021 [PMID: 17572391 DOI: 10.1016/j.biopsych.2007.04.019]
14 **Chistol LT**, Bandini LG, Must A, Phillips S, Cermak SA, Curtin C. Sensory Sensitivity and Food Selectivity in Children with Autism Spectrum Disorder. *J Autism Dev Disord* 2018; **48**: 583-591 [PMID: 29116421 DOI: 10.1007/s10803-017-3340-9]
15 **Cappellotto M**, Olsen A. Food Texture Acceptance, Sensory Sensitivity, and Food Neophobia in Children and Their Parents. *Foods* 2021; **10** [PMID: 34681376 DOI: 10.3390/foods10102327]
16 **Esposito M**, Mirizzi P, Fadda R, Pirollo C, Ricciardi O, Mazza M, Valenti M. Food Selectivity in Children with Autism: Guidelines for Assessment and Clinical Interventions. *Int J Environ Res Public Health* 2023; **20** [PMID: 36982001 DOI: 10.3390/ijerph20065092]
17 **Doreswamy S**, Bashir A, Guarecuco JE, Lahori S, Baig A, Narra LR, Patel P, Heindl SE. Effects of Diet, Nutrition, and Exercise in Children With Autism and Autism Spectrum Disorder: A Literature Review. *Cureus* 2020; **12**: e12222 [PMID: 33489626 DOI: 10.7759/cureus.12222]
18 **Chawner LR**, Blundell-Birtill P, Hetherington MM. Interventions for Increasing Acceptance of New Foods Among Children and Adults with Developmental Disorders: A Systematic Review. *J Autism Dev Disord* 2019; **49**: 3504-3525 [PMID: 31124025 DOI:

10.1007/s10803-019-04075-0]
19 **Lefter R**, Ciobica A, Timofte D, Stanciu C, Trifan A. A Descriptive Review on the Prevalence of Gastrointestinal Disturbances and Their Multiple Associations in Autism Spectrum Disorder. *Medicina (Kaunas)* 2019; **56** [PMID: 31892195 DOI: 10.3390/medicina56010011]
20 **Settanni CR**, Bibbò S, Ianiro G, Rinninella E, Cintoni M, Mele MC, Cammarota G, Gasbarrini A. Gastrointestinal involvement of autism spectrum disorder: focus on gut microbiota. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 599-622 [PMID: 33356668 DOI: 10.1080/17474124.2021.1869938]
21 **Deng W**, Wang S, Li F, Wang F, Xing YP, Li Y, Lv Y, Ke H, Li Z, Lv PJ, Hao H, Chen Y, Xiao X. Gastrointestinal symptoms have a minor impact on autism spectrum disorder and associations with gut microbiota and short-chain fatty acids. *Front Microbiol* 2022; **13**: 1000419 [PMID: 36274684 DOI: 10.3389/fmicb.2022.1000419]
22 **Kamionkowski S**, Shibli F, Ganocy S, Fass R. The relationship between gastroesophageal reflux disease and autism spectrum disorder in adult patients in the United States. *Neurogastroenterol Motil* 2022; **34**: e14295 [PMID: 34859933 DOI: 10.1111/nmo.14295]
23 **Madra M**, Ringel R, Margolis KG. Gastrointestinal Issues and Autism Spectrum Disorder. *Psychiatr Clin North Am* 2021; **44**: 69-81 [PMID: 33526238 DOI: 10.1016/j.psc.2020.11.006]
24 **Kim JY**, Choi MJ, Ha S, Hwang J, Koyanagi A, Dragioti E, Radua J, Smith L, Jacob L, Salazar de Pablo G, Lee SW, Yon DK, Thompson T, Cortese S, Lollo G, Liang CS, Chu CS, Fusar-Poli P, Cheon KA, Shin JI, Solmi M. Association between autism spectrum disorder and inflammatory bowel disease: A systematic review and meta-analysis. *Autism Res* 2022; **15**: 340-352 [PMID: 34939353 DOI: 10.1002/aur.2656]
25 **Wasilewska J**, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks - a possible new overlap syndrome. *Pediatric Health Med Ther* 2015; **6**: 153-166 [PMID: 29388597 DOI: 10.2147/PHMT.S85717]
26 **Maslen C**, Hodge R, Tie K, Laugharne R, Lamb K, Shankar R. Constipation in autistic people and people with learning disabilities. *Br J Gen Pract* 2022; **72**: 348-351 [PMID: 35772989 DOI: 10.3399/bjgp22X720077]
27 **Babinska K**, Celusakova H, Belica I, Szapuova Z, Waczulikova I, Nemcsicsova D, Tomova A, Ostatnikova D. Gastrointestinal Symptoms and Feeding Problems and Their Associations with Dietary Interventions, Food Supplement Use, and Behavioral Characteristics in a Sample of Children and Adolescents with Autism Spectrum Disorders. *Int J Environ Res Public Health* 2020; **17** [PMID: 32882981 DOI: 10.3390/ijerph17176372]
28 **Brignell A**, Chenausky KV, Song H, Zhu J, Suo C, Morgan AT. Communication interventions for autism spectrum disorder in minimally verbal children. *Cochrane Database Syst Rev* 2018; **11**: CD012324 [PMID: 30395694 DOI: 10.1002/14651858.CD012324.pub2]
29 **Pasta A**, Formisano E, Calabrese F, Plaz Torres MC, Bodini G, Marabotto E, Pisciotta L, Giannini EG, Furnari M. Food Intolerances, Food Allergies and IBS: Lights and Shadows. *Nutrients* 2024; **16** [PMID: 38257158 DOI: 10.3390/nu16020265]
30 **Saeed NK**, Al-Beltagi M, Bediwy AS, El-Sawaf Y, Toema O. Gut microbiota in various childhood disorders: Implication and indications. *World J Gastroenterol* 2022; **28**: 1875-1901 [PMID: 35664966 DOI: 10.3748/wjg.v28.i18.1875]
31 **Berding K**, Donovan SM. Diet Can Impact Microbiota Composition in Children With Autism Spectrum Disorder. *Front Neurosci* 2018; **12**: 515 [PMID: 30108477 DOI: 10.3389/fnins.2018.00515]
32 **Berry RC**, Novak P, Withrow N, Schmidt B, Rarback S, Feucht S, Criado KK, Sharp WG. Nutrition Management of Gastrointestinal Symptoms in Children with Autism Spectrum Disorder: Guideline from an Expert Panel. *J Acad Nutr Diet* 2015; **115**: 1919-1927 [PMID: 26164551 DOI: 10.1016/j.jand.2015.05.016]
33 **Fulceri F**, Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, Calderoni S, Muratori F. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. *Dig Liver Dis* 2016; **48**: 248-254 [PMID: 26748423 DOI: 10.1016/j.dld.2015.11.026]
34 **Johnson E**, van Zijl K, Kuyler A. Pain communication in children with autism spectrum disorder: A scoping review. *Paediatr Neonatal Pain* 2023; **5**: 127-141 [PMID: 38149220 DOI: 10.1002/pne2.12115]
35 **Leader G**, Abberton C, Cunningham S, Gilmartin K, Grudzien M, Higgins E, Joshi L, Whelan S, Mannion A. Gastrointestinal Symptoms in Autism Spectrum Disorder: A Systematic Review. *Nutrients* 2022; **14** [PMID: 35406084 DOI: 10.3390/nu14071471]
36 **Mannion A**, Leader G. Relationship Between Gastrointestinal Symptoms in Autism Spectrum Disorder and Parent Stress, Anxiety, Depression, Quality of Life and Social Support. *J Autism Dev Disord* 2023 [PMID: 37656363 DOI: 10.1007/s10803-023-06110-7]
37 **Chakraborty P**, Carpenter KLH, Major S, Deaver M, Vermeer S, Herold B, Franz L, Howard J, Dawson G. Gastrointestinal problems are associated with increased repetitive behaviors but not social communication difficulties in young children with autism spectrum disorders. *Autism* 2021; **25**: 405-415 [PMID: 32972215 DOI: 10.1177/1362361320959503]
38 **Karhu E**, Zukerman R, Eshraghi RS, Mittal J, Deth RC, Castejon AM, Trivedi M, Mittal R, Eshraghi AA. Nutritional interventions for autism spectrum disorder. *Nutr Rev* 2020; **78**: 515-531 [PMID: 31876938 DOI: 10.1093/nutrit/nuz092]
39 **Wang Z**, Ding R, Wang J. The Association between Vitamin D Status and Autism Spectrum Disorder (ASD): A Systematic Review and Meta-Analysis. *Nutrients* 2020; **13** [PMID: 33383952 DOI: 10.3390/nu13010086]
40 **Hanna M**, Jaqua E, Nguyen V, Clay J. B Vitamins: Functions and Uses in Medicine. *Perm J* 2022; **26**: 89-97 [PMID: 35933667 DOI: 10.7812/TPP/21.204]
41 **Rizvi S**, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The role of vitamin e in human health and some diseases. *Sultan Qaboos Univ Med J* 2014; **14**: e157-e165 [PMID: 24790736]
42 **Babaknejad N**, Sayehmiri F, Sayehmiri K, Mohamadkhani A, Bahrami S. The Relationship between Zinc Levels and Autism: A Systematic Review and Meta-analysis. *Iran J Child Neurol* 2016; **10**: 1-9 [PMID: 27843460]
43 **Vela G**, Stark P, Socha M, Sauer AK, Hagmeyer S, Grabrucker AM. Zinc in gut-brain interaction in autism and neurological disorders. *Neural Plast* 2015; **2015**: 972791 [PMID: 25878905 DOI: 10.1155/2015/972791]
44 **Gunes S**, Ekinci O, Celik T. Iron deficiency parameters in autism spectrum disorder: clinical correlates and associated factors. *Ital J Pediatr* 2017; **43**: 86 [PMID: 28934988 DOI: 10.1186/s13052-017-0407-3]
45 **Baj J**, Flieger W, Flieger M, Forma A, Sitarz E, Skórzyńska-Dziduszko K, Grochowski C, Maciejewski R, Karakuła-Juchnowicz H. Autism spectrum disorder: Trace elements imbalances and the pathogenesis and severity of autistic symptoms. *Neurosci Biobehav Rev* 2021; **129**: 117-132 [PMID: 34339708 DOI: 10.1016/j.neubiorev.2021.07.029]
46 **Błażewicz A**, Grabrucker AM. Metal Profiles in Autism Spectrum Disorders: A Crosstalk between Toxic and Essential Metals. *Int J Mol Sci* 2022; **24** [PMID: 36613749 DOI: 10.3390/ijms24010308]
47 **Neumeyer AM**, Cano Sokoloff N, McDonnell EI, Macklin EA, McDougle CJ, Holmes TM, Hubbard JL, Misra M. Nutrition and Bone Density in Boys with Autism Spectrum Disorder. *J Acad Nutr Diet* 2018; **118**: 865-877 [PMID: 29409733 DOI: 10.1016/j.jand.2017.11.006]

48 **Bent S**, Bertoglio K, Hendren RL. Omega-3 fatty acids for autistic spectrum disorder: a systematic review. *J Autism Dev Disord* 2009; **39**: 1145-1154 [PMID: 19333748 DOI: 10.1007/s10803-009-0724-5]

49 **Dighriri IM**, Alsubaie AM, Hakami FM, Hamithi DM, Alshekh MM, Khobrani FA, Dalak FE, Hakami AA, Alsueaadi EH, Alsaawi LS, Alshammari SF, Alqahtani AS, Alawi IA, Aljuaid AA, Tawhari MQ. Effects of Omega-3 Polyunsaturated Fatty Acids on Brain Functions: A Systematic Review. *Cureus* 2022; **14**: e30091 [PMID: 36381743 DOI: 10.7759/cureus.30091]

50 **Rodrigues EL**, Figueiredo PS, Marcelino G, de Cássia Avellaneda Guimarães R, Pott A, Santana LF, Hiane PA, do Nascimento VA, Bogo D, de Cássia Freitas K. Maternal Intake of Polyunsaturated Fatty Acids in Autism Spectrum Etiology and Its Relation to the Gut Microbiota: What Do We Know? *Nutrients* 2023; **15** [PMID: 37049390 DOI: 10.3390/nu15071551]

51 **DiNicolantonio JJ**, O'Keefe JH. The Importance of Marine Omega-3s for Brain Development and the Prevention and Treatment of Behavior, Mood, and Other Brain Disorders. *Nutrients* 2020; **12** [PMID: 32759851 DOI: 10.3390/nu12082333]

52 **Pancheva RZ**, Nikolova S, Serbezova A, Zaykova K, Zhelyazkova D, Dimitrov L. Evidence or no evidence for essential fatty acids in the treatment of autism spectrum disorders? *Front Nutr* 2023; **10**: 1251083 [PMID: 37727635 DOI: 10.3389/fnut.2023.1251083]

53 **Loef M**, Walach H. The omega-6/omega-3 ratio and dementia or cognitive decline: a systematic review on human studies and biological evidence. *J Nutr Gerontol Geriatr* 2013; **32**: 1-23 [PMID: 23451843 DOI: 10.1080/21551197.2012.752335]

54 **Posar A**, Visconti P. Omega-3 supplementation in autism spectrum disorders: A still open question? *J Pediatr Neurosci* 2016; **11**: 225-227 [PMID: 27857792 DOI: 10.4103/1817-1745.193363]

55 **Muñoz-Garach A**, García-Fontana B, Muñoz-Torres M. Nutrients and Dietary Patterns Related to Osteoporosis. *Nutrients* 2020; **12** [PMID: 32635394 DOI: 10.3390/nu12071986]

56 **Reider CA**, Chung RY, Devarshi PP, Grant RW, Hazels Mitmesser S. Inadequacy of Immune Health Nutrients: Intakes in US Adults, the 2005-2016 NHANES. *Nutrients* 2020; **12** [PMID: 32531972 DOI: 10.3390/nu12061735]

57 **Kittana M**, Ahmadani A, Williams KE, Attlee A. Nutritional Status and Feeding Behavior of Children with Autism Spectrum Disorder in the Middle East and North Africa Region: A Systematic Review. *Nutrients* 2023; **15** [PMID: 36771417 DOI: 10.3390/nu15030711]

58 **Fekete M**, Lehoczki A, Tarantini S, Fazekas-Pongor V, Csípő T, Csizmadia Z, Varga JT. Improving Cognitive Function with Nutritional Supplements in Aging: A Comprehensive Narrative Review of Clinical Studies Investigating the Effects of Vitamins, Minerals, Antioxidants, and Other Dietary Supplements. *Nutrients* 2023; **15** [PMID: 38140375 DOI: 10.3390/nu15245116]

59 **Nogay NH**, Nahikian-Nelms M. Effects of nutritional interventions in children and adolescents with autism spectrum disorder: an overview based on a literature review. *Int J Dev Disabil* 2023; **69**: 811-824 [PMID: 37885847 DOI: 10.1080/20473869.2022.2036921]

60 **Zielińska M**, Łuszczki E, Dereń K. Dietary Nutrient Deficiencies and Risk of Depression (Review Article 2018-2023). *Nutrients* 2023; **15** [PMID: 37299394 DOI: 10.3390/nu15112433]

61 **Bose I**, Baldi G, Kiess L, de Pee S. The "Fill the Nutrient Gap" analysis: An approach to strengthen nutrition situation analysis and decision making towards multisectoral policies and systems change. *Matern Child Nutr* 2019; **15**: e12793 [PMID: 30698364 DOI: 10.1111/mcn.12793]

62 **Hyman SL**, Stewart PA, Schmidt B, Cain U, Lemcke N, Foley JT, Peck R, Clemons T, Reynolds A, Johnson C, Handen B, James SJ, Courtney PM, Molloy C, Ng PK. Nutrient intake from food in children with autism. *Pediatrics* 2012; **130** Suppl 2: S145-S153 [PMID: 23118245 DOI: 10.1542/peds.2012-0900L]

63 **Conti MV**, Breda C, Basilico S, Luzzi A, Voto L, Santero S, De Filippo G, Cena H. Dietary recommendations to customize canteen menus according to the nutritional and sensory needs of individuals with autism spectrum disorder. *Eat Weight Disord* 2023; **28**: 66 [PMID: 37526770 DOI: 10.1007/s40519-023-01590-z]

64 **Margari L**, Marzulli L, Gabellone A, de Giambattista C. Eating and Mealtime Behaviors in Patients with Autism Spectrum Disorder: Current Perspectives. *Neuropsychiatr Dis Treat* 2020; **16**: 2083-2102 [PMID: 32982247 DOI: 10.2147/NDT.S224779]

65 **Reche-Olmedo L**, Torres-Collado L, Compañ-Gabucio LM, Garcia-de-la-Hera M. The Role of Occupational Therapy in Managing Food Selectivity of Children with Autism Spectrum Disorder: A Scoping Review. *Children (Basel)* 2021; **8** [PMID: 34828737 DOI: 10.3390/children8111024]

66 **Tardy AL**, Pouteau E, Marquez D, Yilmaz C, Scholey A. Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence. *Nutrients* 2020; **12** [PMID: 31963141 DOI: 10.3390/nu12010228]

67 **Wierzejska RE**. Dietary Supplements-For Whom? The Current State of Knowledge about the Health Effects of Selected Supplement Use. *Int J Environ Res Public Health* 2021; **18** [PMID: 34501487 DOI: 10.3390/ijerph18178897]

68 **Satish Kumar L**, Pugalenthi LS, Ahmad M, Reddy S, Barkhane Z, Elmadi J. Probiotics in Irritable Bowel Syndrome: A Review of Their Therapeutic Role. *Cureus* 2022; **14**: e24240 [PMID: 35602835 DOI: 10.7759/cureus.24240]

69 **Corsello A**, Pugliese D, Gasbarrini A, Armuzzi A. Diet and Nutrients in Gastrointestinal Chronic Diseases. *Nutrients* 2020; **12** [PMID: 32899273 DOI: 10.3390/nu12092693]

70 **Ardoin TW**, Hamer D, Mason N, Reine A, Barleycorn L, Francis D, Johnson A. Effectiveness of a Patient-Centered Dietary Educational Intervention. *Ochsner J* 2022; **22**: 113-128 [PMID: 35756590 DOI: 10.31486/toj.21.0075]

71 **Ausderau KK**, St John B, Kwaterski KN, Nieuwenhuis B, Bradley E. Parents' Strategies to Support Mealtime Participation of Their Children With Autism Spectrum Disorder. *Am J Occup Ther* 2019; **73**: 7301205070p1-7301205070p10 [PMID: 30839262 DOI: 10.5014/ajot.2019.024612]

72 **Adams JB**, Audhya T, Geis E, Gehn E, Fimbres V, Pollard EL, Mitchell J, Ingram J, Hellmers R, Laake D, Matthews JS, Li K, Naviaux JC, Naviaux RK, Adams RL, Coleman DM, Quig DW. Comprehensive Nutritional and Dietary Intervention for Autism Spectrum Disorder-A Randomized, Controlled 12-Month Trial. *Nutrients* 2018; **10** [PMID: 29562612 DOI: 10.3390/nu10030369]

73 **Ranjan S**, Nasser JA. Nutritional status of individuals with autism spectrum disorders: do we know enough? *Adv Nutr* 2015; **6**: 397-407 [PMID: 26178024 DOI: 10.3945/an.114.007914]

74 **Kawicka A**, Regulska-Ilow B. How nutritional status, diet and dietary supplements can affect autism. A review. *Rocz Panstw Zakl Hig* 2013; **64**: 1-12 [PMID: 23789306]

75 **Marí-Bauset S**, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M. Food selectivity in autism spectrum disorders: a systematic review. *J Child Neurol* 2014; **29**: 1554-1561 [PMID: 24097852 DOI: 10.1177/0883073813498821]

76 **Cornish E**. Gluten and casein free diets in autism: a study of the effects on food choice and nutrition. *J Hum Nutr Diet* 2002; **15**: 261-269 [PMID: 12153499 DOI: 10.1046/j.1365-277x.2002.00372.x]

77 **Nanda A**, Janga LSN, Sambe HG, Yasir M, Man RK, Gogikar A, Mohammed L. Adverse Effects of Stimulant Interventions for Attention Deficit Hyperactivity Disorder (ADHD): A Comprehensive Systematic Review. *Cureus* 2023; **15**: e45995 [PMID: 37900465 DOI:

10.7759/cureus.45995]
78 **Delgado CF**, Ullery MA, Jordan M, Duclos C, Rajagopalan S, Scott K. Lead Exposure and Developmental Disabilities in Preschool-Aged Children. *J Public Health Manag Pract* 2018; **24**: e10-e17 [PMID: 28257404 DOI: 10.1097/PHH.0000000000000556]
79 **Martinez-Torres V**, Torres N, Davis JA, Corrales-Medina FF. Anemia and Associated Risk Factors in Pediatric Patients. *Pediatric Health Med Ther* 2023; **14**: 267-280 [PMID: 37691881 DOI: 10.2147/PHMT.S389105]
80 **Błażewicz A**, Szymańska I, Astel A, Stenzel-Bembenek A, Dolliver WR, Makarewicz A. Assessment of Changes over Time of Lipid Profile, C-Reactive Protein Level and Body Mass Index in Teenagers and Young Adults on Different Diets Belonging to Autism Spectrum Disorder. *Nutrients* 2020; **12** [PMID: 32859040 DOI: 10.3390/nu12092594]
81 **Adams JB**, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, Gehn E, Loresto M, Mitchell J, Atwood S, Barnhouse S, Lee W. Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. *Nutr Metab (Lond)* 2011; **8**: 34 [PMID: 21651783 DOI: 10.1186/1743-7075-8-34]
82 **Bhattacharya A**, Pal B, Mukherjee S, Roy SK. Assessment of nutritional status using anthropometric variables by multivariate analysis. *BMC Public Health* 2019; **19**: 1045 [PMID: 31382936 DOI: 10.1186/s12889-019-7372-2]
83 **Wasserman H**, O'Donnell JM, Gordon CM. Use of dual energy X-ray absorptiometry in pediatric patients. *Bone* 2017; **104**: 84-90 [PMID: 27989544 DOI: 10.1016/j.bone.2016.12.008]
84 **Berger MM**, Shenkin A, Dizdar OS, Amrein K, Augsburger M, Biesalski HK, Bischoff SC, Casaer MP, Gundogan K, Lepp HL, de Man AME, Muscogiuri G, Pietka M, Pironi L, Rezzi S, Schweinlin A, Cuerda C. ESPEN practical short micronutrient guideline. *Clin Nutr* 2024; **43**: 825-857 [PMID: 38350290 DOI: 10.1016/j.clnu.2024.01.030]
85 **Min KC**, Seo SM, Woo HS. Effect of oral motor facilitation technique on oral motor and feeding skills in children with cerebral palsy : a case study. *BMC Pediatr* 2022; **22**: 626 [PMID: 36324103 DOI: 10.1186/s12887-022-03674-8]
86 **Reilly S**, Skuse D, Mathisen B, Wolke D. The objective rating of oral-motor functions during feeding. *Dysphagia* 1995; **10**: 177-191 [PMID: 7614860 DOI: 10.1007/BF00260975]
87 **Sığan SN**, Uzunhan TA, Aydınlı N, Eraslan E, Ekici B, Calışkan M. Effects of oral motor therapy in children with cerebral palsy. *Ann Indian Acad Neurol* 2013; **16**: 342-346 [PMID: 24101813 DOI: 10.4103/0972-2327.116923]
88 **Banzato A**, Cerchiari A, Pezzola S, Ranucci M, Scarfò E, Berardi A, Tofani M, Galeoto G. Evaluation of the Effectiveness of Functional Chewing Training Compared with Standard Treatment in a Population of Children with Cerebral Palsy: A Systematic Review of Randomized Controlled Trials. *Children (Basel)* 2022; **9** [PMID: 36553319 DOI: 10.3390/children9121876]
89 **Hartman RE**, Patel D. Dietary Approaches to the Management of Autism Spectrum Disorders. *Adv Neurobiol* 2020; **24**: 547-571 [PMID: 32006373 DOI: 10.1007/978-3-030-30402-7_19]
90 **Matthews JS**, Adams JB. Ratings of the Effectiveness of 13 Therapeutic Diets for Autism Spectrum Disorder: Results of a National Survey. *J Pers Med* 2023; **13** [PMID: 37888059 DOI: 10.3390/jpm13101448]
91 **Gow RV**, Hibbeln JR. Omega-3 fatty acid and nutrient deficits in adverse neurodevelopment and childhood behaviors. *Child Adolesc Psychiatr Clin N Am* 2014; **23**: 555-590 [PMID: 24975625 DOI: 10.1016/j.chc.2014.02.002]
92 **Kałużna-czaplińska J**, Jóźwik-pruska J. Nutritional strategies and personalized diet in autism-choice or necessity? *Trends in Food Science & Technology* 2016; **49**: 45-50 [DOI: 10.1016/j.tifs.2016.01.005]
93 **Croall ID**, Hoggard N, Hadjivassiliou M. Gluten and Autism Spectrum Disorder. *Nutrients* 2021; **13** [PMID: 33572226 DOI: 10.3390/nu13020572]
94 **Baspinar B**, Yardimci H. Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems? *Eurasian J Med* 2020; **52**: 292-297 [PMID: 33209084 DOI: 10.5152/eurasianjmed.2020.19230]
95 **Lerner A**, Shoenfeld Y, Matthias T. Adverse effects of gluten ingestion and advantages of gluten withdrawal in nonceliac autoimmune disease. *Nutr Rev* 2017; **75**: 1046-1058 [PMID: 29202198 DOI: 10.1093/nutrit/nux054]
96 **Shattock P**, Whiteley P. Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention. *Expert Opin Ther Targets* 2002; **6**: 175-183 [PMID: 12223079 DOI: 10.1517/14728222.6.2.175]
97 **Aljada B**, Zohni A, El-Matary W. The Gluten-Free Diet for Celiac Disease and Beyond. *Nutrients* 2021; **13** [PMID: 34836247 DOI: 10.3390/nu13113993]
98 **Jones AL**. The Gluten-Free Diet: Fad or Necessity? *Diabetes Spectr* 2017; **30**: 118-123 [PMID: 28588378 DOI: 10.2337/ds16-0022]
99 **Coman L**, Ianculescu M, Paraschiv E, Alexandru A, Bădărău I. Smart Solutions for Diet-Related Disease Management: Connected Care, Remote Health Monitoring Systems, and Integrated Insights for Advanced Evaluation. *Appl Sci* 2024; **14**: 2351 [DOI: 10.3390/app14062351]
100 **Pennesi CM**, Klein LC. Effectiveness of the gluten-free, casein-free diet for children diagnosed with autism spectrum disorder: based on parental report. *Nutr Neurosci* 2012; **15**: 85-91 [PMID: 22564339 DOI: 10.1179/1476830512Y.0000000003]
101 **Vici G**, Belli L, Biondi M, Polzonetti V. Gluten free diet and nutrient deficiencies: A review. *Clin Nutr* 2016; **35**: 1236-1241 [PMID: 27211234 DOI: 10.1016/j.clnu.2016.05.002]
102 **Lee AR**, Wolf RL, Lebwohl B, Ciaccio EJ, Green PHR. Persistent Economic Burden of the Gluten Free Diet. *Nutrients* 2019; **11** [PMID: 30769836 DOI: 10.3390/nu11020399]
103 **Piwowarczyk A**, Horvath A, Łukasik J, Pisula E, Szajewska H. Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review. *Eur J Nutr* 2018; **57**: 433-440 [PMID: 28612113 DOI: 10.1007/s00394-017-1483-2]
104 **Thiruvengadam M**, Venkidasamy B, Thirupathi P, Chung IM, Subramanian U. β-Casomorphin: A complete health perspective. *Food Chem* 2021; **337**: 127765 [PMID: 32799161 DOI: 10.1016/j.foodchem.2020.127765]
105 **Alharthi A**, Alhazmi S, Alburae N, Bahieldin A. The Human Gut Microbiome as a Potential Factor in Autism Spectrum Disorder. *Int J Mol Sci* 2022; **23** [PMID: 35163286 DOI: 10.3390/ijms23031363]
106 **Marí-Bauset S**, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M. Evidence of the gluten-free and casein-free diet in autism spectrum disorders: a systematic review. *J Child Neurol* 2014; **29**: 1718-1727 [PMID: 24789114 DOI: 10.1177/0883073814531330]
107 **Vanga SK**, Raghavan V. How well do plant based alternatives fare nutritionally compared to cow's milk? *J Food Sci Technol* 2018; **55**: 10-20 [PMID: 29358791 DOI: 10.1007/s13197-017-2915-y]
108 **Alamri ES**. Efficacy of gluten- and casein-free diets on autism spectrum disorders in children. *Saudi Med J* 2020; **41**: 1041-1046 [PMID: 33026043 DOI: 10.15537/smj.2020.10.25308]
109 **Craig WJ**. Nutrition concerns and health effects of vegetarian diets. *Nutr Clin Pract* 2010; **25**: 613-620 [PMID: 21139125 DOI: 10.1177/0884533610385707]

110 **Zafirovski K**, Aleksoska MT, Thomas J, Hanna F. Impact of Gluten-Free and Casein-Free Diet on Behavioural Outcomes and Quality of Life of Autistic Children and Adolescents: A Scoping Review. *Children (Basel)* 2024; **11** [PMID: 39062311 DOI: 10.3390/children11070862]

111 **Hurwitz S**. The Gluten-Free, Casein-Free Diet and Autism. *J Early Interv* 2013; **35**: 3-19 [DOI: 10.1177/1053815113484807]

112 **Shaaban S**, Al-Beltagi M, El Rashidy O, Nassar M, El Gendy Y. Ketogenic diet in childhood epilepsy: clinical algorithm in a tertiary care center. *Front Pediatr* 2023; **11**: 1221781 [PMID: 37484774 DOI: 10.3389/fped.2023.1221781]

113 **Wang C**, Zhang W. Can The Ketogenic Diet Improve Autism Spectrum Disorder? From Perspectives on Diversity Interventions and Treatment. *EHSS* 2023; **22**: 155-161 [DOI: 10.54097/ehss.v22i.12413]

114 **Gough SM**, Casella A, Ortega KJ, Hackam AS. Neuroprotection by the Ketogenic Diet: Evidence and Controversies. *Front Nutr* 2021; **8**: 782657 [PMID: 34888340 DOI: 10.3389/fnut.2021.782657]

115 **Yudkoff M**, Daikhin Y, Horyn O, Nissim I, Nissim I. Ketosis and brain handling of glutamate, glutamine, and GABA. *Epilepsia* 2008; **49** Suppl 8: 73-75 [PMID: 19049594 DOI: 10.1111/j.1528-1167.2008.01841.x]

116 **Li Q**, Liang J, Fu N, Han Y, Qin J. A Ketogenic Diet and the Treatment of Autism Spectrum Disorder. *Front Pediatr* 2021; **9**: 650624 [PMID: 34046374 DOI: 10.3389/fped.2021.650624]

117 **Ashtary-Larky D**, Bagheri R, Bavi H, Baker JS, Moro T, Mancin L, Paoli A. Ketogenic diets, physical activity and body composition: a review. *Br J Nutr* 2022; **127**: 1898-1920 [PMID: 34250885 DOI: 10.1017/S0007114521002609]

118 **Cervenka MC**, Wood S, Bagary M, Balabanov A, Bercovici E, Brown MG, Devinsky O, Di Lorenzo C, Doherty CP, Felton E, Healy LA, Klein P, Kverneland M, Lambrechts D, Langer J, Nathan J, Munn J, Nguyen P, Phillips M, Roehl K, Tanner A, Williams C, Zupec-Kania B. International Recommendations for the Management of Adults Treated With Ketogenic Diet Therapies. *Neurol Clin Pract* 2021; **11**: 385-397 [PMID: 34840865 DOI: 10.1212/CPJ.0000000000001007]

119 **Zhu H**, Bi D, Zhang Y, Kong C, Du J, Wu X, Wei Q, Qin H. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. *Signal Transduct Target Ther* 2022; **7**: 11 [PMID: 35034957 DOI: 10.1038/s41392-021-00831-w]

120 **Allan NP**, Yamamoto BY, Kunihiro BP, Nunokawa CKL, Rubas NC, Wells RK, Umeda L, Phankitnirundorn K, Torres A, Peres R, Takahashi E, Maunakea AK. Ketogenic Diet Induced Shifts in the Gut Microbiome Associate with Changes to Inflammatory Cytokines and Brain-Related miRNAs in Children with Autism Spectrum Disorder. *Nutrients* 2024; **16** [PMID: 38794639 DOI: 10.3390/nu16101401]

121 **Dowis K**, Banga S. The Potential Health Benefits of the Ketogenic Diet: A Narrative Review. *Nutrients* 2021; **13** [PMID: 34068325 DOI: 10.3390/nu13051654]

122 **Batch JT**, Lamsal SP, Adkins M, Sultan S, Ramirez MN. Advantages and Disadvantages of the Ketogenic Diet: A Review Article. *Cureus* 2020; **12**: e9639 [PMID: 32923239 DOI: 10.7759/cureus.9639]

123 **Crosby L**, Davis B, Joshi S, Jardine M, Paul J, Neola M, Barnard ND. Ketogenic Diets and Chronic Disease: Weighing the Benefits Against the Risks. *Front Nutr* 2021; **8**: 702802 [PMID: 34336911 DOI: 10.3389/fnut.2021.702802]

124 **McGaugh E**, Barthel B. A Review of Ketogenic Diet and Lifestyle. *Mo Med* 2022; **119**: 84-88 [PMID: 36033148]

125 **Aronica L**, Volek J, Poff A, D'agostino DP. Genetic variants for personalised management of very low carbohydrate ketogenic diets. *BMJ Nutr Prev Health* 2020; **3**: 363-373 [PMID: 33521546 DOI: 10.1136/bmjnph-2020-000167]

126 **Varesio C**, Grumi S, Zanaboni MP, Mensi MM, Chiappedi M, Pasca L, Ferraris C, Tagliabue A, Borgatti R, De Giorgis V. Ketogenic Dietary Therapies in Patients with Autism Spectrum Disorder: Facts or Fads? A Scoping Review and a Proposal for a Shared Protocol. *Nutrients* 2021; **13** [PMID: 34208488 DOI: 10.3390/nu13062057]

127 **Dubrovsky A**, Kitts CL. Effect of the Specific Carbohydrate Diet on the Microbiome of a Primary Sclerosing Cholangitis and Ulcerative Colitis Patient. *Cureus* 2018; **10**: e2177 [PMID: 29651370 DOI: 10.7759/cureus.2177]

128 **Kakodkar S**, Farooqui AJ, Mikolaitis SL, Mutlu EA. The Specific Carbohydrate Diet for Inflammatory Bowel Disease: A Case Series. *J Acad Nutr Diet* 2015; **115**: 1226-1232 [PMID: 26210084 DOI: 10.1016/j.jand.2015.04.016]

129 **Ābele S**, Meija L, Folkmanis V, Tzivian L. Specific Carbohydrate Diet (SCD/GAPS) and Dietary Supplements for Children with Autistic Spectrum Disorder. Proceedings of the Latvian Academy of Sciences. Section B. Natural, Exact, and Applied Sciences. 2021; 75: 417-425 [DOI: 10.2478/prolas-2021-0062]

130 **Gottschall E**. Digestion-gut-autism connection: the Specific Carbohydrate Diet. *Med Veritas: The J Med Truth* 2004; **1**: 261-271 [DOI: 10.1588/medver.2004.01.00029]

131 **Barnhill K**, Devlin M, Moreno HT, Potts A, Richardson W, Schutte C, Hewitson L. Brief Report: Implementation of a Specific Carbohydrate Diet for a Child with Autism Spectrum Disorder and Fragile X Syndrome. *J Autism Dev Disord* 2020; **50**: 1800-1808 [PMID: 30076499 DOI: 10.1007/s10803-018-3704-9]

132 **Rivera N**, Nguyen K, Kalami V, Blankenburg R, Ming Yeh A. Perspectives on Specific Carbohydrate Diet Education from Inflammatory Bowel Disease Patients and Caregivers: A Needs Assessment. *JPGN Rep* 2022; **3**: e222 [PMID: 37168623 DOI: 10.1097/PG9.0000000000000222]

133 **Obih C**, Wahbeh G, Lee D, Braly K, Giefer M, Shaffer ML, Nielson H, Suskind DL. Specific carbohydrate diet for pediatric inflammatory bowel disease in clinical practice within an academic IBD center. *Nutrition* 2016; **32**: 418-425 [PMID: 26655069 DOI: 10.1016/j.nut.2015.08.025]

134 **Żarnowska I**, Chrapko B, Gwizda G, Nocuń A, Mitosek-Szewczyk K, Gasior M. Therapeutic use of carbohydrate-restricted diets in an autistic child; a case report of clinical and 18FDG PET findings. *Metab Brain Dis* 2018; **33**: 1187-1192 [PMID: 29644487 DOI: 10.1007/s11011-018-0219-1]

135 **Hagström N**, Lövestam E, Koochek A, Berntson L. A qualitative evaluation of the specific carbohydrate diet for juvenile idiopathic arthritis based on children's and parents' experiences. *Pediatr Rheumatol Online J* 2023; **21**: 127 [PMID: 37858222 DOI: 10.1186/s12969-023-00914-8]

136 **Lewis JD**, Sandler RS, Brotherton C, Brensinger C, Li H, Kappelman MD, Daniel SG, Bittinger K, Albenberg L, Valentine JF, Hanson JS, Suskind DL, Meyer A, Compher CW, Bewtra M, Saxena A, Dobes A, Cohen BL, Flynn AD, Fischer M, Saha S, Swaminath A, Yacyshyn B, Scherl E, Horst S, Curtis JR, Braly K, Nessel L, McCauley M, McKeever L, Herfarth H; DINE-CD Study Group. A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults With Crohn's Disease. *Gastroenterology* 2021; **161**: 837-852.e9 [PMID: 34052278 DOI: 10.1053/j.gastro.2021.05.047]

137 **Schwartz NRM**, McNichol SR, Devine B, Phipps AI, Roth JA, Suskind DL. Assessing Barriers to use of the Specific Carbohydrate Diet in Pediatric Inflammatory Bowel Disease: A Qualitative Study. *JPGN Rep* 2022; **3**: e239 [PMID: 37168638 DOI: 10.1097/PG9.0000000000000239]

138 **Perler BK**, Friedman ES, Wu GD. The Role of the Gut Microbiota in the Relationship Between Diet and Human Health. *Annu Rev Physiol* 2023; **85**: 449-468 [PMID: 36375468 DOI: 10.1146/annurev-physiol-031522-092054]

139 **Aziz T**, Hussain N, Hameed Z, Lin L. Elucidating the role of diet in maintaining gut health to reduce the risk of obesity, cardiovascular and other age-related inflammatory diseases: recent challenges and future recommendations. *Gut Microbes* 2024; **16**: 2297864 [PMID: 38174551 DOI: 10.1080/19490976.2023.2297864]

140 **Wellens J**, Vermeire S, Sabino J. Let Food Be Thy Medicine-Its Role in Crohn's Disease. *Nutrients* 2021; **13** [PMID: 33802429 DOI: 10.3390/nu13030832]

141 **Burgis JC**, Nguyen K, Park KT, Cox K. Response to strict and liberalized specific carbohydrate diet in pediatric Crohn's disease. *World J Gastroenterol* 2016; **22**: 2111-2117 [PMID: 26877615 DOI: 10.3748/wjg.v22.i6.2111]

142 **Wahbeh GT**, Ward BT, Lee DY, Giefer MJ, Suskind DL. Lack of Mucosal Healing From Modified Specific Carbohydrate Diet in Pediatric Patients With Crohn Disease. *J Pediatr Gastroenterol Nutr* 2017; **65**: 289-292 [PMID: 28825776 DOI: 10.1097/MPG.0000000000001619]

143 **Hodges RE**, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab* 2015; **2015**: 760689 [PMID: 26167297 DOI: 10.1155/2015/760689]

144 **Wu HJ**, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012; **3**: 4-14 [PMID: 22356853 DOI: 10.4161/gmic.19320]

145 **Horn J**, Mayer DE, Chen S, Mayer EA. Role of diet and its effects on the gut microbiome in the pathophysiology of mental disorders. *Transl Psychiatry* 2022; **12**: 164 [PMID: 35443740 DOI: 10.1038/s41398-022-01922-0]

146 **Conlon MA**, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 2014; **7**: 17-44 [PMID: 25545101 DOI: 10.3390/nu7010017]

147 **Tengeler AC**, Kozicz T, Kiliaan AJ. Relationship between diet, the gut microbiota, and brain function. *Nutr Rev* 2018; **76**: 603-617 [PMID: 29718511 DOI: 10.1093/nutrit/nuy016]

148 **Parvez S**, Malik KA, Ah Kang S, Kim HY. Probiotics and their fermented food products are beneficial for health. *J Appl Microbiol* 2006; **100**: 1171-1185 [PMID: 16696665 DOI: 10.1111/j.1365-2672.2006.02963.x]

149 **Jones BL**, Orton AL, Tindall SW, Christensen JT, Enosakhare O, Russell KA, Robins AM, Larriviere-McCarl A, Sandres J, Cox B, Thomas C, Reynolds C. Barriers to Healthy Family Dinners and Preventing Child Obesity: Focus Group Discussions with Parents of 5-to-8-Year-Old Children. *Children (Basel)* 2023; **10** [PMID: 37371184 DOI: 10.3390/children10060952]

150 **Helland MH**, Nordbotten GL. Dietary Changes, Motivators, and Barriers Affecting Diet and Physical Activity among Overweight and Obese: A Mixed Methods Approach. *Int J Environ Res Public Health* 2021; **18** [PMID: 34682331 DOI: 10.3390/ijerph182010582]

151 **Swelum AA**, El-Saadony MT, Abdo M, Ombarak RA, Hussein EOS, Suliman G, Alhimaidi AR, Ammari AA, Ba-Awadh H, Taha AE, El-Tarabily KA, Abd El-Hack ME. Nutritional, antimicrobial and medicinal properties of Camel's milk: A review. *Saudi J Biol Sci* 2021; **28**: 3126-3136 [PMID: 34025186 DOI: 10.1016/j.sjbs.2021.02.057]

152 **Ho TM**, Zou Z, Bansal N. Camel milk: A review of its nutritional value, heat stability, and potential food products. *Food Res Int* 2022; **153**: 110870 [PMID: 35227464 DOI: 10.1016/j.foodres.2021.110870]

153 **Benmeziane-Derradji F**. Evaluation of camel milk: gross composition-a scientific overview. *Trop Anim Health Prod* 2021; **53**: 308 [PMID: 33961132 DOI: 10.1007/s11250-021-02689-0]

154 **Arain MA**, Salman HM, Ali M, Khaskheli GB, Barham GS, Marghazani IB, Ahmed S. A Review on Camel Milk Composition, Techno-Functional Properties and Processing Constraints. *Food Sci Anim Resour* 2024; **44**: 739-757 [PMID: 38974725 DOI: 10.5851/kosfa.2023.e18]

155 **Behrouz S**, Saadat S, Memarzia A, Sarir H, Folkerts G, Boskabady MH. The Antioxidant, Anti-Inflammatory and Immunomodulatory Effects of Camel Milk. *Front Immunol* 2022; **13**: 855342 [PMID: 35493477 DOI: 10.3389/fimmu.2022.855342]

156 **Al-Ayadhi LY**, Elamin NE. Camel Milk as a Potential Therapy as an Antioxidant in Autism Spectrum Disorder (ASD). *Evid Based Complement Alternat Med* 2013; **2013**: 602834 [PMID: 24069051 DOI: 10.1155/2013/602834]

157 **Kocyigit E**, Abdurakhmanov R, Kocyigit BF. Potential role of camel, mare milk, and their products in inflammatory rheumatic diseases. *Rheumatol Int* 2024; **44**: 425-434 [PMID: 38183445 DOI: 10.1007/s00296-023-05516-x]

158 **Al-Ayadhi LY**, Halepoto DM, Al-Dress AM, Mitwali Y, Zainah R. Behavioral Benefits of Camel Milk in Subjects with Autism Spectrum Disorder. *J Coll Physicians Surg Pak* 2015; **25**: 819-823 [PMID: 26577969]

159 **Adams CM**. Patient report: autism spectrum disorder treated with camel milk. *Glob Adv Health Med* 2013; **2**: 78-80 [PMID: 24349886 DOI: 10.7453/gahmj.2013.094]

160 **Mostafa GA**, Bjørklund G, Ayadhi LA. Therapeutic Effect of Camel Milk in Children with Autism: Its Impact on Serum Levels of Vasoactive Intestinal Peptide. *International Journal of Medical Science and Clinical Invention* 2021; **8**: 5698-5707 [DOI: 10.18535/ijmsci/v8i10.05]

161 **Hamzawy MA**, El-Ghandour YB, Abdel-Aziem SH, Ali ZH. Leptin and camel milk abate oxidative stress status, genotoxicity induced in valproic acid rat model of autism. *Int J Immunopathol Pharmacol* 2018; **32**: 2058738418785514 [PMID: 30004275 DOI: 10.1177/2058738418785514]

162 **Cheikh Ismail L**, Osaili TM, Mohamad MN, Zakaria H, Ali A, Tarek A, Ashfaq A, Al Abdouli MA, Saleh ST, Daour RA, AlRajaby R, Stojanovska L, Al Dhaheri AS. Camel milk consumption patterns and perceptions in the UAE: a cross-sectional study. *J Nutr Sci* 2022; **11**: e59 [PMID: 35912304 DOI: 10.1017/jns.2022.55]

163 **Seifu E**. Recent advances on camel milk: Nutritional and health benefits and processing implications-A review. *AIMSAGRI* 2022; **7**: 777-804 [DOI: 10.3934/agrfood.2022048]

164 **Maryniak NZ**, Stage MH, Ballegaard AR, Sancho AI, Hansen EB, Bøgh KL. Camel Milk Cannot Prevent the Development of Cow's Milk Allergy-A Study in Brown Norway Rats. *Mol Nutr Food Res* 2023; **67**: e2200359 [PMID: 36415026 DOI: 10.1002/mnfr.202200359]

165 **Kaskous S**. Importance of camel milk for human health. *Emir J Food Agric* 2016; **28**: 158 [DOI: 10.9755/ejfa.2015-05-296]

166 **Abdellatif B**, McVeigh C, Bendriss G, Chaari A. The Promising Role of Probiotics in Managing the Altered Gut in Autism Spectrum Disorders. *Int J Mol Sci* 2020; **21** [PMID: 32532137 DOI: 10.3390/ijms21114159]

167 **Feng P**, Zhao S, Zhang Y, Li E. A review of probiotics in the treatment of autism spectrum disorders: Perspectives from the gut-brain axis. *Front Microbiol* 2023; **14**: 1123462 [PMID: 37007501 DOI: 10.3389/fmicb.2023.1123462]

168 **Appleton J**. The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health. *Integr Med (Encinitas)* 2018; **17**: 28-32 [PMID: 31043907]

169 **Li Q**, Zheng T, Ding H, Chen J, Li B, Zhang Q, Yang S, Zhang S, Guan W. Exploring the Benefits of Probiotics in Gut Inflammation and Diarrhea-From an Antioxidant Perspective. *Antioxidants (Basel)* 2023; **12** [PMID: 37507882 DOI: 10.3390/antiox12071342]

170 **Hemarajata P**, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol* 2013; **6**: 39-51 [PMID: 23320049 DOI: 10.1177/1756283X12459294]

171 **Ansari F**, Neshat M, Pourjafar H, Jafari SM, Samakkhah SA, Mirzakhani E. The role of probiotics and prebiotics in modulating of the gut-brain axis. *Front Nutr* 2023; **10**: 1173660 [PMID: 37565035 DOI: 10.3389/fnut.2023.1173660]

172 **Patusco R**, Ziegler J. Role of Probiotics in Managing Gastrointestinal Dysfunction in Children with Autism Spectrum Disorder: An Update for Practitioners. *Adv Nutr* 2018; **9**: 637-650 [PMID: 30202938 DOI: 10.1093/advances/nmy031]

173 **Lalonde R**, Strazielle C. Probiotic effects on anxiety-like behavior in animal models. *Rev Neurosci* 2022; **33**: 691-701 [PMID: 35381125 DOI: 10.1515/revneuro-2021-0173]

174 **Brüssow H**. Probiotics and prebiotics in clinical tests: an update. *F1000Res* 2019; **8** [PMID: 31354938 DOI: 10.12688/f1000research.19043.1]

175 **Golbaghi N**, Naeimi S, Darvishi A, Najari N, Cussotto S. Probiotics in autism spectrum disorder: Recent insights from animal models. *Autism* 2024; 13623613241246911 [PMID: 38666595 DOI: 10.1177/13623613241246911]

176 **He X**, Liu W, Tang F, Chen X, Song G. Effects of Probiotics on Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis of Clinical Trials. *Nutrients* 2023; **15** [PMID: 36986145 DOI: 10.3390/nu15061415]

177 **Reid G**, Jass J, Sebulsky MT, McCormick JK. Potential uses of probiotics in clinical practice. *Clin Microbiol Rev* 2003; **16**: 658-672 [PMID: 14557292 DOI: 10.1128/CMR.16.4.658-672.2003]

178 **Roe AL**, Boyte ME, Elkins CA, Goldman VS, Heimbach J, Madden E, Oketch-Rabah H, Sanders ME, Sirois J, Smith A. Considerations for determining safety of probiotics: A USP perspective. *Regul Toxicol Pharmacol* 2022; **136**: 105266 [PMID: 36206977 DOI: 10.1016/j.yrtph.2022.105266]

179 **Aponte M**, Murru N, Shoukat M. Therapeutic, Prophylactic, and Functional Use of Probiotics: A Current Perspective. *Front Microbiol* 2020; **11**: 562048 [PMID: 33042069 DOI: 10.3389/fmicb.2020.562048]

180 **Davani-Davari D**, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, Berenjian A, Ghasemi Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods* 2019; **8** [PMID: 30857316 DOI: 10.3390/foods8030092]

181 **Kaur AP**, Bhardwaj S, Dhanjal DS, Nepovimova E, Cruz-Martins N, Kuča K, Chopra C, Singh R, Kumar H, Şen F, Kumar V, Verma R, Kumar D. Plant Prebiotics and Their Role in the Amelioration of Diseases. *Biomolecules* 2021; **11** [PMID: 33809763 DOI: 10.3390/biom11030440]

182 **You S**, Ma Y, Yan B, Pei W, Wu Q, Ding C, Huang C. The promotion mechanism of prebiotics for probiotics: A review. *Front Nutr* 2022; **9**: 1000517 [PMID: 36276830 DOI: 10.3389/fnut.2022.1000517]

183 **Fusco W**, Lorenzo MB, Cintoni M, Porcari S, Rinninella E, Kaitsas F, Lener E, Mele MC, Gasbarrini A, Collado MC, Cammarota G, Ianiro G. Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. *Nutrients* 2023; **15** [PMID: 37432351 DOI: 10.3390/nu15092211]

184 **Silva YP**, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. *Front Endocrinol (Lausanne)* 2020; **11**: 25 [PMID: 32082260 DOI: 10.3389/fendo.2020.00025]

185 **Saurman V**, Margolis KG, Luna RA. Autism Spectrum Disorder as a Brain-Gut-Microbiome Axis Disorder. *Dig Dis Sci* 2020; **65**: 818-828 [PMID: 32056091 DOI: 10.1007/s10620-020-06133-5]

186 **Prince N**, Peralta Marzal LN, Markidi A, Ahmed S, Adolfs Y, Pasterkamp RJ, Kumar H, Roeselers G, Garssen J, Kraneveld AD, Perez-Pardo P. Prebiotic diet normalizes aberrant immune and behavioral phenotypes in a mouse model of autism spectrum disorder. *Acta Pharmacol Sin* 2024; **45**: 1591-1603 [PMID: 38589690 DOI: 10.1038/s41401-024-01268-x]

187 **Robinson-Agramonte MLA**, Noris García E, Fraga Guerra J, Vega Hurtado Y, Antonucci N, Semprún-Hernández N, Schultz S, Siniscalco D. Immune Dysregulation in Autism Spectrum Disorder: What Do We Know about It? *Int J Mol Sci* 2022; **23** [PMID: 35328471 DOI: 10.3390/ijms23063033]

188 **Palmer JK**, van der Pols JC, Sullivan KA, Staudacher HM, Byrne R. A Double-Blind Randomised Controlled Trial of Prebiotic Supplementation in Children with Autism: Effects on Parental Quality of Life, Child Behaviour, Gastrointestinal Symptoms, and the Microbiome. *J Autism Dev Disord* 2024 [PMID: 38291245 DOI: 10.1007/s10803-024-06239-z]

189 **Billeci L**, Callara AL, Guiducci L, Prosperi M, Morales MA, Calderoni S, Muratori F, Santocchi E. A randomized controlled trial into the effects of probiotics on electroencephalography in preschoolers with autism. *Autism* 2023; **27**: 117-132 [PMID: 35362336 DOI: 10.1177/13623613221082710]

190 **Rahim F**, Toguzbaeva K, Qasim NH, Dzhusupov KO, Zhumagaliuly A, Khozhamkul R. Probiotics, prebiotics, and synbiotics for patients with autism spectrum disorder: a meta-analysis and umbrella review. *Front Nutr* 2023; **10**: 1294089 [PMID: 38148790 DOI: 10.3389/fnut.2023.1294089]

191 **Alsubaiei SRM**, Alfawaz HA, Almubarak AY, Alabdali NA, Ben Bacha A, El-Ansary A. Independent and Combined Effects of Probiotics and Prebiotics as Supplements or Food-Rich Diets on a Propionic-Acid-Induced Rodent Model of Autism Spectrum Disorder. *Metabolites* 2022; **13** [PMID: 36676975 DOI: 10.3390/metabo13010050]

192 **Quigley EMM**. Prebiotics and Probiotics in Digestive Health. *Clin Gastroenterol Hepatol* 2019; **17**: 333-344 [PMID: 30267869 DOI: 10.1016/j.cgh.2018.09.028]

193 **Markowiak P**, Śliżewska K. Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. *Nutrients* 2017; **9** [PMID: 28914794 DOI: 10.3390/nu9091021]

194 **Zhang S**, Han F, Wang Q, Fan F. Probiotics and Prebiotics in the Treatment of Autism Spectrum Disorder: A Narrative Review. *J Integr Neurosci* 2024; **23**: 20 [PMID: 38287844 DOI: 10.31083/j.jin2301020]

195 **Bertoglio K**, Jill James S, Deprey L, Brule N, Hendren RL. Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism. *J Altern Complement Med* 2010; **16**: 555-560 [PMID: 20804367 DOI: 10.1089/acm.2009.0177]

196 **Halczuk K**, Kaźmierczak-Barańska J, Karwowski BT, Karmańska A, Cieślak M. Vitamin B12-Multifaceted In Vivo Functions and In Vitro Applications. *Nutrients* 2023; **15** [PMID: 37375638 DOI: 10.3390/nu15122734]

197 **Moore LD**, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology* 2013; **38**: 23-38 [PMID: 22781841 DOI: 10.1038/npp.2012.112]

198 **Bjørklund G**, Tinkov AA, Hosnedlová B, Kizek R, Ajsuvakova OP, Chirumbolo S, Skalnaya MG, Peana M, Dadar M, El-Ansary A, Qasem H, Adams JB, Aaseth J, Skalny AV. The role of glutathione redox imbalance in autism spectrum disorder: A review. *Free Radic Biol Med* 2020; **160**: 149-162 [PMID: 32745763 DOI: 10.1016/j.freeradbiomed.2020.07.017]

199 **Wu F**, Xu K, Liu L, Zhang K, Xia L, Zhang M, Teng C, Tong H, He Y, Xue Y, Zhang H, Chen D, Hu A. Vitamin B(12) Enhances Nerve Repair and Improves Functional Recovery After Traumatic Brain Injury by Inhibiting ER Stress-Induced Neuron Injury. *Front Pharmacol* 2019; **10**: 406 [PMID: 31105562 DOI: 10.3389/fphar.2019.00406]

200 **Rossignol DA**, Frye RE. The Effectiveness of Cobalamin (B12) Treatment for Autism Spectrum Disorder: A Systematic Review and Meta-

Analysis. *J Pers Med* 2021; **11** [PMID: 34442428 DOI: 10.3390/jpm11080784]

201 **Čorejová A**, Fazekaš T, Jánošíková D, Repiský J, Pospíšilová V, Miková M, Rauová D, Ostatníková D, Kyselovič J, Hrabovská A. Improvement of the Clinical and Psychological Profile of Patients with Autism after Methylcobalamin Syrup Administration. *Nutrients* 2022; **14** [PMID: 35631176 DOI: 10.3390/nu14102035]

202 **Markun S**, Gravestock I, Jäger L, Rosemann T, Pichierri G, Burgstaller JM. Effects of Vitamin B12 Supplementation on Cognitive Function, Depressive Symptoms, and Fatigue: A Systematic Review, Meta-Analysis, and Meta-Regression. *Nutrients* 2021; **13** [PMID: 33809274 DOI: 10.3390/nu13030923]

203 **Liu X**, Lin J, Zhang H, Khan NU, Zhang J, Tang X, Cao X, Shen L. Oxidative Stress in Autism Spectrum Disorder-Current Progress of Mechanisms and Biomarkers. *Front Psychiatry* 2022; **13**: 813304 [PMID: 35299821 DOI: 10.3389/fpsyt.2022.813304]

204 **Hendren RL**, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism. *J Child Adolesc Psychopharmacol* 2016; **26**: 774-783 [PMID: 26889605 DOI: 10.1089/cap.2015.0159]

205 **Frye RE**, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW, Walters L, James SJ. Effectiveness of methylcobalamin and folinic Acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status. *Autism Res Treat* 2013; **2013**: 609705 [PMID: 24224089 DOI: 10.1155/2013/609705]

206 **Obersby D**, Chappell D, Dunnett A, Tsiami A. Efficacy of Methylcobalamin to Normalise Elevated Homocysteine of Vitamin B12 Deficient Vegetarians: A Double Blind Placebo Control Study. *Curr Res Nutr Food Sci* 2015; **3**: 187-196 [DOI: 10.12944/crnfsj.3.3.02]

207 **Lukovac T**, Hil OA, Popović M, Jovanović V, Savić T, Pavlović AM, Pavlović D. Serum Biomarker Analysis in Pediatric ADHD: Implications of Homocysteine, Vitamin B12, Vitamin D, Ferritin, and Iron Levels. *Children (Basel)* 2024; **11** [PMID: 38671715 DOI: 10.3390/children11040497]

208 **Gu WJ**, Lu JM, Yang GQ, Guo QH, Dou JT, Mu YM, Pan CY. [Effects of intervention therapy of methylcobalamin and folic acid on plasma homocysteine concentration and homocysteine thiolactonases/paraoxonase activity in patients with type 2 diabetes mellitus]. *Zhonghua Yi Xue Za Zhi* 2007; **87**: 256-258 [PMID: 17425871]

209 **Frye RE**, Rossignol DA, Scahill L, McDougle CJ, Huberman H, Quadros EV. Treatment of Folate Metabolism Abnormalities in Autism Spectrum Disorder. *Semin Pediatr Neurol* 2020; **35**: 100835 [PMID: 32892962 DOI: 10.1016/j.spen.2020.100835]

210 **Duthie SJ**, Narayanan S, Brand GM, Pirie L, Grant G. Impact of folate deficiency on DNA stability. *J Nutr* 2002; **132**: 2444S-2449S [PMID: 12163709 DOI: 10.1093/jn/132.8.2444S]

211 **Gao Y**, Sheng C, Xie RH, Sun W, Asztalos E, Moddemann D, Zwaigenbaum L, Walker M, Wen SW. New Perspective on Impact of Folic Acid Supplementation during Pregnancy on Neurodevelopment/Autism in the Offspring Children - A Systematic Review. *PLoS One* 2016; **11**: e0165626 [PMID: 27875541 DOI: 10.1371/journal.pone.0165626]

212 **Roufael M**, Bitar T, Sacre Y, Andres C, Hleihel W. Folate-Methionine Cycle Disruptions in ASD Patients and Possible Interventions: A Systematic Review. *Genes (Basel)* 2023; **14** [PMID: 36980981 DOI: 10.3390/genes14030709]

213 **Crider KS**, Yang TP, Berry RJ, Bailey LB. Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role. *Adv Nutr* 2012; **3**: 21-38 [PMID: 22332098 DOI: 10.3945/an.111.000992]

214 **Neggers Y**. The Relationship between Folic Acid and Risk of Autism Spectrum Disorders. *Healthcare (Basel)* 2014; **2**: 429-444 [PMID: 27429286 DOI: 10.3390/healthcare2040429]

215 **Liwinski T**, Lang UE. Folate and Its Significance in Depressive Disorders and Suicidality: A Comprehensive Narrative Review. *Nutrients* 2023; **15** [PMID: 37686891 DOI: 10.3390/nu15173859]

216 **Jiang Y**, Guo C, Kuang M, Lin L, Xu G, Pan N, Weng X, Jing J, Shi L, Yi Q, Wang X. Examining associations of folic acid supplements administered to mothers during pre-conceptional and prenatal periods with autism spectrum disorders in their offspring: insights from a multi-center study in China. *Front Public Health* 2024; **12**: 1321046 [PMID: 38299071 DOI: 10.3389/fpubh.2024.1321046]

217 **Iglesias Vázquez L**, Canals J, Arija V. Review and meta-analysis found that prenatal folic acid was associated with a 58% reduction in autism but had no effect on mental and motor development. *Acta Paediatr* 2019; **108**: 600-610 [PMID: 30466185 DOI: 10.1111/apa.14657]

218 **Wiens D**, DeSoto MC. Is High Folic Acid Intake a Risk Factor for Autism?-A Review. *Brain Sci* 2017; **7** [PMID: 29125540 DOI: 10.3390/brainsci7110149]

219 **Goodrich AJ**, Volk HE, Tancredi DJ, McConnell R, Lurmann FW, Hansen RL, Schmidt RJ. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. *Autism Res* 2018; **11**: 69-80 [PMID: 29120534 DOI: 10.1002/aur.1885]

220 **Rodriguez-Carnero G**, Lorenzo PM, Canton-Blanco A, Mendizabal L, Arregi M, Zulueta M, Simon L, Macia-Cortiñas M, Casanueva FF, Crujeiras AB. Genetic Variants in Folate and Cobalamin Metabolism-Related Genes in Pregnant Women of a Homogeneous Spanish Population: The Need for Revisiting the Current Vitamin Supplementation Strategies. *Nutrients* 2022; **14** [PMID: 35807880 DOI: 10.3390/nu14132702]

221 **Smith AD**, Kim YI, Refsum H. Is folic acid good for everyone? *Am J Clin Nutr* 2008; **87**: 517-533 [PMID: 18326588 DOI: 10.1093/ajcn/87.3.517]

222 **Field MS**, Stover PJ. Safety of folic acid. *Ann N Y Acad Sci* 2018; **1414**: 59-71 [PMID: 29155442 DOI: 10.1111/nyas.13499]

223 **Calderón-Ospina CA**, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. *CNS Neurosci Ther* 2020; **26**: 5-13 [PMID: 31490017 DOI: 10.1111/cns.13207]

224 **Parra M**, Stahl S, Hellmann H. Vitamin B_6 and Its Role in Cell Metabolism and Physiology. *Cells* 2018; **7** [PMID: 30037155 DOI: 10.3390/cells7070084]

225 **Obeid R**, Herrmann W. Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia. *FEBS Lett* 2006; **580**: 2994-3005 [PMID: 16697371 DOI: 10.1016/j.febslet.2006.04.088]

226 **Field DT**, Cracknell RO, Eastwood JR, Scarfe P, Williams CM, Zheng Y, Tavassoli T. High-dose Vitamin B6 supplementation reduces anxiety and strengthens visual surround suppression. *Hum Psychopharmacol* 2022; **37**: e2852 [PMID: 35851507 DOI: 10.1002/hup.2852]

227 **Rimland B**, Callaway E, Dreyfus P. The effect of high doses of vitamin B6 on autistic children: a double-blind crossover study. *Am J Psychiatry* 1978; **135**: 472-475 [PMID: 345827 DOI: 10.1176/ajp.135.4.472]

228 **Rimland B**. Controversies in the treatment of autistic children: vitamin and drug therapy. *J Child Neurol* 1988; **3** Suppl: S68-S72 [PMID: 3058789 DOI: 10.1177/0883073888003001s13]

229 **Khan F**, Rahman MS, Akhter S, Momen ABI, Raihan SG. Vitamin B6 and Magnesium on Neurobehavioral Status of Autism Spectrum Disorder: A Randomized, Double-Blind, Placebo Controlled Study. *Bangla J Med* 2021; **32**: 12-18 [DOI: 10.3329/bjm.v32i1.51089]

230 **Mousain-Bosc M**, Roche M, Polge A, Pradal-Prat D, Rapin J, Bali JP. Improvement of neurobehavioral disorders in children supplemented

with magnesium-vitamin B6. II. Pervasive developmental disorder-autism. *Magnes Res* 2006; **19**: 53-62 [PMID: 16846101]
231 **Nye C**, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev* 2005; **2005**: CD003497 [PMID: 16235322 DOI: 10.1002/14651858.CD003497.pub2]
232 **Sato K**. Why is vitamin B6 effective in alleviating the symptoms of autism? *Med Hypotheses* 2018; **115**: 103-106 [PMID: 29685187 DOI: 10.1016/j.mehy.2018.04.007]
233 **Obara T**, Ishikuro M, Tamiya G, Ueki M, Yamanaka C, Mizuno S, Kikuya M, Metoki H, Matsubara H, Nagai M, Kobayashi T, Kamiyama M, Watanabe M, Kakuta K, Ouchi M, Kurihara A, Fukuchi N, Yasuhara A, Inagaki M, Kaga M, Kure S, Kuriyama S. Potential identification of vitamin B6 responsiveness in autism spectrum disorder utilizing phenotype variables and machine learning methods. *Sci Rep* 2018; **8**: 14840 [PMID: 30287864 DOI: 10.1038/s41598-018-33110-w]
234 **Hadtstein F**, Vrolijk M. Vitamin B-6-Induced Neuropathy: Exploring the Mechanisms of Pyridoxine Toxicity. *Adv Nutr* 2021; **12**: 1911-1929 [PMID: 33912895 DOI: 10.1093/advances/nmab033]
235 **Noah L**, Pickering G, Mazur A, Dubray C, Hitier S, Dualé C, Pouteau E. Impact of magnesium supplementation, in combination with vitamin B6, on stress and magnesium status: secondary data from a randomized controlled trial. *Magnes Res* 2020; **33**: 45-57 [PMID: 33210604 DOI: 10.1684/mrh.2020.0468]
236 **Sorrenti V**, Buriani A, Davinelli S, Scapagnini G, Fortinguerra S. Vitamin D Physiology, Deficiency, Genetic Influence, and the Effects of Daily vs. Bolus Doses of Vitamin D on Overall Health: A Clinical Approach. *Nutraceutical* 2023; **3**: 403-420 [DOI: 10.3390/nutraceuticals3030030]
237 **Bilezikian JP**, Formenti AM, Adler RA, Binkley N, Bouillon R, Lazaretti-Castro M, Marcocci C, Napoli N, Rizzoli R, Giustina A. Vitamin D: Dosing, levels, form, and route of administration: Does one approach fit all? *Rev Endocr Metab Disord* 2021; **22**: 1201-1218 [PMID: 34940947 DOI: 10.1007/s11154-021-09693-7]
238 **Wang J**, Huang H, Liu C, Zhang Y, Wang W, Zou Z, Yang L, He X, Wu J, Ma J, Liu Y. Research Progress on the Role of Vitamin D in Autism Spectrum Disorder. *Front Behav Neurosci* 2022; **16**: 859151 [PMID: 35619598 DOI: 10.3389/fnbeh.2022.859151]
239 **Khazai N**, Judd SE, Tangpricha V. Calcium and vitamin D: skeletal and extraskeletal health. *Curr Rheumatol Rep* 2008; **10**: 110-117 [PMID: 18460265 DOI: 10.1007/s11926-008-0020-y]
240 **Aranow C**. Vitamin D and the immune system. *J Investig Med* 2011; **59**: 881-886 [PMID: 21527855 DOI: 10.2310/JIM.0b013e31821b8755]
241 **Eyles DW**. Vitamin D: Brain and Behavior. *JBMR Plus* 2021; **5**: e10419 [PMID: 33553986 DOI: 10.1002/jbm4.10419]
242 **Sourander A**, Upadhyaya S, Surcel HM, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Silwal S, Sucksdorff M, McKeague IW, Brown AS. Maternal Vitamin D Levels During Pregnancy and Offspring Autism Spectrum Disorder. *Biol Psychiatry* 2021; **90**: 790-797 [PMID: 34602240 DOI: 10.1016/j.biopsych.2021.07.012]
243 **Kittana M**, Ahmadani A, Stojanovska L, Attlee A. The Role of Vitamin D Supplementation in Children with Autism Spectrum Disorder: A Narrative Review. *Nutrients* 2021; **14** [PMID: 35010901 DOI: 10.3390/nu14010026]
244 **Kasatkina LA**, Tarasenko AS, Krupko OO, Kuchmerovska TM, Lisakovska OO, Trikash IO. Vitamin D deficiency induces the excitation/inhibition brain imbalance and the proinflammatory shift. *Int J Biochem Cell Biol* 2020; **119**: 105665 [PMID: 31821883 DOI: 10.1016/j.biocel.2019.105665]
245 **Jiang Y**, Dang W, Sui L, Gao T, Kong X, Guo J, Liu S, Nie H, Jiang Z. Associations Between Vitamin D and Core Symptoms in ASD: An Umbrella Review. *NDS* 2024; **16**: 59-91 [DOI: 10.2147/nds.s470462]
246 **Zhang M**, Wu Y, Lu Z, Song M, Huang X, Mi L, Yang J, Cui X. Effects of Vitamin D Supplementation on Children with Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *Clin Psychopharmacol Neurosci* 2023; **21**: 240-251 [PMID: 37119216 DOI: 10.9758/cpn.2023.21.2.240]
247 **Song L**, Luo X, Jiang Q, Chen Z, Zhou L, Wang D, Chen A. Vitamin D Supplementation is Beneficial for Children with Autism Spectrum Disorder: A Meta-analysis. *Clin Psychopharmacol Neurosci* 2020; **18**: 203-213 [PMID: 32329301 DOI: 10.9758/cpn.2020.18.2.203]
248 **Dalle Carbonare L**, Valenti MT, Del Forno F, Caneva E, Pietrobelli A. Vitamin D: Daily vs. Monthly Use in Children and Elderly-What Is Going On? *Nutrients* 2017; **9** [PMID: 28672793 DOI: 10.3390/nu9070652]
249 **Razzaque MS**. Can adverse effects of excessive vitamin D supplementation occur without developing hypervitaminosis D? *J Steroid Biochem Mol Biol* 2018; **180**: 81-86 [PMID: 28734988 DOI: 10.1016/j.jsbmb.2017.07.006]
250 **Li YJ**, Ou JJ, Li YM, Xiang DX. Dietary Supplement for Core Symptoms of Autism Spectrum Disorder: Where Are We Now and Where Should We Go? *Front Psychiatry* 2017; **8**: 155 [PMID: 28878697 DOI: 10.3389/fpsyt.2017.00155]
251 **Cauvet É**, Van't Westeinde A, Toro R, Kuja-Halkola R, Neufeld J, Mevel K, Bölte S. Sex Differences Along the Autism Continuum: A Twin Study of Brain Structure. *Cereb Cortex* 2019; **29**: 1342-1350 [PMID: 30566633 DOI: 10.1093/cercor/bhy303]
252 **Kępka A**, Ochocińska A, Chojnowska S, Borzym-Kluczyk M, Skorupa E, Knaś M, Waszkiewicz N. Potential Role of L-Carnitine in Autism Spectrum Disorder. *J Clin Med* 2021; **10** [PMID: 33805796 DOI: 10.3390/jcm10061202]
253 **Longo N**, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. *Biochim Biophys Acta* 2016; **1863**: 2422-2435 [PMID: 26828774 DOI: 10.1016/j.bbamcr.2016.01.023]
254 **Nabi SU**, Rehman MU, Arafah A, Taifa S, Khan IS, Khan A, Rashid S, Jan F, Wani HA, Ahmad SF. Treatment of Autism Spectrum Disorders by Mitochondrial-targeted Drug: Future of Neurological Diseases Therapeutics. *Curr Neuropharmacol* 2023; **21**: 1042-1064 [PMID: 36411568 DOI: 10.2174/1570159X21666221121095618]
255 **Virmani MA**, Cirulli M. The Role of l-Carnitine in Mitochondria, Prevention of Metabolic Inflexibility and Disease Initiation. *Int J Mol Sci* 2022; **23** [PMID: 35269860 DOI: 10.3390/ijms23052717]
256 **Demarquoy C**, Demarquoy J. Autism and carnitine: A possible link. *World J Biol Chem* 2019; **10**: 7-16 [PMID: 30622681 DOI: 10.4331/wjbc.v10.i1.7]
257 **Malaguarnera M**, Cauli O. Effects of l-Carnitine in Patients with Autism Spectrum Disorders: Review of Clinical Studies. *Molecules* 2019; **24** [PMID: 31766743 DOI: 10.3390/molecules24234262]
258 **Mehrazad-Saber Z**, Kheirouri S, Noorazar SG. Effects of l-Carnosine Supplementation on Sleep Disorders and Disease Severity in Autistic Children: A Randomized, Controlled Clinical Trial. *Basic Clin Pharmacol Toxicol* 2018; **123**: 72-77 [PMID: 29430839 DOI: 10.1111/bcpt.12979]
259 **Geier DA**, Kern JK, Davis G, King PG, Adams JB, Young JL, Geier MR. A prospective double-blind, randomized clinical trial of levocarnitine to treat autism spectrum disorders. *Med Sci Monit* 2011; **17**: PI15-PI23 [PMID: 21629200 DOI: 10.12659/msm.881792]
260 **Fahmy SF**, El-hamamsy MH, Zaki OK, Badary OA. l-Carnitine supplementation improves the behavioral symptoms in autistic children. *Res*

Autism Spectr Disord 2013; **7**: 159-166 [DOI: 10.1016/j.rasd.2012.07.006]

261 **Wang W**, Pan D, Liu Q, Chen X, Wang S. L-Carnitine in the Treatment of Psychiatric and Neurological Manifestations: A Systematic Review. *Nutrients* 2024; **16** [PMID: 38674921 DOI: 10.3390/nu16081232]

262 **Pancheva R**, Chamova R, Marinov D, Toneva A, Dzhogova M, Eyubova S, Usheva N. Therapeutic diets and supplementation: exploring their impact on autism spectrum disorders in childhood – A narrative review of recent clinical trials. *Res Autism Spectr Disord* 2024; **112**: 102352 [DOI: 10.1016/j.rasd.2024.102352]

263 **Calder PC**. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* 2013; **75**: 645-662 [PMID: 22765297 DOI: 10.1111/j.1365-2125.2012.04374.x]

264 **Veselinović A**, Petrović S, Žikić V, Subotić M, Jakovljević V, Jeremić N, Vučić V. Neuroinflammation in Autism and Supplementation Based on Omega-3 Polyunsaturated Fatty Acids: A Narrative Review. *Medicina (Kaunas)* 2021; **57** [PMID: 34577816 DOI: 10.3390/medicina57090893]

265 **Djuricic I**, Calder PC. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. *Nutrients* 2021; **13** [PMID: 34371930 DOI: 10.3390/nu13072421]

266 **Healy-Stoffel M**, Levant B. N-3 (Omega-3) Fatty Acids: Effects on Brain Dopamine Systems and Potential Role in the Etiology and Treatment of Neuropsychiatric Disorders. *CNS Neurol Disord Drug Targets* 2018; **17**: 216-232 [PMID: 29651972 DOI: 10.2174/1871527317666180412153612]

267 **Jiang Y**, Dang W, Nie H, Kong X, Jiang Z, Guo J. Omega-3 polyunsaturated fatty acids and/or vitamin D in autism spectrum disorders: a systematic review. *Front Psychiatry* 2023; **14**: 1238973 [PMID: 37654990 DOI: 10.3389/fpsyt.2023.1238973]

268 **Surette ME**. The science behind dietary omega-3 fatty acids. *CMAJ* 2008; **178**: 177-180 [PMID: 18195292 DOI: 10.1503/cmaj.071356]

269 **Cheng YS**, Tseng PT, Chen YW, Stubbs B, Yang WC, Chen TY, Wu CK, Lin PY. Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat* 2017; **13**: 2531-2543 [PMID: 29042783 DOI: 10.2147/NDT.S147305]

270 **Doaei S**, Bourbour F, Teymoori Z, Jafari F, Kalantari N, Abbas Torki S, Ashoori N, Nemat Gorgani S, Gholamalizadeh M. The effect of omega-3 fatty acids supplementation on social and behavioral disorders of children with autism: a randomized clinical trial. *Pediatr Endocrinol Diabetes Metab* 2021; **27**: 12-18 [PMID: 33599431 DOI: 10.5114/pedm.2020.101806]

271 **James S**, Montgomery P, Williams K. Omega-3 fatty acids supplementation for autism spectrum disorders (ASD). *Cochrane Database Syst Rev* 2011; CD007992 [PMID: 22071839 DOI: 10.1002/14651858.CD007992.pub2]

272 **de la Torre-Aguilar MJ**, Gomez-Fernandez A, Flores-Rojas K, Martin-Borreguero P, Mesa MD, Perez-Navero JL, Olivares M, Gil A, Gil-Campos M. Docosahexaenoic and Eicosapentaenoic Intervention Modifies Plasma and Erythrocyte Omega-3 Fatty Acid Profiles But Not the Clinical Course of Children With Autism Spectrum Disorder: A Randomized Control Trial. *Front Nutr* 2022; **9**: 790250 [PMID: 35425788 DOI: 10.3389/fnut.2022.790250]

273 **Bays HE**. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 2007; **99**: 35C-43C [PMID: 17368277 DOI: 10.1016/j.amjcard.2006.11.020]

274 **DiNicolantonio JJ**, O'Keefe J. The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies. *Mo Med* 2021; **118**: 453-459 [PMID: 34658440]

275 **Simopoulos AP**. Evolutionary aspects of diet: the omega-6/omega-3 ratio and the brain. *Mol Neurobiol* 2011; **44**: 203-215 [PMID: 21279554 DOI: 10.1007/s12035-010-8162-0]

276 **Abdelhamid AS**, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KH, AlAbdulghafoor FK, Summerbell CD, Worthington HV, Song F, Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018; **7**: CD003177 [PMID: 30019766 DOI: 10.1002/14651858.CD003177.pub3]

277 **Aranceta J**, Pérez-Rodrigo C. Recommended dietary reference intakes, nutritional goals and dietary guidelines for fat and fatty acids: a systematic review. *Br J Nutr* 2012; **107** Suppl 2: S8-22 [PMID: 22591906 DOI: 10.1017/S0007114512001444]

278 **Bandini LG**, Curtin C, Phillips S, Anderson SE, Maslin M, Must A. Changes in Food Selectivity in Children with Autism Spectrum Disorder. *J Autism Dev Disord* 2017; **47**: 439-446 [PMID: 27866350 DOI: 10.1007/s10803-016-2963-6]

279 **Cerchiari A**, Giordani C, Franceschetti S, Mazzafoglia S, Carosi F, Pizza F, Bella GD, Raponi M, Tofani M. The Efficacy of the Global Intensive Feeding Therapy on Feeding and Swallowing Abilities in Children with Autism Spectrum Disorder: A Pilot Study. *Children (Basel)* 2023; **10** [PMID: 37508738 DOI: 10.3390/children10071241]

280 **Manno CJ**, Fox C, Eicher PS, Kerwin ME. Early oral-motor interventions for pediatric feeding problems: What, when and how. *J Early Intensive Behav Intervent* 2005; **2**: 145-159 [DOI: 10.1037/h0100310]

281 **Maffei MF**, Chenausky KV, Gill SV, Tager-Flusberg H, Green JR. Oromotor skills in autism spectrum disorder: A scoping review. *Autism Res* 2023; **16**: 879-917 [PMID: 37010327 DOI: 10.1002/aur.2923]

282 **Marco EJ**, Hinkley LB, Hill SS, Nagarajan SS. Sensory processing in autism: a review of neurophysiologic findings. *Pediatr Res* 2011; **69**: 48R-54R [PMID: 21289533 DOI: 10.1203/PDR.0b013e3182130c54]

283 **Caldwell AR**, Skidmore ER, Terhorst L, Raina KD, Rogers JC, Danford CA, Bendixen RM. Promoting Routines of Exploration and Play during Mealtime: Estimated Effects and Identified Barriers. *Occup Ther Health Care* 2022; **36**: 46-62 [PMID: 34338588 DOI: 10.1080/07380577.2021.1953205]

284 **Roberts L**, Marx JM, Musher-Eizenman DR. Using food as a reward: An examination of parental reward practices. *Appetite* 2018; **120**: 318-326 [PMID: 28951237 DOI: 10.1016/j.appet.2017.09.024]

285 **Williams K**, Seiverling L. Behavior Analytic Feeding Interventions: Current State of the Literature. *Behav Modif* 2023; **47**: 983-1011 [PMID: 35674422 DOI: 10.1177/01454455221098118]

286 **Chung KM**, Chung E, Lee H. Behavioral Interventions for Autism Spectrum Disorder: A Brief Review and Guidelines With a Specific Focus on Applied Behavior Analysis. *Soa Chongsonyon Chongsin Uihak* 2024; **35**: 29-38 [PMID: 38204739 DOI: 10.5765/jkacap.230019]

287 **Nekitsing C**, Hetherington MM, Blundell-Birtill P. Developing Healthy Food Preferences in Preschool Children Through Taste Exposure, Sensory Learning, and Nutrition Education. *Curr Obes Rep* 2018; **7**: 60-67 [PMID: 29446037 DOI: 10.1007/s13679-018-0297-8]

288 **Camilleri LJ**, Maras K, Brosnan M. The impact of using digitally-mediated social stories on the perceived competence and attitudes of parents and practitioners supporting children with autism. *PLoS One* 2022; **17**: e0262598 [PMID: 35041714 DOI: 10.1371/journal.pone.0262598]

289 **Haines J**, Haycraft E, Lytle L, Nicklaus S, Kok FJ, Merdji M, Fisberg M, Moreno LA, Goulet O, Hughes SO. Nurturing Children's Healthy Eating: Position statement. *Appetite* 2019; **137**: 124-133 [PMID: 30797837 DOI: 10.1016/j.appet.2019.02.007]

290 **Donahoe JW**, Palmer DC. Acquired reinforcement: Implications for autism. *Am Psychol* 2022; **77**: 439-452 [PMID: 35201786 DOI: 10.1037/amp0000970]

291 **Boudreau BA**, Vladescu JC, Kodak TM, Argott PJ, Kisamore AN. A comparison of differential reinforcement procedures with children with autism. *J Appl Behav Anal* 2015; **48**: 918-923 [PMID: 26174019 DOI: 10.1002/jaba.232]

292 **Fiske KE**, Isenhower RW, Bamond MJ, Delmolino L, Sloman KN, LaRue RH. Assessing the value of token reinforcement for individuals with autism. *J Appl Behav Anal* 2015; **48**: 448-453 [PMID: 25930718 DOI: 10.1002/jaba.207]

293 **Fishbein M**, Cox S, Swenny C, Mogren C, Walbert L, Fraker C. Food chaining: a systematic approach for the treatment of children with feeding aversion. *Nutr Clin Pract* 2006; **21**: 182-184 [PMID: 16556929 DOI: 10.1177/0115426506021002182]

294 **Tanner A**, Andreone BE. Using Graduated Exposure and Differential Reinforcement to Increase Food Repertoire in a Child with Autism. *Behav Anal Pract* 2015; **8**: 233-240 [PMID: 27703925 DOI: 10.1007/s40617-015-0077-9]

295 **Nimbley E**, Golds L, Sharpe H, Gillespie-Smith K, Duffy F. Sensory processing and eating behaviours in autism: A systematic review. *Eur Eat Disord Rev* 2022; **30**: 538-559 [PMID: 35737818 DOI: 10.1002/erv.2920]

296 **Allirot X**, da Quinta N, Chokupermal K, Urdaneta E. Involving children in cooking activities: A potential strategy for directing food choices toward novel foods containing vegetables. *Appetite* 2016; **103**: 275-285 [PMID: 27125429 DOI: 10.1016/j.appet.2016.04.031]

297 **Kähkönen K**, Rönkä A, Hujo M, Lyytikäinen A, Nuutinen O. Sensory-based food education in early childhood education and care, willingness to choose and eat fruit and vegetables, and the moderating role of maternal education and food neophobia. *Public Health Nutr* 2018; **21**: 2443-2453 [PMID: 29734970 DOI: 10.1017/S1368980018001106]

298 **Scaglioni S**, De Cosmi V, Ciappolino V, Parazzini F, Brambilla P, Agostoni C. Factors Influencing Children's Eating Behaviours. *Nutrients* 2018; **10** [PMID: 29857549 DOI: 10.3390/nu10060706]

299 **Mahmood L**, Flores-Barrantes P, Moreno LA, Manios Y, Gonzalez-Gil EM. The Influence of Parental Dietary Behaviors and Practices on Children's Eating Habits. *Nutrients* 2021; **13** [PMID: 33808337 DOI: 10.3390/nu13041138]

300 **Gray HL**, Pang T, Agazzi H, Shaffer-Hudkins E, Kim E, Miltenberger RG, Waters KA, Jimenez C, Harris M, Stern M. A nutrition education intervention to improve eating behaviors of children with autism spectrum disorder: Study protocol for a pilot randomized controlled trial. *Contemp Clin Trials* 2022; **119**: 106814 [PMID: 35671902 DOI: 10.1016/j.cct.2022.106814]

301 **Rogers LG**, Magill-evans J, Rempel GR. Mothers' Challenges in Feeding their Children with Autism Spectrum Disorder—Managing More Than Just Picky Eating. *J Dev Phys Disabil* 2012; **24**: 19-33 [DOI: 10.1007/s10882-011-9252-2]

302 **Powell F**, Farrow C, Meyer C, Haycraft E. The importance of mealtime structure for reducing child food fussiness. *Matern Child Nutr* 2017; **13** [PMID: 27062194 DOI: 10.1111/mcn.12296]

303 **Sharp WG**, Burrell TL, Berry RC, Stubbs KH, McCracken CE, Gillespie SE, Scahill L. The Autism Managing Eating Aversions and Limited Variety Plan vs Parent Education: A Randomized Clinical Trial. *J Pediatr* 2019; **211**: 185-192.e1 [PMID: 31056202 DOI: 10.1016/j.jpeds.2019.03.046]

304 **Balk SJ**, Bochner RE, Ramdhanie MA, Reilly BK; COUNCIL ON ENVIRONMENTAL HEALTH AND CLIMATE CHANGE; SECTION ON OTOLARYNGOLOGY–HEAD AND NECK SURGERY. Preventing Excessive Noise Exposure in Infants, Children, and Adolescents. *Pediatrics* 2023; **152** [PMID: 37864408 DOI: 10.1542/peds.2023-063753]

305 **Acharya BD**, Karki A, Prasertsukdee S, Reed D, Rawal L, Baniya PL, Boyd RN. Effect of Adaptive Seating Systems on Postural Control and Activity Performance: A Systematic Review. *Pediatr Phys Ther* 2023; **35**: 397-410 [PMID: 37747975 DOI: 10.1097/PEP.0000000000001042]

306 **Nair AS**, Priya RS, Rajagopal P, Pradeepa C, Senthil R, Dhanalakshmi S, Lai KW, Wu X, Zuo X. A case study on the effect of light and colors in the built environment on autistic children's behavior. *Front Psychiatry* 2022; **13**: 1042641 [PMID: 36532166 DOI: 10.3389/fpsyt.2022.1042641]

307 **Chen N**, Watanabe K, Kobayakawa T, Wada M. Relationships between autistic traits, taste preference, taste perception, and eating behaviour. *Eur Eat Disord Rev* 2022; **30**: 628-640 [PMID: 35690923 DOI: 10.1002/erv.2931]

308 **Baraskewich J**, von Ranson KM, McCrimmon A, McMorris CA. Feeding and eating problems in children and adolescents with autism: A scoping review. *Autism* 2021; **25**: 1505-1519 [PMID: 33653157 DOI: 10.1177/1362361321995631]

309 **Suwalska J**, Bogdański P. Social Modeling and Eating Behavior-A Narrative Review. *Nutrients* 2021; **13** [PMID: 33916943 DOI: 10.3390/nu13041209]

310 **Hodder RK**, O'Brien KM, Tzelepis F, Wyse RJ, Wolfenden L. Interventions for increasing fruit and vegetable consumption in children aged five years and under. *Cochrane Database Syst Rev* 2020; **5**: CD008552 [PMID: 32449203 DOI: 10.1002/14651858.CD008552.pub7]

311 **Mura Paroche M**, Caton SJ, Vereijken CMJL, Weenen H, Houston-Price C. How Infants and Young Children Learn About Food: A Systematic Review. *Front Psychol* 2017; **8**: 1046 [PMID: 28790935 DOI: 10.3389/fpsyg.2017.01046]

312 **Wardle J**, Herrera ML, Cooke L, Gibson EL. Modifying children's food preferences: the effects of exposure and reward on acceptance of an unfamiliar vegetable. *Eur J Clin Nutr* 2003; **57**: 341-348 [PMID: 12571670 DOI: 10.1038/sj.ejcn.1601541]

313 **Harding C**, Cockerill H. Managing eating and drinking difficulties (dysphagia) with children who have learning disabilities: What is effective? *Clin Child Psychol Psychiatry* 2015; **20**: 395-405 [PMID: 24414040 DOI: 10.1177/1359104513516650]

314 **Blaine RE**, Blaine KP, Cheng K, Banuelos C, Leal A. Priorities, barriers, and facilitators for nutrition-related care for autistic children: a qualitative study comparing interdisciplinary health professional and parent perspectives. *Front Pediatr* 2023; **11**: 1198177 [PMID: 37650046 DOI: 10.3389/fped.2023.1198177]

315 **Sarcia B**. The Impact of Applied Behavior Analysis to Address Mealtime Behaviors of Concern Among Individuals with Autism Spectrum Disorder. *Psychiatr Clin North Am* 2021; **44**: 83-93 [PMID: 33526239 DOI: 10.1016/j.psc.2020.11.007]

316 **Sartore GM**, Pourliakas A, Lagioia V. Peer support interventions for parents and carers of children with complex needs. *Cochrane Database Syst Rev* 2021; **12**: CD010618 [PMID: 34923624 DOI: 10.1002/14651858.CD010618.pub2]

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CASE REPORT

Diazoxide toxicity in congenital hyperinsulinism: A case report

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Abstract

BACKGROUND

Diazoxide is the sole approved drug for congenital hyperinsulinism; however, diuretic administration and vigilant monitoring are crucial to prevent and promptly identify potentially life-threatening adverse effects. This report aims to highlight a seldom-considered rare side effect of diazoxide. We believe that this brief report is of general interest to *World Journal of Clinical Pediatric* readership and increase the physicians' awareness of the guideline importance. Moreover, it underlines the importance of stopping immediately the drug if suspected side effects.

CASE SUMMARY

The manuscript describes a patient diagnosed with congenital hyperinsulinism (CHI) treated with diazoxide not overlapping with diuretic. He resulted in sudden respiratory distress and therefore was transferred to the Neonatal Intensive Care Unit. The cardiological evaluation showed pericardial effusion and left ventricular myocardial hypertrophy, absent before. In suspicion of an iatrogenic effect of diazoxide it was progressively reduced until stop while introducing diuretic treatment, with resolution of symptoms. Once clinically stabilized, an 18 fluoro-diydroxy-phenylalanine positron emission tomography/computed tomography (PET/CT) was performed to differentiate between a focal or diffuse form of CHI. The PET/CT highlighted the presence of a single focal accumulation of the tracer located in the pancreatic tail, consistent with a focal form of hyperin-

sulinism. At the age of four months, the patient underwent a distal pancreatectomy with histological confirmation of a focal form of nesidioblastosis, resulting in a curative operation.

CONCLUSION
Diuretic administration and vigilant monitoring of diazoxide therapy are crucial to prevent and promptly identify potentially life-threatening adverse effects.

Key Words: Diazoxide; Hypoglycemia; Congenital hyperinsulinism; Side effect; Case report

Core Tip: Diazoxide can be effective in treating congenital hyperinsulinism, but its use requires diuretic administration and careful surveillance to prevent and promptly diagnose potential life-threatening adverse effects. Although diazoxide cardiopulmonary side effects were previously described in sporadic case reports, the United States Food and Drug Administration (FDA) has clearly listed them as severe adverse events since 2015. Despite this, numerous reports were published after the FDA statement, describing the increasing rate of these diazoxide side effects. Further studies are needed to identify the underlying mechanism and precise predisposing factors.

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INTRODUCTION

Congenital hyperinsulinism (CHI) comprises a rare group of hypoketotic hypoglycemia disorders, characterized by abnormal insulin secretion leading to transient or persistent hypoglycemia[1]. While transient forms are linked to perinatal factors (*i.e.* Infant of diabetic mother, intrauterine growth retardation, maternal toxemia, birth asphyxia and perinatal stress) and can resolve rapidly (lasting less than 6 months), persisting forms of CHI typically persist beyond 6 months of age and are often associated with mutations in genes involved in regulating pancreatic β-cell function (*e.g.* *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A*, *HK1*, *PGM1*, *PMM2*) or genetic syndromes (*e.g.* Beckwith Wiedemann); however in some of these forms the exact genetic cause remains unknown[2]. If misdiagnosed, this condition can lead to irreversible brain damage[3]. The treatment of CHI depends on the underlying condition and can be medical, surgical or both. Currently, the only approved treatment for CHI is diazoxide, though some patients may be resistant or intolerant, necessitating alternative options[4,5]. Surgical intervention may be curative in focal forms of CHI[6], while others can benefit from administration of continuous enteral glucose or drugs such as octreotide or its long-acting analogs[7]. This report aims to describe a rare side effect of diazoxide that, though documented in literature, lacks defined incidence, pathogenesis, and timing of appearance.

CASE PRESENTATION

Chief complaints

The manuscript describes a patient diagnosed with CHI treated with diazoxide not overlapping with diuretic. He resulted in sudden respiratory distress and therefore was transferred to the Neonatal Intensive Care Unit (NICU). The cardiological evaluation showed pericardial effusion and left ventricular myocardial hypertrophy, absent before. In suspicion of an iatrogenic effect of diazoxide it was progressively reduced until stop while introducing diuretic treatment, with resolution of symptoms

History of present illness

The patient was referred to our center at the age of 45 days of life (see History of past illness) for the suspicion of diazoxide-resistant CHI.

Once admitted, we conducted glucose monitoring without altering the ongoing treatment (diazoxide 15mg/kg/day). We opted not to reintroduce thiazide, considering the baby's age and the normal findings of the recent cardiac ultrasound scan (US). The baby showed poor glycemic control (average glycemia 40-60 mg/dL), so a second-line therapy with subcutaneous octreotide was started. Octreotide was administered at an initial dosage of 5 mcg/kg/day in three daily administrations. After four days, the patient developed tachypnea [respiratory rate (RR) = 70 breaths/min], intercostal, subcostal and jugular retractions, tachycardia (180-190 bpm), diuresis contraction (0.6-0.7 mL/kg/h) and mild increase in body weight, with adequate oxygen saturation in room air. Due to respiratory distress, high-flow oxygen therapy

Table 1 Blood tests during relative hypoglycemia and glucagon stimulation test

Glycemia (mg/dL)	Insulin (mcU/mL)	C-peptide (ng/mL)	ACTH (pg/mL)	Cortisol (mcg/dL)	GH (ng/mL)	Glucagon test (mg/dL)
46 (nv > 70)	14.4 (nv < 1.25)	2 (nv < 0.5)	17.1 (nv 4.7-48.8)	17 (nv > 18)	7.76 (nv > 8)	Glycemia 36-85

ACTH: Adrenocorticotropic hormone; GH: Growth hormone.

(maximum flow 10 L/min, maximum FiO2 0.25%) was initiated. Considering the acute presentation and the uncertain etiology of the symptoms, the infant was transferred to the NICU for intensive observation.

History of past illness

The patient was born at 39 gestational weeks through eutocic delivery; he weighed 3300 g (41st weight percentile, -0.24 standard deviation score) and measured 51 cm in length (66th length percentile, 0.4 standard deviation score). The pregnancy was uneventful and no physical abnormalities were observed at birth.

At two hours of life, the infant exhibited hyporeactivity and difficulty in sucking. A blood gas analysis revealed a blood glucose level of 11 mg/dL. Consequently, early enteral feeding with both breast and formula milk was initiated. Despite these measures, persistent hypoglycemia necessitated his transfer to the NICU. Intravenous (IV) infusion therapy with a 10% glucose solution was initiated, but hypoglycemia persisted. Subsequently, IV infusion with glucose 33% was administered *via* an umbilical venous catheter, gradually increased to 50%, achieving an IV glucose infusion rate (GIR) of 10. 4 mg/kg/min. Simultaneously, enteral feeding was supplemented first with fortified breast milk, then with formula milk containing a high-calorie glucolipid preparation, and finally with maltodextrins, resulting in an increased GIR of 15.3 mg/kg/min. On the 4th day of life, blood tests and a glucagon test during hypoglycemia strongly suggested CHI (Table 1).

Due to the high suspicion of CHI, subsequent genetic analysis was carried out and identified a heterozygous variant, c.4477C>Tp. (Arg1493Trp), in the *ABCC8* gene, inherited from the father and classified as a pathogenetic variant. On 22nd day of life, diazoxide and thiazide treatment was initiated, with diazoxide gradually increased to 15 mg/kg/day (administered in three daily doses), resulting in a partial improvement in the glycemic profile. IV glucose infusion was no longer required, but the patient still experienced blood sugar levels < 70 mg/dL 2-3 times/day, leading to suspicion of a resistant-diazoxide form. For this reason the patient was transferred to our center at the age of 45 days of life (see history of present illness).

Personal and family history

The patient is the only child of non-consanguineous parents from India. No family history of endocrinopathies described nor pancreatic diseases.

Physical examination

After four days of second-line therapy with subcutaneous octreotide the patient developed tachypnea (RR = 70 breaths/min), intercostal, subcostal and jugular retractions, tachycardia (180-190 bpm), diuresis contraction (0.6-0.7 mL/kg/h) and mild increase in body weight, with adequate oxygen saturation in room air. Due to respiratory distress, high-flow oxygen therapy (maximum flow 10 L/min, maximum FiO2 0.25%) was initiated.

Laboratory examinations

Urgent laboratory-instrumental tests were performed due to the clinical conditions: Cell blood count, electrolytes, renal-liver function and inflammatory indexes, blood culture resulted negative, blood gas analysis showed respiratory alkalosis, leading us to exclude sepsis and infectious etiologies.

Imaging examinations

The chest X-ray revealed an enlargement of the cardiac image beyond normal limits with clear lungs and pleural spaces (Figure 1).

Subsequent cardiological evaluation with US showed pericardial effusion in the anterolateral site (0.5-0.7 cm), with no pulmonary hypertension signs, and left ventricular myocardial hypertrophy.

MULTIDISCIPLINARY EXPERT CONSULTATION

After consultation with our pediatric anesthesiologist and cardiologist, we suspected cardiovascular iatrogenic side-effect of diazoxide.

FINAL DIAGNOSIS

We diagnosed a diazoxide's side effect; in particular we diagnosed a cardiovascular side effect considering the patient's

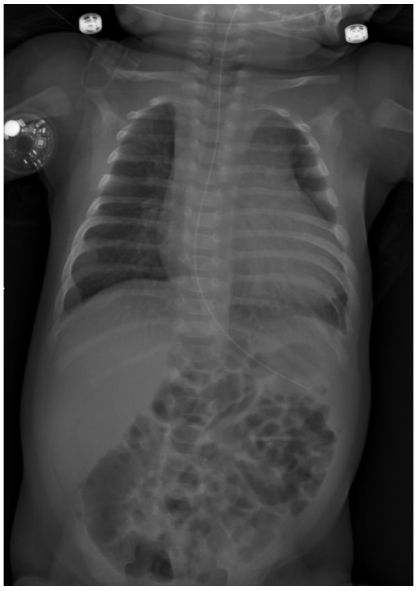

Figure 1 Chest and abdomen X-ray, showing a cardiomediastinal image slightly above normal limits.

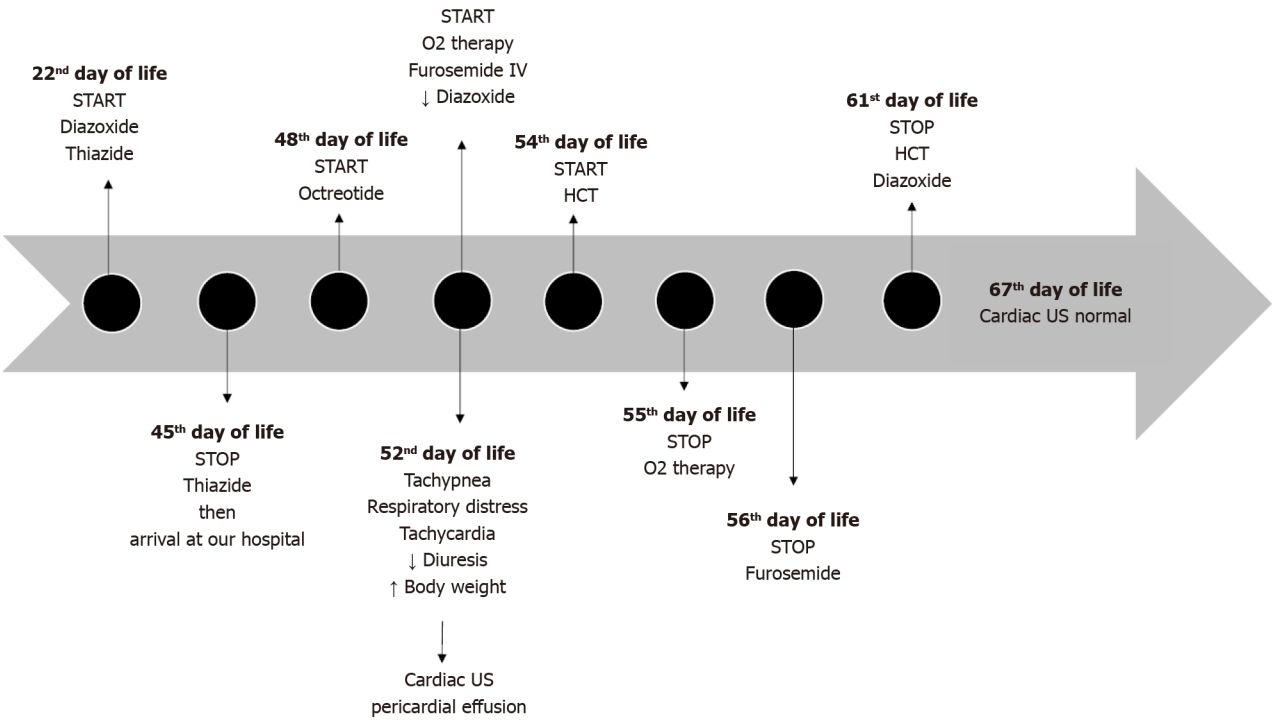

Figure 2 Timeline of therapies. HCT: Hydrochlorothiazide; US: Ultrasound scan.

history and clinical manifestations and the cardiological evaluation.

TREATMENT

On 52nd day of life therapy with IV furosemide was initiated and the diazoxide dosage was progressively reduced until stopped. Octreotide therapy was gradually increased. Furosemide was continued for five days, and hydrochlorothiazide was initiated on the third day, continuing for a total of eight days (Figure 2).

OUTCOME AND FOLLOW-UP

During the permanence in NICU, the infant continued meals with formula integrated with maltodextrins *via* bottle and nasogastric tube. After three days form therapies editing, the patient's conditions improved, prompting the suspension of oxygen support. Daily monitoring by echocardiography revealed a progressive reduction of the pericardial effusion, culminating in complete resolution after 15 days from the onset of symptoms and four days after the complete suspension of diazoxide therapy.

Once clinically stabilized, an 18 fluoro-diydroxy-phenylalanine positron emission tomography/computed tomography (PET/CT) was performed to differentiate between a focal or diffuse form of CHI. The PET/CT highlighted the presence of a single focal accumulation of the tracer located in the pancreatic tail, consistent with a focal form of hyperinsulinism. At the age of four months, the patient underwent a distal pancreatectomy with histological confirmation of a focal form of nesidioblastosis, resulting in a curative operation. The patient's glycemic profile, after surgery, became normal and he did not require anymore administration of glucose, nor other drugs. Nowadays, he's an infant with adequate neurological development. Moreover he presented a complete regression of the cardiological manifestations.

DISCUSSION

Diazoxide currently remains the only drug approved by the United States Food and Drug Administration (FDA) for treatment of CHI[8]. However, over the last 50 years, severe adverse events (SAEs) related to diazoxide have been reported, including necrotizing enterocolitis[9], pericardial effusion[10-13], pulmonary hypertension, respiratory decompensation, congestive heart failure and death[14,15]. In 2015 FDA emphasized the risk of pulmonary hypertension in patients treated with diazoxide. Additionally, the FDA listed risk factors for this side effect[16]: Various studies highlight that patients with a higher risk of cardiopulmonary diazoxide side effects include neonates with transient hyperinsulinism, premature neonates, neonates receiving high fluid rate infusion, neonates with sepsis, meconium aspiration syndrome, pneumonia, and congenital heart disease. Despite these risks, the effectiveness of diazoxide, coupled with a low overall number of SAEs[17], has led to a significant increase in its use over the years. Consequently, the rate of severe cardiorespiratory adverse events has risen from 5% to more than 16%[16,17-22].

The physiological effect of diazoxide is to bind to the SUR1 subunit of the KATP channels keeping them open and thereby inhibiting insulin secretion[18]. In addition, it also binds to the SUR2 subunit expressed in the cardiac muscle, smooth muscles, skeletal muscles and the brain. Due to its action on renal arterioles and renal tubular system, it also has antidiuretic and antihypertensive effects[19,20]. Thus, the off-target effects of diazoxide through its binding to the SUR2 subunit of the KATP channel may explain the most serious side effects (pulmonary hypertension, pericardial effusion and congestive heart failure) even though their physiopathology is not well defined: It remains unclear whether they are caused by primary damage to the cardiovascular system or by a secondary effect due to fluid retention. To reduce the risk of SAEs, the European Society for Pediatric Endocrinology suggests performing a cardiopulmonary assessment (cardiac examination and US) in all infants before starting diazoxide and one week after the beginning of the treatment, even if in the absence of signs of fluid overload[8,21]. They also strongly recommend starting thiazide diuretics at the same time of diazoxide due to risk of fluid retention and pulmonary hypertension[22]. Furthermore, fluid restriction before diazoxide treatment and routine surveillance during the treatment course are advised. These clinical practice guidelines for dosing and monitoring adverse events in infants treated with diazoxide can be highly useful for clinicians treating CHI patients. In line with these recommendations, it is crucial to discontinue the treatment promptly if a diazoxide-related side effect is suspected. Other previous publications describe different diazoxide collateral effects[22] such as hypertrichosis, bone marrow suppression (neutropenia and thrombocytopenia), hyperuricemia and gastrointestinal symptoms (poor appetite and vomiting). While these collateral effects are more frequent and well-known, they are generally considered minor and rarely require discontinuation of the drug.

When the patient was admitted to our center, he was only taking diazoxide. At the age of 45 days, thiazide treatment was discontinued while diazoxide was continued. Before suspending thiazide, cardiac US was normal. We chose to continue diazoxide based on the baby's age and the normal cardiac ultrasound. After three days in our center, we observed that the patient was diazoxide resistant and therefore octreotide was initiated (48 days of life). When the patient became symptomatic (at 52 days of life), he was transferred to NICU due to his serious clinical conditions. The patient was stabilized with High Flow Nasal Cannula and diuretic treatment. We conducted a comprehensive evaluation (blood tests and instrumental work-up) to understand the etiology of the acute symptoms. We considered the possibility of drug side effects and two factors made octreotide side effects more probable. Firstly, the timing of symptom onset: The patient had been taking diazoxide for over a month, while octreotide had only been initiated for 4 days. Additionally, the patient did not have any risk factors for diazoxide side effects, such as IV fluid administration, transient hyperinsulinism, abnormal cardiac ultrasound findings, or prematurity. The most serious octreotide side effect is necrotizing entero colitis, which we ruled out through abdominal X-rays and observation over the following days. However, guidelines recommend immediately discontinuing diazoxide when cardiovascular side effects appear, even if the etiology of symptoms is unclear: It is advised to discontinue diazoxide promptly if the patient develops respiratory distress or fluid overload, while investigating other potential causes of the symptoms. Glycemic control should be managed without diazoxide. This case underscores the challenge of identifying diazoxide's cardiovascular effects, as each patient may present different confounding factors in their medical history (such as concomitant drugs or diseases, the presence or absence of risk factors, timing of symptom onset, *etc.*). It suggests considering diazoxide-related effects even when investigating other potential causes, and emphasizes that the diagnostic workup should not delay diazoxide discontinuation.

CONCLUSION

Diazoxide can be effective in treating CHI, but its use requires diuretic administration and careful surveillance to prevent and promptly diagnose potential life-threatening adverse effects. Although diazoxide cardiopulmonary side effects were previously described in sporadic case reports, the FDA has clearly listed them as SAEs since 2015. Despite this, numerous reports were published after the FDA statement, describing the increasing rate of these diazoxide side effects. Further studies are needed to identify the underlying mechanism and precise predisposing factors of diazoxide cardiopulmonary side effects. In current clinical practice, it is crucial to adhere to guidelines when initiating diazoxide, and if there is suspicion of cardiopulmonary side effects, the treatment should be promptly interrupted. Additionally, for patients with baseline comorbidities such as congenital heart disease or intolerance to diazoxide, alternative therapies for hyperinsulinism should be considered.

FOOTNOTES

Author contributions: Pajno R conduct writing original draft; Visconti C conduct data collection; Bucolo C conduct conceptualization of the case report; Guarneri MP, Barera G and Silvani P proceed manuscript review; Barba PD and Gregnanin M proceed manuscript editing.

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REFERENCES

1 **Demirbilek H**, Hussain K. Congenital Hyperinsulinism: Diagnosis and Treatment Update. *J Clin Res Pediatr Endocrinol* 2017; **9**: 69-87 [PMID: 29280746 DOI: 10.4274/jcrpe.2017.S007]
2 **Galcheva S**, Demirbilek H, Al-Khawaga S, Hussain K. The Genetic and Molecular Mechanisms of Congenital Hyperinsulinism. *Front Endocrinol (Lausanne)* 2019; **10**: 111 [PMID: 30873120 DOI: 10.3389/fendo.2019.00111]
3 **Banerjee I**, Raskin J, Arnoux JB, De Leon DD, Weinzimer SA, Hammer M, Kendall DM, Thornton PS. Congenital hyperinsulinism in infancy and childhood: challenges, unmet needs and the perspective of patients and families. *Orphanet J Rare Dis* 2022; **17**: 61 [PMID: 35183224 DOI: 10.1186/s13023-022-02214-y]
4 **Banerjee I**, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. *Diabet Med* 2019; **36**: 9-21 [PMID: 30246418 DOI: 10.1111/dme.13823]
5 **Sikimic J**, Hoffmeister T, Gresch A, Kaiser J, Barthlen W, Wolke C, Wieland I, Lendeckel U, Krippeit-Drews P, Düfer M, Drews G. Possible New Strategies for the Treatment of Congenital Hyperinsulinism. *Front Endocrinol (Lausanne)* 2020; **11**: 545638 [PMID: 33193079 DOI: 10.3389/fendo.2020.545638]
6 **Barthlen W**, Varol E, Empting S, Wieland I, Zenker M, Mohnike W, Vogelgesang S, Mohnike K. Surgery in Focal Congenital Hyperinsulinism (CHI) - The "Hyperinsulinism Germany International" Experience in 30 Children. *Pediatr Endocrinol Rev* 2016; **14**: 129-137 [PMID: 28508606 DOI: 10.17458/PER.2016.BVE.Surgeryinfocal]
7 **McMahon AW**, Wharton GT, Thornton P, De Leon DD. Octreotide use and safety in infants with hyperinsulinism. *Pharmacoepidemiol Drug Saf* 2017; **26**: 26-31 [PMID: 27910218 DOI: 10.1002/pds.4144]
8 **De Leon DD**, Arnoux JB, Banerjee I, Bergada I, Bhatti T, Conwell LS, Fu J, Flanagan SE, Gillis D, Meissner T, Mohnike K, Pasquini TLS, Shah P, Stanley CA, Vella A, Yorifuji T, Thornton PS. International Guidelines for the Diagnosis and Management of Hyperinsulinism. *Horm Res Paediatr* 2024; **97**: 279-298 [PMID: 37454648 DOI: 10.1159/000531766]
9 **Theodorou CM**, Hirose S. Necrotizing enterocolitis following diazoxide therapy for persistent neonatal hypoglycemia. *J Pediatr Surg Case Rep* 2020; **52** [PMID: 32161713 DOI: 10.1016/j.epsc.2019.101356]
10 **Silvani P**, Camporesi A, Mandelli A, Wolfler A, Salvo I. A case of severe diazoxide toxicity. *Paediatr Anaesth* 2004; **14**: 607-609 [PMID:

15200661 DOI: 10.1111/j.1460-9592.2004.01276.x]

11 **Maffre I**, Vincenti M, Dalla Vale F, Amouroux C, Werner O, Meilhac A, de Barry G, Amedro P. Diazoxide Causality Assessment of a Pericardial Effusion in a Child with Kabuki Syndrome. *J Clin Res Pediatr Endocrinol* 2019; **11**: 218-219 [PMID: 30362323 DOI: 10.4274/jcrpe.galenos.2018.2018.0193]

12 **Avatapalle B**, Banerjee I, Malaiya N, Padidela R. Echocardiography monitoring for diazoxide induced pericardial effusion. *BMJ Case Rep* 2012; **2012** [PMID: 22761225 DOI: 10.1136/bcr.03.2012.6110]

13 **Hastings LA**, Preddy J, McCready M, Neville K, Verge CF. Pericardial Effusion Associated with Diazoxide Treatment for Congenital Hyperinsulinism. *Horm Res Paediatr* 2020; **93**: 206-211 [PMID: 32580193 DOI: 10.1159/000507624]

14 **Timlin MR**, Black AB, Delaney HM, Matos RI, Percival CS. Development of Pulmonary Hypertension During Treatment with Diazoxide: A Case Series and Literature Review. *Pediatr Cardiol* 2017; **38**: 1247-1250 [PMID: 28642988 DOI: 10.1007/s00246-017-1652-3]

15 **Kylat RI**. Pulmonary hypertension occurring with diazoxide use in a preterm infant with hypoglycemia. *Drug Healthc Patient Saf* 2019; **11**: 7-10 [PMID: 30881142 DOI: 10.2147/DHPS.S198255]

16 **US Food and Drug Administration**. FDA drug safety communication: FDA warns about a serious lung condition in infants and newborns treated with Proglycem (diazoxide). 2015. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-lung-condition-infants-and-newborns-treated#:~:text=The%20U.S.%20Food%20and%20Drug%20Administration%20%28FDA%29%20is,treated%20with%20Proglycem%20%28diazoxide%29%20for%20low%20blood%20sugar

17 **Thornton P**, Truong L, Reynolds C, Hamby T, Nedrelow J. Rate of Serious Adverse Events Associated with Diazoxide Treatment of Patients with Hyperinsulinism. *Horm Res Paediatr* 2019; **91**: 25-32 [PMID: 30889588 DOI: 10.1159/000497458]

18 **Shyng S**, Ferrigni T, Nichols CG. Regulation of KATP channel activity by diazoxide and MgADP. Distinct functions of the two nucleotide binding folds of the sulfonylurea receptor. *J Gen Physiol* 1997; **110**: 643-654 [PMID: 9382893 DOI: 10.1085/jgp.110.6.643]

19 **Taylor RM**, Rubin AA. Studies on the renal pharmacology of diazoxide (an antidiuretic benzothiadiazine). *J Pharmacol Exp Ther* 1964; **144**: 284-292 [PMID: 14183441]

20 **Fine LG**, Weber H. Effect of diazoxide on renal handling of sodium in the rat. *Clin Sci Mol Med* 1975; **49**: 277-282 [PMID: 1175343 DOI: 10.1042/cs0490277]

21 **Brar PC**, Heksch R, Cossen K, De Leon DD, Kamboj MK, Marks SD, Marshall BA, Miller R, Page L, Stanley T, Mitchell D, Thornton P. Management and Appropriate Use of Diazoxide in Infants and Children with Hyperinsulinism. *J Clin Endocrinol Metab* 2020; **105** [PMID: 32810255 DOI: 10.1210/clinem/dgaa543]

22 **Herrera A**, Vajravelu ME, Givler S, Mitteer L, Avitabile CM, Lord K, De León DD. Prevalence of Adverse Events in Children With Congenital Hyperinsulinism Treated With Diazoxide. *J Clin Endocrinol Metab* 2018; **103**: 4365-4372 [PMID: 30247666 DOI: 10.1210/jc.2018-01613]

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LETTER TO THE EDITOR

Influence of social media on maternal decision-making and breastfeeding practices

Gowda Parameshwara Prashanth

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Abstract

Breastfeeding practices are influenced by multifactorial determinants including individual characteristics, external support systems, and media influences. This commentary emphasizes such complex factors influencing breastfeeding practices. Potential methodological limitations and the need for diverse sampling in studying breastfeeding practices are highlighted. Further research must explore the interplay between social influences, cultural norms, government policies, and individual factors in shaping maternal breastfeeding decisions.

Key Words: Exclusive breastfeeding; Breastfeeding promotion; Mass communication; Maternal decision-making; Social media

Core Tip: Maternal breastfeeding decisions are influenced by multifactorial biopsychosocial determinants. Inaccurate information on social media may exaggerate potential difficulties in breastfeeding, promote the use of formula milk alternatives, or undermine mothers' confidence in their abilities to breastfeed. Addressing misinformation on social media channels is crucial for empowering informed maternal decision-making.

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TO THE EDITOR

Maternal education about breastfeeding using the Women- and Child-Friendly Institution model (WCFI) in Columbia has been recently found to be significantly associated with increased exclusive breastfeeding (EBF) rates[1]. This research highlights key factors associated with EBF discontinuation and reveals a link between exposure to information from mass communication channels and lower rates of achieving EBF for up to 4 months (OR 0.52; 95%CI: 0.31-0.84). While this finding suggests a negative association between receiving information from mass communication media and maintaining EBF, it is important to consider further expositions on this topic.

Determinants of breastfeeding practice are known to be multifactorial and influenced by a complex interplay of individual characteristics (age, occupation, smoking, obesity, pre-pregnancy feeding patterns), external support systems (social support, birth complications, cesarean delivery), and psychological well-being (stress, anxiety, self-efficacy) apart from ideological, racial, and ethnic determinants[2]. It is clear that no single factor operates in isolation, and the interplay between these elements must be considered to fully grasp how mothers decide on breastfeeding practices. The authors of the study have considered several confounding factors in the analysis of results but may have missed others, such as maternal occupation, socioeconomic status, social support, or infant health, which could influence EBF[1]. Also, the large number of variables considered in the regression analysis relative to the sample size may have lead to overfitting, which potentially reduces the reliability of reported associations. Therefore, conducting a sensitivity analysis would be helpful to address likely biases and to test the robustness of the reported findings apart from addressing multicollinearity among included variables.

Further, providing information on standardizing interview methods could help readers comprehend the influence of interviewer questions on the participant responses. The validity and reliability of the 25-question telephone survey are also worth discussing. Recording the interviews with participant consent could allow quality control and minimize interviewer variation. An additional qualitative research approach with focus group discussions involving participants could provide deeper insights into mothers' breastfeeding experiences and reasons for EBF discontinuation. Some of the other limitations of the study are potential selection and recall biases. Employing a more diversified sampling strategy that includes mothers from different socioeconomic backgrounds could reduce selection bias. Mothers may not accurately recall details about breastfeeding practices and subtle factors influencing them from months or even years earlier.

The findings reported by Murillo Galvis *et al*[1] significantly contribute to the existing knowledge on breastfeeding practices by laying the groundwork for further exploration of the distinct roles that different forms of mass communication media (including digital social media, newspapers, television advertisements, *etc.*) may play in influencing breastfeeding practices. Factors such as maternal age, education level, socioeconomic status, cultural background, and access to healthcare resources may impact the extent to which mothers are influenced by media messages and their subsequent breastfeeding practices[3]. A reciprocal relationship exists between individuals' beliefs in their ability to successfully perform a behavior and their social environments[4]. Media messages about breastfeeding can reflect and perpetuate broader cultural norms, societal attitudes, and healthcare practices related to infant feeding. The quality and content of breastfeeding-related information disseminated as well as individual characteristics and behaviors of mothers are, therefore, worth considering in such investigations.

The problem of misinformation about breastfeeding on social media and other mass communication platforms is complex to tackle. Previous studies indicated that inaccurate or harmful information about breastfeeding, such as exaggerating potential difficulties in breastfeeding and promoting the use of formula milk alternatives undermine mothers' confidence in their abilities to breastfeed[5-7]. Social media has become a key battleground for marketing commercial complementary foods, raising concerns alongside its growing popularity[5]. While traditional marketing methods for infant feeding formulas have been extensively critiqued, the strategies employed in the digital realm remain unexamined. Formula milk companies often use social media and other mass media for subtle and sometimes less obvious marketing that can create an inclination towards supplementing or replacing breastfeeding[6]. Mothers fre-quently seek breastfeeding information and support on social media, but the lack of reliability and the presence of conflicting information can be more confusing than helpful[7].

To conclude, while the current study offers valuable insights into the impact of the WCFI model on EBF, a deeper understanding of breastfeeding practices requires exploring a broader range of influences. Future studies should focus on refining research methodologies to explore how media interactions with cultural norms and individual factors influence breastfeeding practices. Individual characteristics, media literacy, social support systems, and government policies play significant roles in this regard. Given the challenges of misinformation and marketing tactics online, ensuring supportive media environments with accurate information is crucial to empower mothers' infant feeding decisions.

FOOTNOTES

Author contributions: Prashanth GP conceived the idea, collected and interpreted the data, and drafted the manuscript. Prashanth GP approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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REFERENCES

1 **Murillo Galvis M**, Ortegon Ochoa S, Plata García CE, Valderrama Junca MP, Inga Ceballos DA, Mora Gómez DM, Granados CM, Rondón M. Exclusive breastfeeding greater than 50%, success of education in a university hospital in Bogotá: Case-control study. *World J Clin Pediatr* 2024; **13**: 87713 [PMID: 38596436 DOI: 10.5409/wjcp.v13.i1.87713]

2 **Asimaki E**, Dagla M, Sarantaki A, Iliadou M. Main Biopsychosocial Factors Influencing Breastfeeding: a Systematic Review. *Maedica (Bucur)* 2022; **17**: 955-962 [PMID: 36818247 DOI: 10.26574/maedica.2022.17.4.955]

3 **Morse H**, Brown A. The benefits, challenges and impacts of accessing social media group support for breastfeeding: A systematic review. *Matern Child Nutr* 2022; **18**: e13399 [PMID: 35821651 DOI: 10.1111/mcn.13399]

4 **Black R**, McLaughlin M, Giles M. Women's experience of social media breastfeeding support and its impact on extended breastfeeding success: A social cognitive perspective. *Br J Health Psychol* 2020; **25**: 754-771 [PMID: 32623824 DOI: 10.1111/bjhp.12451]

5 **Dearlove T**, Begley A, Scott JA, Devenish-Coleman G. Digital Marketing of Commercial Complementary Foods in Australia: An Analysis of Brand Messaging. *Int J Environ Res Public Health* 2021; **18** [PMID: 34360227 DOI: 10.3390/ijerph18157934]

6 **Pereira-Kotze C**, Doherty T, Swart EC. Use of social media platforms by manufacturers to market breast-milk substitutes in South Africa. *BMJ Glob Health* 2020; **5** [PMID: 33272942 DOI: 10.1136/bmjgh-2020-003574]

7 **Jones A**, Bhaumik S, Morelli G, Zhao J, Hendry M, Grummer-Strawn L, Chad N. Digital Marketing of Breast-Milk Substitutes: a Systematic Scoping Review. *Curr Nutr Rep* 2022; **11**: 416-430 [PMID: 35507274 DOI: 10.1007/s13668-022-00414-3]

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