Exploring potential mechanisms for zinc deficiency to impact in autism spectrum disorder: a narrative review

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Abstract

Autism spectrum disorder (ASD) is a heterogeneous and complex group of life-long neurodevelopmental disorders. How this clinical condition impacts an individual's intellectual, social and emotional capacities, contributing to alterations in the proprioceptive and sensory systems and increasing their selective attitude towards food, is well described in the literature. This complex condition or status exposes individuals with ASD to an increased risk of developing overweight, obesity and non-communicable diseases compared with the neurotypical population. Moreover, individuals with ASD are characterised by higher levels of inflammation, oxidative stress markers and intestinal dysbiosis. All these clinical features may also appear in zinc deficiency (ZD) condition. In fact, zinc is an essential micronutrient for human health, serving as a structural, catalytic and regulatory component in numerous physiological processes. The aim of this narrative review is to explore role of ZD in ASD. Factors affecting zinc absorption, excretion and dietary intake in this vulnerable population are taken into consideration. Starting from this manuscript, the authors encourage future research to investigate the role of ZD in ASD. The perspective is to potentially find another missing piece in the 'ASD clinical puzzle picture' to improve the health status of these individuals.

Key words: **Autism spectrum disorder: Zinc deficiency: Lifestyle: Prevention: Nutrition**

Introduction

Zinc (Zn) is a redox neutral IIB group metal[1] and an essential micronutrient for human health. In fact, it is the second most abundant divalent cation after calcium and serves as a structural, catalytic and regulatory component[2] in numerous physiological processes. It is necessary for the structure of over 2000 transcription factors[2], and more than 300 enzymes depend on it for their functioning[3].

Moreover, it is able to modulate numerous intracellular signalling pathways, as well as influencing the progression of the cell cycle itself, in addition to fulfilling its antioxidant and anti-inflammatory roles[1–4].

Despite its physiological centrality, the mineral content in the human body is very low, at just 2–3 g. Approximately 95% of its content is intracellular, primarily located in muscles, followed by bones, brain, testicles and liver[2,5]. Zinc is not stored in the body and undergoes a rapid turnover. Therefore, maintaining adequate dietary intake is necessary to support all the functions mentioned above[2,5].

Therefore, ensuring the appropriate daily dietary intake is essential to ensure an optimal health. This is particularly crucial for 'vulnerable' individuals who are at higher risk of not meeting the body's requirements[6–8], resulting in the development of Zn deficiency (ZD) and subsequent health implications[2,3,9,10].

The general causes of ZD include inadequate Zn intake, increased Zn requirements, reduced Zn absorption, increased Zn excretion and impaired utilisation[2,5,11].

The prevalence of ZD is estimated to be approximately 17% globally[2], and it is more frequently diagnosed in developing countries[3]. Nevertheless, ZD is also prevalent in developed countries, including Italy, due to multiple factors such as reduced Zn absorption, gastrointestinal (GI) diseases, ageing and/or the presence of specific pathological conditions[12]. Moreover, ZD is shown to be highly prevalent in individuals with autism spectrum disorders (ASD) compared with neurotypical individuals[9]. This could be attributed to the frequent occurrence of food selectivity and the comorbidities that characterise individuals with ASD.

ASD is a heterogeneous and complex group of neurodevelopmental disorders[13]. According to the DSM-V[13], the diagnostic criteria of ASD must involve two dimensions: (A) persistent deficit of social communication and social interaction in multiple contexts; (B) restricted, repetitive patterns of behaviour, interests or activities[13]. This dimensional diagnosis

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must be combined with other specific descriptors that outline the intensity of the disorder, such as: (i) with or without accompanying intellectual impairment; (ii) with or without accompanying language impairment; (iii) associated with a known medical or genetic condition or environmental factor; (iv) associated with another neurodevelopmental, mental or behavioural disorder[13]. Additionally, another crucial evaluation criterion is the level of severity and support required, which is described in three levels: level 3 requires very substantial support; level 2 requires substantial support; level 1 requires support[13]. Furthermore, approximately 75% of individuals with ASD have other comorbidities that impact their physical and mental state, such as attention-deficit/hyperactivity disorder (ADHD), depressive and anxiety disorders, bipolar disorder, obsessive–compulsive disorder, irritable bowel, inflammatory bowel disease, epilepsy, immune disorders, and sensory and sleep disorders[14].

Moreover, traits such as systematic and neurological inflammation, oxidative stress, gastrointestinal (GI) symptoms, overweight and obesity as well as food selectivity (FS) are frequently observed in individuals with ASD, with a significantly higher prevalence than in the general population[6,10,15,16]. In fact, according to a recent meta-analysis, the prevalence of overweight and obesity are respectively 19·8% and 21·8% in individuals with ASD[17]. Delving into the topic of FS, it is a condition characterised by a marked limitation of the repertoire of foods accepted, exposing the individual to the risk of developing obesity and micronutrient deficiency, including ZD[6,18]. The prevalence of FS in the paediatric ASD population ranges from 22·9% to 69·1%[6] and remains an important issue for adolescents and young adults with ASD[10]. The health consequences for these individuals varies depending on the severity of food refusal, the limitations in the food repertoire, and the degree of repetitiveness of feeding behaviour (i.e. high-frequency intake of single food)[6,19]. Therefore, FS, which involves the adoption of an imbalanced dietary pattern, acts as both a risk factor and a maintenance factor for the development of micronutrient deficiencies, including ZD, and overweight or obesity throughout the lifespan of individuals with ASD.

The purpose of this narrative review is to explore the possible connections between ZD and ASD, including the factors that affect Zn absorption, excretion and dietary intake.

The role of Zn in human systems with a focus on individuals with ASD

Zn plays an important role in the development and functioning of the immune, gastrointestinal and nervous systems, all of which are frequently dysregulated in individuals with ASD[2,3,15].

Starting from the immune system, Zn performs immunomodulatory functions by regulating the proliferation and maturation of T and B lymphocytes, natural killer cells and dendritic cells, as well as antibody production, phagocytosis and antigen presentation[3]. Therefore, ZD predisposes individuals to immune disruptions and recurrent infections, including intestinal infectious diseases, which are well described in individuals with ASD[2,6,20,21].

Focusing on the gut, Zn is involved in its morphological development, microbial composition and function, and barrier maintenance[15] due to its essential role in cell turnover and repair systems.

Thus, the negative effects of ZD include dynamic variation in gut microbial composition, increased intestinal permeability (leaky gut), activation of pro-inflammatory pathways, and diarrhoea[2,15,21], which are common manifestations in individuals with ASD[6,15]. Mounting evidence strongly supports a positive relationship between the extent of GI symptoms and the severity of ASD symptomatology[22], as well as a close association between Zn status and autism severity[3]. Considering the central role of the intestine in Zn absorption, as well as the common GI symptoms reported in individuals with ASD, the authors delved into each of those aspects. Several landmark studies from the past few decades have concentrated on the gut microbiota in individuals with ASD, revealing a decreased microbial diversity in this population[23], along with a significant increase in *Clostridioides difficile* and *Candida albicans*, a decrease in *Bifidobacterium* and *Lactobacillus*, and low levels of short-chain fatty acids (SCFAs)[23–25]. Nevertheless, the description of a comprehensive and distinctive gut microbial pattern in individuals with ASD is still under research. Different studies have shown conflicting results, probably due to heterogeneity of the analysed samples in terms of age, diet, pharmacological treatment, geographic area, comorbidities and the severity of neurobehavioral and gastrointestinal symptoms[24,26]. The alterations of gut microbiota in individuals with ASD are known to have a significant impact on the brain through the microbiota–gut–brain axis[15,22,25], exacerbating the typical symptoms of ASD (i.e. limitations in social interactions and communications, and repetitive behaviours)[13,24]. Furthermore, the increased permeability of the intestinal barrier, frequently co-present with dysbiosis, results in the entry of bacterial metabolites, such as lipopolysaccharide (LPS), into the bloodstream. This triggers a significant increase in neurological and systemic inflammation by altering cytokine levels[15,25,27]. Individuals with ASD have been found to have increased levels of these leaky gut syndrome biomarkers[24]. As it is known, the gut–brain axis operates bidirectionally; therefore, neuroinflammation and alterations in neuronal activities significantly impact the composition of the gut microbiota in individuals with ASD from early childhood[25,28].

Dysbiosis and GI symptoms, such as constipation, diarrhoea, bloating, abdominal pain, reflux and vomiting are four times more prevalent in children with ASD compared with neurotypical individuals[25]. Furthermore, there is substantial scientific evidence describing the persistence of GI symptom prevalence into adulthood in individuals with ASD[29]. So, considering that Zn plays a key role in gut health and intestinal microbiota, it may be important to prevent ZD from an early age, so as not to exacerbate dysbiosis and GI symptoms frequently found in individuals with ASD.

Regarding brain activity, Zn plays a key role in neuronal learning and memory processes[2], synaptic plasticity through ProSAP/Shank scaffold, and neurotransmitter metabolism[3], particularly in glutamate. Specifically, Zn^{2+} is necessary for proper assembly, structuring and functioning of the ProSAP/

Shank scaffold[3] protein and is involved in glutamatergic neurotransmission, as Zn^{2+} forms complexes with glutamate in presynaptic vesicles[30,31]. Numerous studies have demonstrated that impairment of the synaptic ProSAP/Shank scaffold promotes the development of behaviours typically observed in ASD[3,9]. Alterations in the balance between excitatory and inhibitory pathways in the nervous system are frequently observed in individuals with ASD[3,31].

Therefore, it may be relevant to prevent ZD conditions as early as possible to avoid exacerbating these neurological alterations.

Ultimately, it is necessary to emphasise the role of ZD in inflammation (systemic and neurological) and oxidative stress, both of which are often present in individuals with ASD[3,15,16]. The literature reports significantly higher plasma and serum levels of proinflammatory cytokines (IL-1β, IL-6, IL-8 and IFN-&x0263;) in individuals with ASD, compared with neurotypical controls[15]. Moreover, an increase in the levels of IL-1β, IL-6 and IFN-&x0263; in the brain are reported in postmortem ASD studies[15].

Individuals with ASD also present elevated levels of reactive oxygen species (ROS) and are considered more vulnerable to oxidative stress due to their reduced glutathione (GSH) reserve capacity and (GSH) antioxidant defence in specific brain regions[16]. Considering that Zn enhances (GSH) biosynthesis[2], an adequate intake of this mineral could reduce oxidative stress in individuals with ASD.

In conclusion, ASD is frequently characterised by alteration of immune, gastrointestinal and neurological systems, which share inflammation as a common factor. Considering at the same time the potential role of Zn in modulating the previously mentioned systems, it is reasonable that alterations in Zn levels could potentially impact on ASD symptomatology[6,20,26,27].

The relationships between the role of zinc in metabolism and ASD comorbidities

Considering the underlying pathogenetic mechanisms of ASD metabolic comorbidities and the role of Zn in the same metabolic systems, it is reasonable to assume that ZD status can contribute to the metabolic comorbidities that are present in individuals with ASD leading to bidirectional relationship (graphical abstract), as further explained below.

Scientific research is currently exploring the role of Zn in diabetes mellitus (DM) in terms of glycaemic control, and its role in obesity and metabolic syndrome[3]. Low Zn levels in individuals with type 2 DM and obesity were observed[3]. A recent systematic review with meta-analysis found that the association between ASD and DM is not currently supported by robust evidence[32].

Starting from the analysis of carbohydrates metabolism, individuals with ASD often exhibit sugar malabsorption, which may be attributed to a decreased expression of disaccharidases, specifically sodium–glucose transporter 1 (SGLT1) and glucose transporter 5 (GLUT5), in the brush border in the intestinal epithelium[25,33]. The remaining sugars in the intestinal lumen can lead to osmotic diarrhoea and can be fermented by the gut microbiota, causing alterations in microbiota composition, small intestinal bacterial overgrowth (SIBO), bloating and flatulence[25]. As 30–50% reduction of disaccharidase activity has been observed in cases of chronic ZD[33] and given the higher prevalence of ZD in individuals with ASD, there is a possible role for Zn in alleviating frequent intestinal symptoms observed in ASD.

Zn has a central role in glycaemic control: it is involved in synthesis, storage and release of insulin, and it is present in insulin granules[1,34,35]. It influences the maintenance of the GLUT4 transporter and modulates the insulin receptor (INSR) signalling pathway[4]. This aspect is particularly significant considering that youths with ASD have, on average, higher homeostatic model assessment of insulin resistance (HOMA-IR) than neurotypical individuals, regardless of their BMI and pharmacological treatment[36].

Moving on to protein metabolism, aside from its role in protein synthesis, protein structure and enzyme catalysis, adequate daily intake of Zn is necessary for proper protein digestion in the gut, due to its role in several digestive enzymes, including carboxypeptidases[1], dipeptidase[37] and aminopeptidase[33]. Therefore, the possible presence of a ZD condition might favour bacterial proteolytic pathway (putrefaction), which may be associated with dysbiosis and gastrointestinal symptoms observed in individuals with ASD[38].

Regarding lipid metabolism, individuals with ASD can experience alterations in their blood lipid profile[39,40], on which Zn appears to have an influence[35,41,42]. The mechanism behind this is currently not understood, but the effects of Zn levels in terms of both prevention and treatment of cardiovascular diseases (CVDs) have been well described in literature[35]. In fact, a systematic review of prospective cohort studies showed that higher serum Zn levels are associated with a lower risk of CVDs. Furthermore, a recent meta-analysis indicated that low-dose (<25 mg/d) and long-term (>12 weeks) Zn supplementation is associated with improved blood lipid parameters[42]. This aspect seems to be more important when considering that, according to a recent study by Bishop et al. 2022, about 75% of adults with ASD have at least one CVD risk factor, compared with 40% in neurotypical individuals[43,44].

Regarding adipose tissue, Zn is involved in several related physiological processes, including leptin synthesis and adipocyte lipid metabolism regulation[3,34]. Given this background, many authors have suggested that Zn status could be associated with the state of adipose tissue in obesity[3]. These results are in line with the known higher inflammatory and oxidative state of this tissue in individuals with overweight and obesity[45]. Considering the role of zinc in the anti-inflammatory and antioxidant systems[3,34], the authors hypothesise that lower Zn levels in adipose tissue might also be present in individuals with ASD. This suggests that screening Zn levels in such individuals may be beneficial for those showing signs of lipid metabolism dysregulation.

In conclusion, considering the possible links discussed thus far, Zn could play a key role in the frequently observed metabolic comorbidities in individuals with ASD. Consequently, the

Table 1. The multiple roles played by Zn in taste perception

Oral mechanisms	Neural mechanisms
Epithelium and taste bud morphology maintenance[47,48] • alkaline phosphatase[47] • carbonic anhydrase VI (gustatin)[51,54] • expression of some TAS2R and of ENaC[49,50] • taste bud normal activity by increasing calcium concentration in saliva[53]	Favor the information transmission from taste cells to gustatory nerve fibres[54] Modulates neuropeptides, such as NPY, and neurotransmitter concentrations in the hypothalamus[54,55] Putative indirect role influencing leptin, insulin and neuropeptide Y (NPY) levels[1,34,35,55–57], which are all hypothesised to influence taste perception[51]

Legend. Explanation of the role of Zn in taste perception, distinguishing between the mechanisms put in place at the oral and neurological level.

importance of screening Zn levels in individuals with ASD who present with metabolic comorbidities, emerges as a crucial aspect to better manage their clinical condition[46].

Sensory perception, food selectivity and Zn in individuals with ASD

The role of Zn in sensory perception, specifically taste perception, can be discussed by distinguishing between the mechanisms at the oral and neurological levels.

In the mouth, Zn participates in the maintenance and regeneration of the lingual epithelium and taste buds[47,48]. Moreover, it is necessary for the activity of alkaline phosphatase and gustatin, which are associated with taste and smell alterations when their activity is low[47]. Animal studies suggest that Zn influences the expression of some taste receptors and membrane channels, such as bitter taste-sensing type 2 receptors (TAS2Rs) and epithelial Na channel (ENaC)[49,50], indicating the role of Zn especially in bitter[51,52] and salty taste perception[53]. The role of Zn bitter taste perception is supported by the involvement of gustatin itself in bitter taste[51] and the finding of a lower frequency of expression of six TAS receptor genes in individuals with hypogeusia compared with healthy controls[50].

Analysing the neural mechanisms, Zn seems to promote the transmission of information to gustatory nerve fibres and to modulate neuropeptides, such as neuropeptide Y (NPY), and neurotransmitter concentrations in the hypothalamus[54,55]. Moreover, current literature is exploring the influence of Zn on the levels of leptin, insulin and NPY[1,34,35,55–57], in relation to taste perception and taste bud physiology. These peptide hormones are present in saliva, and their respective receptors are expressed in taste cells[51]. The multiple roles played by Zn in taste perception are summarised in Table 1.

In light of the evidence described, it is important to consider that alterations in taste sensory perception (e.g. smell, taste and sight) are among the main symptoms of ASD and may persist throughout life[6] and can be modulated by several factors, potentially including ZD. The possible co-presence of ZD in individuals with ASD may also be connected to FS, which can lead to micronutrient malnutrition[6].

FS itself, often present as a life-long clinical feature in individuals with ASD, can be accompanied by a sensory aversion to food, characterised by a rejection of specific textures, temperatures, flavours, colors and smells[6]. This attitude leads to the adoption of a diet mainly composed of processed foods with high energy density, rich in sugar and saturated fatty acids, and, consequently, a reduction of dietary diversity[6]. The typical treatment strategy for FS in individuals with ASD is a personalised, careful and gradual food reintroduction programme using applied behaviour analysis (ABA) techniques[58]. Although useful, these strategies are often time consuming and difficult to carry out over time for individuals and their families, potentially leading to relapses[59]. Due to the potential mechanisms via which ZD could impact in individuals with ASD, described above, it could be relevant to screen ZD in individuals with ASD to design an appropriate and personalised treatment plan. However, there are no current evidence for the role of ZD in FS; therefore, future studies are needed to fill this knowledge gap.

Moreover, taste perception features in individuals with ASD may manifest hyper- or hyposensitivity to food stimuli. In the latter case, individuals may tend towards a greater preference for sweet, salty or spicy foods to achieve an adequate stimulus[6].

Concerning Zn supplementation, which has been used since the 1980s[54], a recent systematic review has highlighted that it is the most frequently employed intervention for the prevention and treatment of taste disorders (i.e. ageusia/dysgeusia)[53]. However, the effectiveness of Zn supplementation and the optimal dosage are still debated and controversial. Moreover, the analysed studies often lacked a control group, and exhibited inconsistencies in terms of intervention duration, sample size, age, sex and comorbidities (often carried out in subjects with cancer or Chronic Kidney Disease). As a result, these studies were generally considered as 'low quality' overall[47]. Regarding ASD, there are currently no clinical trials exploring the role of Zn in improving taste perception, indicating the need for further research in this area.

The authors therefore emphasise the need for further investigation in this regard, specifically focusing on evaluating the potential role of Zn supplementation in individuals with ASD in relation to alterations in sensory perception.

Factors influencing dietary Zn intake, absorption and excretion in ASD

Inadequate dietary intake of absorbable Zn represents the primary cause of ZD[11]. This deficiency may result from low dietary intake and/or low bioavailability of dietary Zn.

Causes of ZD under the category of reduced Zn absorption primarily include Inflammatory Bowel Diseases, inherited diseases (i.e. acrodermatitis enteropathica and cystic fibrosis),

diarrhoea, unbalanced vegetarian or vegan diet, undernutrition or hidden hunger conditions, eating disorders, alcoholism and exocrine pancreatic insufficiency[2]. Causes of ZD under the category of reduced Zn intake are related to food preferences and eating patterns, including conditions such as FS, which is highly prevalent in the ASD population and could lead to suboptimal Zn intake.

Analysing Zn absorption, it is important to point out that the bioavailability of Zn content in food is low, about 20–50%[60,61] and it depends on both quantitative and qualitative factors[61,62]. Among the food products, red meat, certain seafood, dairy products, nuts, seeds, legumes and whole-grain cereals are considered good dietary sources of Zn[62]. Animal products, in particular, are known to provide a more bioavailable source of Zn than plant foods[61].

Factors with a positive, negative or 'neutral' effect on dietary Zn bioavailability are presented in Table 2.

Although a low intake of phytate-rich food by individuals with ASD might promote better absorption of dietary Zn since phytates are the most potent inhibitors of Zn absorption[61,63,64], this is not advisable since a reduced consumption of vegetables and legumes increases the risk of micronutrient inadequacy and dysbiosis due to low fibre content[67]. Moreover, organic acids, such as malic acid found in fruits, citric acid found in fruits and milk, and lactic acid found in yogurt and fermented foods can improve Zn absorption[61,64,65].

Another well-known mechanism that promotes Zn absorption is mediated by the protein content of the diet: free amino acids can bind Zn^{2+} and be transported with it into the enterocyte[61]. Therefore, eating complete meals with all macronutrients is even more recommendable. This recommendation is also supported by the fact that such individuals with ASD generally accept protein sources, with the exception of legumes[6] and fish[68,69], which in some cases have a strong smell and taste.

Increased Zn losses represent another category of ZD causes and may result from GI disorders such as diarrhoea, as well as urinary tract disorders including kidney disease and DM[2].

In this regard, the ratio between the amount of absorbed Zn and the fraction of the mineral excreted is crucial, as it affects the cellular content of Zn and its distribution. Over time, due to the initial protective action of homeostatic mechanisms, it also impacts the plasma Zn concentration itself[2,5]. In fact, the amount of retained Zn in the human body is highly dependent on its dietary content[63]. Therefore, it is not surprising that Zn is primarily excreted with faeces and secondarily with urine[61]. Severe undernutrition and starvation conditions result in both an increase of urinary Zn losses and a sedentary lifestyle[63]. In fact, a chronic reduction in physical activity level (i.e. sedentary lifestyle) is associated with loss of muscle mass. Increased urinary zinc excretion has been observed in individuals with chronic reduction in physical activity levels[63], as zinc is well represented within muscle tissue[2]. Leading a sedentary lifestyle is common among individuals with ASD[70], due also to motor comorbidities, so the presence of increased urinary Zn losses is a concrete potential issue in this population, exposing them (along with the other factors previously described) to an increased risk of ZD.

Table 2. Factors with a positive, negative or 'neutral' effect on dietary Zn bioavailability

Positive effect		Neutral effect	Negative effect	
Levels of zinc in the diet[63]	+++	Cellulose[61,64] Soluble fibre pectin[64] Recommended dietary intake of: Iron[2,61,63,64]	Phytates, i.e. magnesium, calcium or potassium salts of phytic acid[61,63,64] Excessive intake of:	+++
Organic acids:			Iron[2,61,63,64]	+
Citric acid[61,64,65]	++	Copper[2,61,63,64]		
Malic acid*[66,67]	++	Calcium[61,64]	Calcium[61,64]	++
Lactic acid*[64,65]	++	Cadmium[61,64] Tin[61,63]	Cadmium[61,64] Tin[61,63]	++ +
Amount of dietary proteins[61]	+++	Vitamin C, i.e. ascorbic acid[61]	Some insoluble dietary fibres, such as hemicellulose and lignin[64]	+
Amino acid histidine[62,64,65]	++			
Sulphur amino acids, such as cysteine and methionine[62,64,65]	+/++			
Dairy (bovine milk and yogurt) in case of plant-based diets[62,63]	++	Vitamin B9, i.e. folates[63] Oxalates[63,64]	Maillard browning[61,63]	+
Soaking and germination for legumes; fermentation, malting and leavening in case of plant foods[61,64,66]	+++			
Crop biofortification[63]	++	Tannins[63]		

Legend. Factors with a positive, negative or 'neutral' effect on dietary Zn bioavailability. The authors developed a +/++/+++ classification based on two aspects: (i) the number of papers in the literature supporting or not supporting the ability of dietary factors to positively/negatively affect Zn absorption; (ii) the magnitude of the resulting effect indicated in the papers on dietary Zn absorption.

To summarise, Zn absorption is influenced by the composition of food matrix, vegetable food preparation techniques and full meal consumption. On the other hand, Zn elimination is influenced by the possible presence of existing Zn deficiencies or excesses, as well as ongoing catabolic processes, which can be associated with a sedentary lifestyle.

Zn requirements in individuals with ASD. Conclusions and future prospects

Increased Zn requirement constitutes another recognised cause of ZD[2,11]. Considering the potential alterations in Zn absorption, excretion or Zn intake previously discussed, the possibility of increased Zn requirements in this population should be considered. It is important to note that the dietary recommendations provided by national and international organisations are intended for the healthy population[71–75], and currently, there are no specific dietary guidelines available for individuals with ASD.

This gap in the existing guidelines contradicts the need for personalised and adapted management of this disorder, as emphasised by guidelines and action plans developed at the global[76], European[77–80] and Italian[81,82] levels. These guidelines are endorsed by the most authoritative organisations in the field, that is, Autism Speaks[83].

In fact, ASD is a sensitive and lifelong condition that impacts every aspect of life. Hence, there is a crucial need for specific nutritional guidelines to improve the quality of life of those individuals, focusing on their health and inclusion in the community[84]. Considering the role of Zn, the frequent co-presence of ZD risk factors and FS problems in individuals with ASD highlights the potential need for formulating specific dietary recommendations for this population. Furthermore, considering the frequent occurrence of multiple comorbidities in individuals with ASD (e.g. recurrent infection, systemic and neurological inflammation, diarrhoea, microbiota alterations, leaky gut and metabolic disorders), which can either cause or contribute to ZD, relevant attention should be paid on Zn requirement.

Therefore, it is advisable to early detect Zn blood levels and assess dietary intake in individuals with ASD, ideally during infancy at the time of ASD diagnosis, to evaluate the presence of ZD. A potential workflow for proper management would involve following the principles and the structure of the Nutrition Care Process (NCP) developed by the American Dietetic Association, which includes nutrition assessment, nutrition diagnosis, nutrition intervention, nutrition monitoring and evaluation (followed by periodic re-assessment)[85,86].

In reference to the results provided by the assessment phase (interview and clinical data collection), the next step would involve analysing plasma Zn levels[87]. If a ZD condition is identified, that is, <60 μg/dl in healthy adults[88], the most appropriate strategy to address the deficiency would be planned. In this regard, the primary approach to be implemented is to improve dietary intake of Zn. If, on the other hand, the ZD condition is severe and/or persistent, potential supplementation strategies should be considered. In this scenario, recent European Society for Clinical Nutrition and Metabolism

(ESPEN) recommendations suggest 0·5–1 mg/kg/d of elemental zinc (Zn^{2+}) given orally for 3–4 months[87]. Moreover, the ESPEN panel emphasises that organic compounds (such as zinc histidinate, zinc gluconate and zinc orotate) are comparatively better tolerated than inorganic zinc sulphate and zinc chloride[87]. A reasonable approach in this case would be to gradually increase the zinc dosage from supplementation in parallel with an adequate dietary zinc intake, with periodic monitoring of blood levels[87] to tailor treatment to the subject's response while avoiding potential side effects. In fact, at doses >50 mg/d, GI symptoms, such as nausea, abdominal discomfort and diarrhoea, commonly occur[88].

In conclusion, future perspectives could concern the development of a comprehensive screening tool that considers all the factors to which individuals with ASD are generally exposed, which can increase the risk of developing ZD, along with the individual's current symptomatology. This screening tool would take the form of a questionnaire that provides a score indicating the risk of developing ZD, tailored specifically for individuals with ASD.

Competing interests

The authors declare no conflicts of interest.

Authorship

Maria Vittoria Conti, Sara Santero, Alessia Luzzi; methodology: Maria Vittoria Conti, Sara Santero, Alessia Luzzi; writing—original draft preparation: Sara Santero; writing—review and editing: Maria Vittoria Conti, Sara Santero, Alessia Luzzi; visualisation: Hellas Cena; supervision: Hellas Cena. All authors have read and agreed to the published version of the manuscript.

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