

Nutritional challenges in children and adolescents with Down Syndrome

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The Lance Child and Adolescent Health: <https://www.thelancet.com/journals/lanchi/home>

DOI: [10.1016/S2352-4642\(19\)30400-6](https://doi.org/10.1016/S2352-4642(19)30400-6)

Abstract

Several features and comorbidities in DS have nutritional implications and consequences, which needs to be addressed in further detail. In this review, we searched and assessed the literature from year 2000-2019 and found in total 57 nutritionally relevant articles.

In infancy and early childhood, children with DS have high risk of oral motor difficulties and pharyngeal dysphagia with aspiration, which requires systematic attention. To improve nutritional status in children with underweight and clinical signs of feeding problems further evaluation of underlying causes is required. Clinical interventions should promote swallowing safety and development of feeding abilities.

Already from 4-5 years of age overweight may become a concern. To prevent disease later in life, there is an urgent need for more research on nutritional aspects in prevention and treatment of obesity for adolescents with DS. The present review did not find any data to support the use of dietary supplementation except when deficiency is documented. In addition, the literature presented clearly documents the need for more research using larger study samples, and control groups, addressing important nutritional challenges in children and adolescents with DS.

Introduction

Adequate nutrition is fundamental for growth, development and well-being of all children. In children with Down syndrome (DS) attention to nutritional intakes and status is important as several features and comorbidities have nutritional implications and consequences (Table 1). To promote evidence based nutritional care from health professionals there is need to address nutritional issues in this patient group.

DS is caused by trisomy of the whole or a part of chromosome 21. It is the most common cause of mild to moderate intellectual disability, affecting about 1:800-1:900 live born, but with variation between countries due to differences in maternal age and prenatal screening (1, 2). Children with DS have characteristic phenotypic features, psychomotor developmental delay, and increased rate of congenital malformations (3). On individual level children with DS show large variability as some have mild symptoms and complications, whereas other are more severely affected. This also applies to the risk of nutritional related health problems.

When assessing nutrition in DS it is important to be aware of health conditions that may influence nutritional care and dietary advice. Congenital heart defects are found in approximately 45 % of the children, most often atrioventricular septum defect and ventricular septum defect (4). Gastrointestinal tract anomalies such as duodenal atresia, Hirschsprung's disease and anorectal malformations occur in 4-6 % (5-7). The incidence of celiac disease is increased in DS and been shown to vary between different countries, but a recent meta-analysis show numbers in the range of 5-6% compared to 0.5-1% in the general population (8). In addition, these children also have increased risk of comorbidities such as hypotonia and orofacial dysfunction that may affect the child's feeding ability (9) and thyroid disease, as hypothyroidism (10), with potential to influence energy metabolism. Autoimmunity is increased in DS (11) and in a national Danish cohort of children with type 1 diabetes, the prevalence of DS was 4-fold increased compared to the general prevalence of DS in Denmark (12).

Guidelines have been developed to facilitate health supervision in children with DS (13). These describe nutrition and physical activity as areas that require ongoing assessment throughout childhood to achieve and maintain appropriate weight (13). As a group, children with DS have elevated risk of feeding problems and obesity (14, 15). It is well known that childhood establishment of healthy eating habits is important for prevention of disease later in life and increasing longevity in DS is likely to lead to increased manifestation of lifestyle

associated diseases (16). Obesity is known to be associated with type 2 diabetes, cardiovascular disease and some types of cancers. In DS obesity is also linked to reduced functional abilities and activities of daily living (17). Few previous reviews have been conducted on nutritional aspects in this vulnerable group. To further describe and explore nutritional challenges in youth with DS, we searched and assessed the literature with the objective to describe feeding abilities, nutritional intakes and nutritional status in DS and to provide some suggestions for relevant clinical measures and interventions.

Search strategy and selection criteria

Ovid medline was searched for articles using the following search terms “Down syndrome” AND (“nutrition”, “nutritional”, “feeding”, “diet” OR “dietary”) and we limited our search to articles published in English from January 2000 to August 2019. This period was chosen to be relevant for current care practice, due to the increased survival rate of children with DS born with congenital malformations and improvements in medical and nutritional treatment during the last decades. The search identified 351 articles. Titles and abstracts were assessed for studies in children and adolescents with DS. We included original studies using various descriptive and intervention designs, and most recent nutritionally relevant review articles (Figure 1). Case-reports and studies in animal models were excluded. In total 57 articles were identified. Supplementary search was performed for identification of diagnosis-specific growth curves.

Infancy and breastfeeding

Most neonates with DS are offered human milk but the proportion and duration of exclusive breastfeeding are reduced (5, 18). The total number of children with DS exclusively breastfed varies between countries from 43 % in Italy (18), to 48 % in the Netherlands (7), 55 % in Israel (5) and 63 % and 67 % in Mexico (19) and Saudi Arabia (20), respectively. In the Italian study, including 560 children with DS, the mean duration of breastfeeding was 54 days (SD 111) compared to 165 days (SD 120) in controls (18). Congenital malformations, prematurity, perceived milk insufficiency, suckling difficulties and maternal depression were factors found to limit breastfeeding (5, 18, 20, 21). Furthermore, neonatal hospital admission confer risk of reduced breastfeeding.

In children 0-3 months of age most parents describe prolonged meals (30-60 min) (21). This could be exhausting for both the child and parents. In this period, it is normal for parents to

experience stress and difficult emotions such as shock and grief related to having a child with DS. Indeed, frustration and depression in mothers have been reported to be an important factor for termination of breastfeeding (18, 20).

Although some babies with DS in the beginning do struggle with feeding, it is important to recognise that most babies and mothers with time and guidance from competent health professionals can make the transition to breastfeeding (22). Thus, family-oriented support may enhance breast feeding practice, early parent-child bonding and improve long-term child outcomes (22, 23).

Feeding and swallowing problems

Feeding abilities are often reduced in children with DS and approximately 55–60 % have feeding and swallowing problems (24, 25). For a period, typically from 0-3 months, 13-40 % of the children require nasogastric tube for adequate nutrition (5, 21, 26), whereas 2 -5 % of the children receive gastrostomy (5, 21). Children with atrioventricular septal defect are more likely to need gastrostomy (27).

For early detection of feeding problems, all children should be clinically screened for feeding and swallowing concerns. Structural and functional oropharyngeal abnormalities, immature neuromotor development and hypotonia leads to poorer neuromotor function and are associated with sucking problems, poor lip seal, slow sucking, dysphagia and aspiration (9, 21, 25, 28). Oral motor difficulties have been described in 64 % and pharyngeal dysphagia with aspiration in 57 % (25). In the cases where aspiration was detected, almost all (90 %) aspirated silently. A recent study found aspiration in 32 % of infants evaluated before 6 months of age, whereas aspiration was detected in 52 % of children between 6-12 months of age (29). In this study, children subjected to swallow assessment after 6 months of age were more likely to have unchanged findings on follow-up, compared to children evaluated before 6 months of age. This suggests that early referral to swallowing assessment may to some extent prevent complications due to swallowing abnormalities. High rates of pharyngeal dysphagia was also described by O'Neill and colleagues, who found that 58 % of children with DS (n=201) got this diagnosis after videofluoroscopic swallowing assessment(28). For this reason, we suggest that videofluoroscopic swallowing assessment, should be offered early to children with clinical symptoms during meals (24, 25). In children with pharyngeal dysphagia such an assessment should be followed by feeding modification recommendations. Relevant dietary interventions to improve swallow safety, includes thickened liquids (77 %),

changed feeding procedure to control flow rate or bolus size (8 %) and in some children (7%) no oral intake (25).

Age at introduction to solid food is for most children with DS similar as in typically developed children, with 46 % introduced to solids between 6-9 months and 38 % between 9-12 months of age (20). Despite this, learning to eat solid foods from the first bits of pureed food and baby cereal to regular table foods is a long process. Development of feeding abilities and self-feeding skills are, as other developmental milestones, often delayed in children with DS (14, 30). As the skills required become more advanced, children with DS are increasingly delayed, and the age difference for achievement increases between children with and without DS (30). Indeed, feeding problems may remain as a challenge with predominant problems in oral phase, followed by pharyngeal phase and oesophageal phase in children with DS 2 – 7 years of age (14). In the oral phase, immature chewing pattern and poor bolus control are common concerns. In children 1-4 years of age, common difficulties are chewy, firm and gummy/rubbery food texture, whereas creamy, soft and puree texture are often reported to be accepted (31). However, with increased age, also crispy, dry and hard food texture were more likely to be managed by the child (31).

Issues related to dental health are also highly relevant when assessing feeding and swallowing issues in children with DS, as these children have increased risk of dental abnormalities and severe tooth wear (32, 33) which also potentially can affect the child's ability to chew. Parents and health professionals should be aware that prolonged bottle feeding and use of pacifier (more than 24 months) have been associated with development of open bite and cross bite (34).

Structural training programs to strengthen oral motor function and adjustment of food consistency are relevant interventions for children with poor oropharyngeal motor abilities (35). Some children (20 %) also have oral sensory processing difficulties (14, 25) and can benefit from interventions to address such difficulties. Behaviour typically seen in oral hyposensitivity includes overstuffing of food, foods held in mouth without chewing, drooling or preference of intense flavours. In contrast, behaviours typically seen in oral hypersensitivity are food selectivity regarding texture or temperature, a “picky eater”. Preference for selected types of foods were reported as a common food related behaviour in children with DS (36). Despite the fact that children with DS have higher rates of feeding problems and often reduced feeding skills, no correlation between parent reported difficult

mealtime behaviours and feeding skills was observed (37). In addition, parents of toddlers with DS do not report more challenging mealtime behaviours than parents of typically developed children (37).

Parental feeding practice and eating behaviours

Reports on parental feeding practice showed that parents had greater weight concern, used more restrictions (36) and less pressure to eat in their feeding practice of their child with DS compared to siblings (38). Similar, among parents of overweight children with DS use of restrictions and monitoring of food intakes was more frequent (39). A total of 57 % of the parents reported that their child with DS frequently continued to eat as long as food remained present (36). The potential impact of parental practice on eating behaviour and risk of overweight in youth with DS has not been properly investigated. Eating behaviour is an important issue to address in future studies as it has potential implications both for young children and in older children related to development of obesity. Eating behaviour is an important issue to address in future studies as it has potential implications both for young children and in older children related to development of obesity.

Nutritional status

The mean birth weight and birth length is reduced in new-borns with DS, with mean birth weight closer to the mean of unaffected children than birth length (6). Reduced growth rate leading to short stature in adult age is a well-known characteristic of most persons with DS.

Growth charts for persons with DS from birth to 18 or 20 years of age have been developed based on several national cohorts (40-46). Traditionally growth curves may be useful in children to monitor growth and nutritional status. For children with DS diagnosis-specific weight-for-length charts can be used to screen for growth faltering and wasting but may be less precise in determining overweight (40).

As consequence of the increased risk of overweight and obesity, the mean body mass index (BMI) percentile for age of children with DS increases during childhood, when plotted on curves developed for the general population. Based on data from the French DS- cohort (41), mean BMI was at 25th percentile (perc) in girls and boys from 0-1 year. Further, it was at 50th perc in girls at 3 years and in boys at 4 years of age, respectively and thereafter at 75th perc for girls at 5 years of age and boys 12 years of age. In 18 year olds mean BMI was at 80th perc for girls and above 75th perc for boys with DS (41). Therefore, when using DS-specific

BMI curves it is important to recognize that these only describe the normal distribution of BMI values in the cohort and do not necessarily represent ideal weight status (40, 41). Plotting a person on such DS specific curve only provide information about weight status compared to peers with DS and can classify a person with DS to be normal weight, that otherwise, by use of standard curves, would classify as overweight or obese (47). However, due to the shorter stature of individuals with DS, the curves and cut-offs developed for typical children have been found to overestimate obesity and percent body fat as measured by dual-energy X-ray absorptiometry (DXA)(48). Therefore, additional examinations may be required to screen for overweight and obesity and associated health outcomes. Measuring skinfolds at four location (triceps, biceps, subscapular and suprailiac) is an alternative method to assess adiposity, and equations have been developed for children with reduced growth (49). Compared to percent body fat by DXA the reduced growth prediction equation performed well in children with DS (49). Another option may be the use of waist circumference. Strong correlation between waist circumference measures and percent body fat measured by bioelectrical impedance (BIA) ($r= 0.85$) has been described in a small study (50). Even though these results indicate that BIA and WC could be promising methods in clinical practise, additional validation is required before this could be recommended.

Prevalence of iron deficiency anemia was investigated in an uncontrolled study of 149 children with DS (0-20 years). This study found that 5 % of children younger than 10 years of age and about 14 % of children 10 years or older had iron deficiency anemia (51). This study further described an association between lower than average hemoglobin and delays in motor milestones as starting to walk after the age of two (51). In contrast, in a larger cohort of 856 children with DS iron deficiency was more common (10%) in children less than 36 months of age compared to those older than three years (4%) (52). In this study the use of additional parameters to haemoglobin, like ferritin and red cell distribution width to assess iron status is suggested. High risk of low 25-hydroxy-vitamin D levels compared to controls was found in an Italian study where in total 73 % of the sample ($n= 31$) with DS had vitamin D deficiency (53). These studies suggest that blood tests regarding iron deficiency and vitamin levels may be of clinical importance.

Obesity

Prevention and treatment of obesity are important issues for youth with DS. In a review addressing overweight and obesity in DS decreased resting energy expenditure, increased

leptin levels, untreated hypothyroidism, unhealthy diet and low physical activity were described as factors likely to contribute to excessive weight gain (15). In line with this, a more recent study on total energy expenditure using doubly labelled water in nine children with DS (mean 10.0 years, SD 3.9), found that those persons with DS required 500-800 fewer calories per day compared to typically developed children (54). Studies on nutritional intake however, did not find decreased energy intake in children with DS compared to controls, but rather, increased energy intake (55) or no difference in energy intake between children with and without DS (56).

In theory, reduced cognitive abilities may influence food choices and activity levels in children. However, no clear effect of the degree of intellectual disability on nutritional status was found when adolescents with DS and mild or moderate intellectual disability were compared (57). Poor knowledge of healthy foods has been described in children with DS 11-18 years of age (58). Even so, an intervention study consisting of 18-session education program on physical activity, healthy eating and motivational skills, only resulted in a shift towards decreased consumption frequency of sweets, and with no other changes in dietary habits observed (59).

To date, most interventions for obesity have been exercise-based and with mixed and inconclusive effects on weight loss (15). Some studies have however been multicomponent interventions. In a small 6-months nutrition and exercise intervention study (n=21), no weight loss was achieved in the group receiving 16-session nutrition and exercise education program with individualized diet and exercise plans (60). However, in the group where parents also received education in behavioural strategies, such as diet and activity monitoring, short term goal setting and positive reinforcement, participants lost an average of 2.7 kg. At 1-year follow-up mean weight loss was 2.0 kg (60). This study points to the possible importance of family-oriented interventions and education on maintenance strategies as possible critical success factor, but needs to be further evaluated in larger samples.

Nutritional intakes and assessments

Assessment of nutritional intakes is an essential component in prevention and treatment of abnormal weight status and micronutrient deficits. However, few studies have addressed dietary intakes in children and adolescents with DS and no specific dietary pattern in this group have been shown to be associated with increased risk of overweight (15). Intakes below recommended dietary allowances (RDA) of various micronutrients was found in some

individuals (55, 61), and compared to siblings, reduced intakes of protein and certain micronutrients have been documented (56) (Table 2).

Parents of young children are most often able to present a fair picture of their child's typical dietary habits and nutritional intake. Due to the widespread use of dietary supplements in children with DS (62) all assessments of nutritional intakes in this population should include questions about use of herbal and dietary supplements. As children with DS grow older, additional methods may be required to provide adequate dietary data. Technology based methods like image-based mobile food records have been found to be accepted, feasible and promising for nutritional assessment in adolescents with DS (63, 64).

Dietary supplementation studies

Vitamins, minerals and antioxidants from the diet are important cofactors in many biochemical processes throughout the body. To ensure short- and long-term health, most countries have developed recommendations for daily intakes. The study by Reza and colleagues found a positive effect on bone mineral density of exercise with and without intake of calcium and vitamin D from enriched milk. The interventions in this study mimic general recommendations of physical activity and intakes of calcium and vitamin D from foods, and provide some evidence that adherence to these general recommendations also have positive effects on bone health in children with DS (65). Likewise, in the study by Stagi and colleagues, a positive, but inadequate effect was documented by supplementing with 10 µg/day of vitamin D3 in a population with low 25-hydroxy vitamin D status as baseline (53). This study did not investigate total intake of vitamin D in diets but described reduced intake of vitamin D from fortified milk in the DS-group. The study points towards the importance of adequate intake to prevent low vitamin D status and that adherence to general recommendations may be inadequate in already deficit persons.

The presence of an extra copy of chromosome 21 leads to overexpression of genes located on the chromosome, and further metabolic alterations leading to elevated oxidative stress and abnormalities in zinc metabolism (66, 67). This has led to hypothesis that dietary interventions with higher intakes than general recommendations of selected antioxidants, vitamin and minerals in supplements can contribute to normalize biochemical processes, and by this ameliorate the syndromes effect on the nerve system and intellectual ability.

Table 3 summarize the most recent dietary intervention studies and their findings. Although several studies report improvements in biochemical markers, no study have so far been able

to translate this into improvements in clinical outcomes. An important limitation is that most studies include small samples and do not include any description of clinical outcome measures. The randomised controlled trial by Ellis and colleagues (68) had a stricter study design and included a relatively large sample of infants with DS (n=156) with mean age of 4 months at enrolment. They investigated the effect of antioxidants and folate supplementation and did not find any improvements on biochemical measured oxidative stress or cognitive functions, measured by development of major motor milestones and language development (68). Further, a systematic review from 2002 by Salman did not find evidence of effects on cognitive function or psychomotor development by any combination of supplement with vitamins or minerals (69). No studies on safety of dietary supplements were found and this is a concern, as some of the doses used were high. Gastrointestinal distress was reported as a side effect of dietary supplementation (62, 68). No association between use of vitamin supplements and risk of leukaemia has been documented in children with DS (70).

Despite the lack of evidence of effect, the use of various dietary supplementations remains common in children with DS. In a survey with more than 1100 responders from USA, 49 % currently gave or had given their child supplements, where antioxidants and vitamins were the most popular supplement categories (62). On average, the children used three supplements (range 1-18). A total of 87 % of the parents reported improvements in language, immunity and attention. This demonstrates a discrepancy between the scientific literature and parent opinions that needs to be systematically addressed.

Dietary issues related to celiac disease and diabetes type 1

As previously mentioned, children with DS have increased risk of celiac disease (8) and type 1 diabetes (12). The only available treatment for celiac disease is gluten free diet. In a small study of nine persons with DS diagnosed with celiac disease, at 1-year follow-up clinical improvements in anemia and diarrhea, and improved behaviors with less irritability was observed in persons with good diet compliance (71). Apart from this, no other studies were identified describing aspects related to diets or determinants of diet compliance in children with DS and celiac disease or diabetes.

Limitations and future perspectives

Research on nutritional challenges in DS is limited with few intervention studies performed. Several studies include small numbers of participants and with wide age distributions and

inadequate descriptions of health status. In addition, many studies include cohorts followed up at specialist clinics and may therefore be selective populations. There is need for more in depth studies with representative samples and controlled study designs, using cutting edge methods and technologies. This review shows that there is an urgent need for studies addressing energy requirements, nutritional intakes and status that should be the basis for development of targeted randomized clinical interventions. In such studies knowledge about relevant health issues DS in general and nutritional issues in DS in particular, is needed for such studies to be of quality and relevance for medical doctors and clinical dietitians working with this group.

Conclusions

Increased focus on nutritional measures is important for the health and well-being of children and adolescents with DS. Specific clinical features of DS have nutritional relevance and needs to be addressed systematically. There are different nutritional implications in the various age groups with feeding problem as predominant in the first years of life. In this phase clinical screening for feeding problems and evaluation of children with feeding difficulties and low weight gain is important. Excessive weight gain is a concern for many children with DS already from 4-5 years of age. This calls for early prevention to avoid later disease. The switch between preventing the risk of undernutrition in first year of living and obesity in later years represent a treatment challenge. Clearly, there is a need for more research on nutritional aspects in prevention and treatment of obesity.

Conflict of interest

The authors declared no conflicts of interest

Contributors section

Marianne Nordstrøm: Performed literature search and identified relevant articles. Read included studies and drafted the manuscript and tables. Made the figures, finalized draft, and participated in discussions and revision of manuscript.

Sigrun Hope: Contributed in planning of first draft. Contributed with clinical cases and relevant pathology linked to nutrition. Contributed and commented on first draft and commented on revised manuscript.

Kjetil Retterstøl: Contributed in planning of literature search and the use of selection criteria and first draft, and with clinical examples and relevant pathology linked to nutrition. Commented and contributed in finalizing manuscript and during revision of manuscript.

Svein O. Kolset: Contributed in planning of literature search and use of selection criteria. Performed literature searches. Contributed to outline of manuscript and preliminary draft and finalizing of manuscript. Participated in discussions and revision of manuscript.

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Table 1: Clinical features of DS with nutritional relevance

Hypotonia
Oropharyngeal abnormalities
Gastrointestinal malformations and dysmotility
Reduced growth rate
Hypothyroidism
Celiac disease
Type 1 diabetes
Intellectual disability
Behavioural and psychiatric disorders

Table 2: Studies on nutritional intakes in children with Down syndrome

	Study design	Age	Country	Method	Results
Magenis et al (2018)	Case-control (DS n=19 and controls n=19)	5-18 years	Brazil	Parent completed 3-day food record	In DS-group higher intakes of energy, protein and carbohydrates compared to controls Proportions with intakes below RDA: Vitamin D 74 %, niacin 21 %, folate 26 %, pantothenic acid 37 %, calcium 26 %, thiamin 11 % Compared to controls no significant difference in proportions with suboptimal intakes of micronutrients
Samarkandy et al (2012)	Case-control (DS n=108 Sibling controls n= 113)	5-12 years	Saudi Arabia	Parent completed 3-day food record	No significant difference in energy intake between children with DS and siblings Children with DS had lower intakes of protein, retinol, riboflavin, calcium and potassium
Grammatikopoulou et al (2008)	Cross-sectional (n=34)	2-18 years	Greece	Parent completed 3-day food record	Children 2-9 years (n=11) was compared to adolescents 10-18 years (n=23) and as expected highest intakes in total energy and

					<p>macronutrients was found in the oldest group</p> <p>For children 2-9 years suboptimal intakes of micronutrients presented as mean percentage of RDA; folate 81%, vitamin D 70 %, vitamin E 35 %, vitamin K 49 % and iron 76%</p> <p>For adolescents 10-18 years suboptimal intakes of micronutrients presented as mean percentage of RDA; folate 84 %, biotin 60 %, vitamin D 94 %, vitamin E 87 %, vitamin K 43 % and calcium 90 %</p>
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BMI=Body mass index

RDA= Recommended dietary allowances

Table 3: Dietary intervention studies in children with Down syndrome

	Study design	Age	Country	Method	Results
Parisotto et al (2014)	Case-control (DS n=21 controls n=18)	3-14 years	Brazil	<p>Measurements of antioxidant enzymatic activity from whole blood, hemolysates and in serum samples</p> <p>6-months intervention only in the DS-group with daily supplement of antioxidants: vitamin E 400 mg, vitamin C 500 mg</p>	<p>Differences in antioxidant enzymatic activity was found between persons with DS and controls</p> <p>More normalized antioxidant enzymatic activity values were described in children with DS after intervention.</p> <p>Increased vitamin E levels in whole blood of children with DS after intervention</p>
Lakshmi et al (2008)	Case-Control (DS n=40 Controls n=40)	5-16 years	India	Serum measurement of acetylcholinesterase and butyrylcholinesterase	The values of acetylcholinesterase and butyrylcholinesterase was reduced in children with DS compared to controls before intervention

				6-months intervention only in the DS-group with daily supplements of: Zinc 1 mg/ kg body weight, vitamin A 1.5 mg, vitamin E 17 mg, ascorbic acid 100 mg, thiamine 10 mg, riboflavin 10 mg, phyroxidine hydrochloride 3 mg, cyanocobalamin 5µg, niacin 50 mg, folate 1 mg, calcium phantothenate 12.5 mg, copper 2.5 mg, selenium 60 µg manganese 1.4 mg and chromium 5µg	These measures were increased and almost normalized after intervention
Ellis et al (2008)	Four-armed single-blinded randomized controlled trial (In total n=156) A: Antioxidants and folate (n=41) B: Antioxidants (n=40) C: Folate (n=36) D: Placebo (n=39)	Infants < 7 months	United Kingdom	18-months intervention study Antioxidants: Selenium 10 µg, zinc 5 mg, vitamin A 0.9 mg, vitamin E 100 mg and vitamin C 50 mg Folate: 0.1 mg Clinical improvements were measured with quotient on Griffiths mental developmental scale and MacArthur communicative development inventory Measurements of activity in antioxidant enzymes in red blood cells and biomarker of lipid peroxidation in urine	No evidence of clinically or statistically significant effects of antioxidants or folate on any of the outcomes measured
Nachvak et al (2004)	Three-armed randomized controlled trial (DS n=93, sibling controls n=26)	7-15 years	Iran	Measurements of oxidative stress markers: serum thiobarbitubic acid reactive substances	Higher levels of oxidative stress markers were found in children with DS compared to their siblings

	A: α -tocopherol B: α -lipoic acid C: Placebo			(TBARS) and urinary 8-hydroxy-2-deoxyguanosine (8OHdG) 4-months intervention only in DS-group A: α -tocopherol: 268 mg/day B: α -lipoic acid: 100 mg/day	No change in TBARS from any intervention. Significant decrease in urinary 8OHdG in α -tocopherol-group compared to placebo
Marreiro et al (2009)	Uncontrolled intervention study (DS n= 16)	10-19 years	Brazil	4-week intervention with daily 30 mg zinc supplementation Zinc related nutritional status was evaluated by measures in plasma and erythrocytes Measurement of serum concentration of thyroid hormones (T_4 and T_3).	Increased concentration of zinc in plasma and reduced in erythrocytes after intervention No difference in serum concentration of thyroid hormones
Gualandri et al (2003)	Uncontrolled intervention study (DS n=33)	1-14 years	Italy	In children with compromised redox balance at baseline 30-day intervention with daily supplementation: α -lipoic acid 200 mg and L-cysteine 200 mg Measurement of thiol groups, septic reactive oxygen species (ROS) and total antioxidant status in serum	Thirteen persons dropped-out and results are based on assessment of 20 individuals Significant increase in serum thiol groups and antioxidant capacity in serum Significant decrease in serum total and septic ROS
Reza et al (2013)	Four-armed randomized controlled trial (DS n=48) A: Exercise and calcium B: Calcium C: Exercise	7-12 years	Iran	4-months intervention Exercise: 45 min weight-bearing activities 3 times per week Calcium: Daily intake of 500 ml vitamin D enriched cow milk.	At baseline all groups had approximately 430 mg/day dietary intake of calcium and similar physical activity pattern Post intervention all groups had significant higher BMD.

	D: No intervention			Containing 200 mg/day calcium. Measurement by DXA of bone mineral density (BMD) at right proximal femur neck	Combined exercise and calcium group; 14.6 % increase, exercise-group 8.6 % increase, calcium-group 3.5 % increase, no intervention 1.3 % increase
Stagi et al (2015)	Controlled intervention study (DS n=31, controls n=99)	4-19 years	Italy	Measured plasma 25(OH)D levels, serum calcium, and phosphate, bone specific alkaline phosphate, parathyroid hormone Evaluation of dietary vitamin D intake by parent interview on use of vitamin D fortified milk Intervention: Oral daily 10 µg vitamin D3 supplement from November through May	At baseline 25(OH) D levels were significant reduced in DS group. In DS 45 % showed deficient levels (<20 ng/mL) and 32 % severe deficiency (≤10 ng/mL) Elevated PTH levels in DS-group compared to controls Children with DS consume less vitamin D fortified milk After intervention Increased 25(OH) D plasma levels in DS-group but not controls and in DS-group still significantly reduced compared to controls. In DS 29 % showed deficient 25(OH) D level and 22 % severe deficiency DS-group still higher levels of PTH compared to controls

Figure

Suggested nutritional assessment in children with Down syndrome

