THE USE OF NUTRITIONAL SUPPLEMENTS AMONG CHILDREN WITH DOWN SYNDROME

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ACT TEAM 2612

NUTRITIONAL SUPPLEMENTS FOR PEOPLE WITH DOWN SYNDROME, DO THEY REALLY HAVE BENEFICIAL EFFECTS?

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Executive summary

Down syndrome (DS) or trisomy 21 is the most common genetic cause of intellectual disability. It is characterized by a delayed psychomotor development. The extra copy of chromosome 21 often results in specific nutritional challenges for children with DS, such as nutritional deficiencies and other food-related problems. Considering the fact that a balanced diet is a crucial component of a healthy lifestyle, nutritional supplements are a popular topic among caregivers of children with DS. However, there is still a lack of knowledge regarding the usage and health effects of nutritional supplements. Therefore, the aim of this research was to get insight into the current situation concerning nutritional supplement usage among Dutch children aged 0-18 with DS and eventually provide an applicable advice to Stichting Downsyndroom (SDS) regarding this topic. For this research, both literature research and fieldwork were performed. The fieldwork was split into three parts: a questionnaire, interviews and market research. The questionnaire and interviews were used to gain a more detailed insight into the usage of nutritional supplements by children with DS and the motivation of the caregivers behind this. Furthermore, two pediatricians, two dieticians, all specialized in DS, and the founder of the supplement supplier NutriChem were interviewed to get a more detailed overview regarding the provision of nutritional supplements to children with DS, and to determine the knowledge of experts on the available nutritional supplements for these children. Lastly, the market research was performed to investigate what supplements are currently on the market for children with DS, what nutrients they contain and in what doses.

Most common nutritional deficiencies among children with DS are vitamin D, vitamin C, iron and zinc deficiencies. In addition, children with DS often experience issues with oral motor skills and are more prone to develop obesity. From the results, it can be concluded that vitamin D, general multivitamins, vitamin C, multivitamins aimed for people with DS, probiotics and fish oil are the most provided nutritional supplements by caregivers to their children with DS. Different conclusions can be drawn with regard to the dosages of these supplements. The most commonly used multivitamins aimed at people with DS (MSB NeuroPlus, NuTriVene-D) often exceed daily values (DV's) of nutrients. Most caregivers who provide their children with nutritional supplements do this to improve their immune system and to improve the development and overall health of their child. However, experts are critical in providing supplements due to the lack of scientific evidence, and have a clear preference for obtaining nutrients via the diet. However, some caregivers still provide supplements to their children with DS as they observe positive effects. The sources from which most caregivers acquire information are their physician, the internet, social media or people in their network (e.g. fellow caregivers). In this study, PAHL consultancy found that 61% of the caregivers responding to our questionnaire provided nutritional supplements to their children with DS. A lot of research has been conducted concerning the topic of nutritional supplementation. However, it stands out that many results of different studies are contradicting and based on studies with methodological shortcomings. For now, nutritional supplements are not recommended with an exception of vitamin D. If caregivers still like to provide supplements to their children, general multivitamins, instead of multivitamins aimed at people with DS, are preferred as they are more likely to contain a safe dosage.

Further research could focus on the effects of placebos, as it appears from interviews that supporters of supplements notice improvement in their child with DS. Caregivers who give supplements to their children may also create a more nurturing environment than those who do not, which can also have an effect on a child's health. Lastly, the role of marketing, commerce and legislation in the world of nutritional supplements could also be more included in further research. All in all, due to the current lack of scientific evidence more research with a validated methodology is urgently needed.

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Introduction

Down syndrome (DS) is the most common genetic cause of intellectual disability (Bittles, Bower, Hussain & Glasson, 2007). It is mainly characterized by a delayed psychomotor development, which comprises both physical and cognitive functioning (Silverman, 2007; Weijerman, 2018). According to the most recent data (2015), approximately 190 newborn children with DS were registered in the Netherlands, which amounts to 11,1 per 10.000 neonates (de Graaf et al., 2017). Because DS is the result of an extra copy of chromosome 21, it is also called trisomy 21 (Martin, Klusek, Estigarribia & Roberts, 2009). Although the diagnosis of DS is mainly based on clinical features, the golden standard remains chromosomal analysis (Agarwal Gupta & Kabra, 2014). In addition to this postnatal diagnosis, prenatal screening exists (Agarwal Gupta & Kabra, 2014). Prenatal screening for DS determines the likelihood of babies being born with DS (Agarwal Gupta & Kabra, 2014). This test can be performed either during the first trimester or second trimester of pregnancy (Agarwal Gupta & Kabra, 2014). From April 2017 onwards, non-invasive prenatal testing (NIPT), a much more precise prenatal screening test, is offered to all pregnant women in the Netherlands in their first trimester (Harraway, 2017). If a positive prenatal screen is confirmed by karyotyping, expectant parents can use this information either for preparing for the birth of a child with DS, or they can decide to terminate the pregnancy (Agarwal Gupta & Kabra, 2014). People with DS can generally live a happy, healthy and relatively independent life (Agarwal Gupta & Kabra, 2014). Early intervention, a good home environment and parental care, the availability of appropriate and specialized medical care and education are all important support factors that contribute to an improved quality of life (Agarwal Gupta & Kabra, 2014).

Etiology of DS

Trisomy 21 can arise in two different ways, either by nondisjunction or translocation of chromosome 21 (Marilyn & Bull, 2020). Nondisjunction results in the presence of 47 chromosomes in total (Marilyn & Bull, 2020). This occurs in 96% of the cases of people with DS and also includes the genetic diagnosis of mosaicism of trisomy 21 (Marilyn & Bull, 2020; Radboudumc, n.d.). Mosaicism of trisomy 21 is however generally associated with fewer clinical features of DS because these individuals have both trisomic and euploid cells (Papavassiliou, Charalsawadi, Rafferty, Jackson-Cook, 2015). Translocation results in the addition of an extra chromosome 21 to another chromosome and is the cause of DS in the other 4% of the cases (Marilyn & Bull, 2020). About a quarter of this 4% has an inherited form of such a translocation (Radboudumc, n.d.). This means that in only 1% of all children with DS, the extra chromosome has a hereditary origin (Radboudumc, n.d.). The clinical characteristics associated with DS do not differ between these two different causes of trisomy 21 (Marilyn & Bull, 2020). The genetic causes of trisomy 21 can have both maternal and paternal origins (Coppedè, 2016). However, more than 90% of the children with DS receive the extra chromosome from the maternal side (Coppedè, 2016).

Predisposing factors for DS

There are some factors that might increase the probability of having a child with DS. First of all, advanced maternal age has long been known to play a role in the development of DS, especially after the mother reaches the age of 35 (Coppedè, 2016). The older a woman is when conceiving a child, the higher the probability of having a child with DS (Coppedè, 2016; Weijerman et al., 2008). Secondly, an abnormal folate metabolism might also increase this probability (Philips, 2008). Folate is an essential B-vitamin which plays a crucial role during DNA methylation (Coppedè, 2016). Because an abnormal folate metabolism can affect DNA methylation, this might result in an altered gene expression (Philips, 2008). Maternal polymorphisms in either the *MTHFR* gene or the *MTRR* gene, which both play a role in folate metabolism, have been shown to increase the probability of having a child with DS with an odds ratio of 1.91 and 2.57, respectively (Hobbs et al., 2000). If a mother has polymorphisms in both genes, the probability increases even more, with an odds ratio of 4.08 (Hobbs et al., 2000).

Characteristics of DS

People with DS are more likely to have certain well-recognized physical characteristics (Agarwal Gupta & Kabra, 2014; Mayo Clinic, 2018). For instance, they are more often of a short height, have a small head and neck with a flattened face, short hands with broad fingers and a slightly protruding tongue (Agarwal Gupta & Kabra, 2014; Mayo Clinic, 2018). Additionally, DS is characterized by cognitive impairment, usually in the mild to moderate range (Parizot, Dard, janel & Vialard, 2019). People with DS have weaknesses in, for example, language development, adaptive functioning, processing speed, executive functions and verbal memory (Grieco, Pulsifer, Seligsohn, Skotko & Schwartz, 2015; Mayo Clinic, 2018; Silverman, 2007). In addition, people with DS have an increased probability of developing dementia (Keator et al., 2020). Especially the prevalence of Alzheimer's disease is high among people with DS, since more than 75% of the people with DS aged 60 years and older develop Alzheimer's disease (Keator et al., 2020). During childhood, people with DS show specific behavioral profiles, with higher rates of externalizing behaviors, like hyperactivity, impulsivity and non-compliance, in early childhood and among school-aged children (Grieco et al., 2015). Besides this, they show higher rates of internalizing symptoms, such as social withdrawal, anxiety and depression, as teenagers (Grieco et al., 2015). Furthermore, in contrast to controls, children with DS have a lower birth weight and a delayed growth, especially during the initial years of life (Agarwal Gupta & Kabra, 2014; Weijerman, 2008). Comorbidities and/or feeding problems, which are more common among children with DS, can aggravate this delay in growth (Agarwal Gupta & Kabra, 2014).

Comorbidities related to DS

As mentioned above, people with DS often show distinct comorbidities in different stages of life affecting the hematological, cardiovascular, respiratory, endocrine, gastrointestinal, renal, sensory, musculoskeletal, immune, neurological and genitourinary systems (Arumugam et al., 2015). For example, children with DS have an elevated risk of congenital heart disease, pulmonary-artery hypertension, visual and hearing impairments, epilepsy and hypothyroidism (Hithersay, Hamburg, Knight & Strydom, 2017; Weijerman, 2008; Marilyn & Bull, 2020). Moreover, children with DS have a highly increased risk of leukemia, as they are 20 times more likely to develop this compared to children without the condition (Bittles et al., 2007). Another well-known comorbidity is the development of obesity during adolescence and adulthood (Agarwal Gupta & Kabra, 2014). Factors that are thought to contribute to this development include a poor basic metabolic rate, a positive energy balance, hypothyroidism and high leptin levels (Agarwal Gupta & Kabra, 2014; van Gameren-Oosterom et al., 2012). Furthermore, people with DS are more likely to have auto-immune diseases and skeletal syndromes compared to their peers without DS (Marilyn & Bull, 2020). In addition, in comparison to people without DS, people with DS more often have autism and attention deficit hyperactivity disorder (ADHD) (Startin et al., 2020). Finally, DS is associated with impaired fertility and it contributes to premature menopause in women and spermatogenesis defects in men (Parizot et al., 2019).

Life expectancy of people with DS

Due to improved health care, better knowledge of comorbidities and other supportive resources, the life expectancy of people with DS has greatly increased over the last decades to approximately 60 years presently (Arumugam et al., 2015). This is an enormous increase, considering that in 1949 the life expectancy was estimated at only 12 years (Bittles et al., 2007; de Graaf et al., 2011). However, there is still much improvement to be made, both from a health perspective and a socio-professional perspective, as mortality is still higher in children with DS compared to children without DS (Arumugam et al., 2015).

The importance of a healthy diet

In general, it is well known that an important part of a healthy lifestyle includes a balanced diet (Price, 2005). A balanced diet provides the nutrients and energy that are required to survive and stay healthy (Price, 2005). Additionally, it reduces the probability of developing several (chronic) diseases (Price, 2005). Crucial components of a healthy and varied diet are a sufficient amount of fruit and vegetables, fibers, unsaturated fatty acids and starchy foods including bread, potatoes, rice

and pasta (Price, 2005). Besides this, it is important to drink enough fluids to prevent dehydration (Price, 2005). When proper nutrients cannot be sufficiently obtained from the diet, they can be supplemented (Nederlandse Voedsel- en Warenautoriteit). Nutritional supplements are products that are intended to supplement the normal diet and are a concentrated source of vitamins and minerals or other bioactive substances (Nederlands Voedsel- en Warenautoriteit, n.d.). Most people do not need nutritional supplements, because they already consume enough vitamins and minerals through a varied diet (Nederlandse Voedsel- en Warenautoriteit, n.d.). Supplementation advice only applies to special groups that need extra vitamins or minerals, for instance pregnant women, the elderly, young children, and people with deficiencies due to diseases or dietary habits (Nederlandse Voedsel- en Warenautoriteit, n.d.).

Nutritional challenges and supplements in DS

Beside the comorbidities that were mentioned earlier, children with DS generally have specific nutritional challenges, such as nutritional deficiencies and other food-related problems (Nordstrøm et al., 2020). Several studies have already investigated these nutritional challenges among children with DS, however, this has not been identified so far. These studies mentioned multiple challenges, such as difficulties in chewing and swallowing, lower (self-)feeding abilities, caloric overconsumption and multiple nutritional deficiencies (Magenis et al., 2018; Nordstrøm et al., 2020; Thiel & Fowkes, 2004). The food-related challenges that are related to DS can cause insufficient nutritional intake or suboptimal digestion and absorption of nutrients, which can in turn lead to nutritional deficiencies, such as vitamin or mineral deficiencies (Nordstrøm et al., 2020). These deficiencies can result in for example, fatigue, growth retardation, constipation and a disturbed intestinal peristalsis (Mazurek & Wyka, 2015). Therefore, nutritional supplements might be a good way to achieve a healthy nutritional status in children with DS, contributing to a healthier life in general. More importantly, the use of nutritional supplements by children with DS is already a hot topic among the caregivers of these children. With caregivers is meant the primary caregiver of the child, such as the parent(s). Recently, several manufacturers are responding to this hot topic by claiming that the intake of (specific) nutritional supplements by people with DS can provide health benefits. For instance, manufacturers claim that supplementation by people with DS can result in improved cognitive abilities, alleviated gastrointestinal or thyroid dysfunction, and a reduction in infections due to an enhanced immune function (Blair et al., 2008). Although several manufacturers make such health claims, double-blinded and peer-reviewed results from long-term studies are scarce and almost all trials that have been published have methodological shortcomings (Roizen, 2005). Furthermore, current recommendations concerning the use of nutritional supplements among children with DS are mostly based on experiences by caregivers of these children (Stichting Downsyndroom, n.d.). Often, these caregivers are eager to see results (Stichting Downsyndroom, n.d.). Besides that their success stories are single cases, these results are therefore not very reliable (Stichting Downsyndroom, n.d.). Overall, it is hard to implement these findings in a scientific manner (Stichting Downsyndroom, n.d.).

Supplement usage among children with DS

As mentioned previously, the use of nutritional supplements is a widely discussed and popular topic among caregivers of children with DS. Because of the claimed health benefits and single success stories, many caregivers of children with DS feel urged to provide nutritional supplements to their children (Wageningen University & Research, 2020). A recent study by Feldman Lewanda et al. (2018) investigated the global nutritional supplement use among children with DS. The authors demonstrated that 49% of the caregivers, the majority of whom came from the United States, actually did provide nutritional supplements to their children (Feldman Lewanda, Faust Gallegos & Summar, 2018). Many caregivers give nutritional supplements to their children under the guise of "no harm, no foul" (Wageningen University & Research). However, ignorance on the effects and working mechanisms of nutritional supplements can cause significant health issues (Stichting Downsyndroom, n.d.). For instance, too high doses of nutrients can be detrimental to health, as they are able to accumulate in the body (Hayes, 2008; Stichting Downsyndroom, n.d.). In addition, people with DS have a higher expression of certain enzymes, because of their surplus of genetic material (Stichting Downsyndroom, n.d.). Although, it is possible that people with DS might benefit

from higher doses of certain nutrients, the combination of a higher expression of certain enzymes with high doses of vitamins and minerals, might lead to damage to the body's cells (Stichting Downsyndroom, n.d.). Hence, this indicates that there still is a lack of proven benefit and safety regarding the use of nutritional supplements for people with DS (Feldman Lewanda et al., 2018). The need for knowledge of supplement use in combination with DS should therefore be emphasized (Stichting Downsyndroom, n.d.).

Clinical relevance and research question

Besides the fact that there is a lack of evidence concerning the health benefits of nutritional supplements, there are many more issues that arise with respect to the use of supplements among children with DS (Salman, 2002). The whole concept of nutritional supplement usage is relatively new, which certainly contributes to the fact that there is still much unknown (Kamiński, Kręgielska-Narożna & Bogdański, 2020). This relates to, for example, the effect of the physiology of children with DS, the current availability of supplements specific for people with this condition, the current diet of children with DS, the recommendations of experts and many more. This is what PAHL consultancy team, composed of students from Wageningen University & Research (WUR), investigated, commissioned by Stichting Downsyndroom (SDS). In short, this foundation promotes, among other priorities, a healthy lifestyle for people with DS to be able to participate in society (Stichting Downsyndroom, n.d.). Considering the fact that nutritional supplements might contribute to a healthy lifestyle and the previously mentioned knowledge gap on nutritional supplements, the research question of this study comprised: 'What is the current situation concerning the usage of nutritional supplements among Dutch children aged 0-18 with DS?'. Additionally, an applicable advice is provided to SDS for caregivers on nutritional supplement usage regarding the need, the safety and the potential health effects for children with DS.

Methodology

To acquire more knowledge, outline the current situation, answer the research question and ultimately give an applicable advice, that is both valuable and accurate, the following sub questions were composed:

1. Which nutrition-related problems or nutritional deficiencies are common among children with DS?
2. What nutritional supplements are currently given by caregivers to their children with DS and to what extent?
3. What is the motivation of caregivers of children with DS to provide nutritional supplements to their children and based on what information do they do this?
4. What is the opinion and advice of doctors, dietitians and (an)other expert(s) on the provision of nutritional supplements to children with DS?
5. What supplements linked to nutritional deficiencies seen in children with DS are currently on the market, what do they claim, and do they contain safe doses?
6. Is there scientific evidence for the health effects of the available supplements for children with DS?

The current study included a combination of prospective and retrospective data collection, as both fieldwork and literature research were performed. The fieldwork consisted of conducting a questionnaire, interviews, and market research. Therefore, this study comprised a mixture of qualitative and quantitative research. Important to mention is that the focus of this report is mainly on the fieldwork, as this is necessary to gain more insight into the current nutritional supplement situation among children with DS. However, the literature research also comprises an essential, but smaller part of this research. Table 1 indicates which research methods were used to answer the specific sub questions mentioned above.

Table 1: Justification of research methodology

Sub research question	**Literature research**	**Fieldwork**	**Quantitative**	**Qualitative**	**Prospective**	**Retrospective**
1	X	X	X	X	X	X
2		X	X	X	X	
3		X	X	X	X	
4		X		X	X	
5		X		X		X
6	X	X		X	X	X

Fieldwork

The fieldwork of this research consisted of different components and included:

- Conducting an internet search in different search engines and on forums dedicated to nutritional supplements and DS.
- Conducting a questionnaire on nutritional supplementation among caregivers of Dutch children aged 0-18 with DS.
- Conducting interviews on nutritional supplementation with caregivers of Dutch children aged 0-18 with DS.
- Conducting interviews on nutritional supplementation with doctors, dieticians and (an)other expert(s) specialized in DS.
- Inventory of supplements that are currently on the market for children with DS.

Exploratory internet search
To obtain a first impression about the current situation concerning nutritional supplementation and knowledge about this, the field work started with an exploratory internet search. Moreover, this search was used as input for the composition of the questionnaire and interviews with caregivers and experts. In this exploration phase, the focus was mainly on different Facebook groups, internet forums, and websites that were found after conducting an internet search. Examples of this are groups/forums especially for caregivers of children with DS. For the internet search, both Dutch and English search terms were used in the search engines Google, Bing and DuckDuckGo, in the browsers Google Chrome, Safari and Microsoft Edge. Multiple search engines and browsers were used to increase the validity of the exploration phase, as different browsers/search engines can yield different results. Examples of search terms used are: *voedingssupplementen Downsyndroom*, *trisomy 21*, and *supplements Down syndrome*. In addition, the website of SDS was used. The findings of this exploratory phase were compared to the results of the questionnaires and interviews to assess whether they were (somewhat) similar. Subsequently, the acquired knowledge was used to conduct further research into individual supplements, for which more specific search terms were used, like: *MSB NeuroPlus*, *NuTriVene* and *LTO3*. Internet forums and Facebook groups gave an extensive and useful representation of what is known and which supplements are popular among caregivers of children with DS.

Questionnaire
To help answer sub questions 1, 2 and 3 a questionnaire was designed. The goal of this questionnaire was to assess which nutritional deficiencies are reported in children with DS, what supplements are given by caregivers, what the motivation to give nutritional supplements is and where this information comes from. The questionnaire was programmed in Logic8 EyeQuestion version 4.11 and could therefore be provided to the participants via a simple link. Caregivers of children with DS were approached for this questionnaire via social media and the newsletter of the foundation SDS. Selection criteria for participation in the questionnaire included being a primary caregiver of at least one child aged 0-18 with DS and having a good understanding of the Dutch language. Before taking part in the questionnaire, the participants first had to give their consent for participating in the research and the use of their results (see Appendix 1). Additionally, information regarding the anonymity and legal retention period of the results was provided. The questionnaire was verified by the Food & Biobased Research department of the WUR, employees of the foundation SDS and one caregiver of a child with DS affiliated with SDS before it was published online. This was done to gain insight into the efficiency of the questionnaire. The questionnaire mainly consisted of closed questions as this is more motivating for respondents to answer and leads to less missing data (Reja, Manfreda, Hlebec & Vehovar, 2003). However, an option was added to each question where the caregivers could enter a short answer (other, namely …) in case their answer was not included in the answer options. In addition, there was a possibility for other comments at the end of the questionnaire. Some of these comments elaborated on answers given in the questionnaire and were used in processing the data of the questionnaire.

The reliability of the questionnaire was guaranteed by adhering to a fixed question sequence. Thus, each participant received the questions in the same order and, because the questionnaire was filled in online, participants were unable to continue to the next question until the current question was answered. Besides this, the definition of nutritional supplements was mentioned in the questionnaire to prevent confusion about this term. Unfortunately, it was beyond our control to enforce the circumstances in which the questionnaire was administered.

After completing the questionnaire, participants could decide whether they wanted to participate in a giveaway of three bol.com gift cards, each worth €20. For this, they could optionally fill in their email address. It was made clear that this address would not be used for other purposes than the giveaway. The giveaway was included to make participation attractive and to thank the participants.

The data obtained from the questionnaire was analyzed using the programs IBM SPSS Statistics 26 and Google Sheets. To ensure the external validity of the questionnaire, it is of value that the data

analysis has been performed correctly. The data analysis was carried out by two people who checked each other's work to prevent mistakes. Mostly descriptive statistics were used to depict the results obtained from the questionnaire. For some analyses, results were split into groups based on age and gender of the child with DS or based on whether the child was provided with nutritional supplements or not. In the results, it is indicated in what way the results were split per table or graph. For a continuous variable like body mass index (BMI), the average and standard deviation were calculated. For categorical/ordinal variables (general health and eating habits), frequency tables were made in which the mode and median were depicted. The results obtained from the questionnaire contributed to answering sub questions 1, 2 and 3.

Interviews

Selection criteria for participation in the interviews with caregivers were the same as those for the questionnaires. SDS approached suitable caregivers of children with DS for the interviews and shared their contact details with PAHL consultancy. Subsequently, these caregivers were contacted and an appointment was made to conduct the interview via Microsoft Teams. Prior to the interview, the caregivers were required to fill out a consent form (see Appendix 3), concerning the rights of the caregiver, their anonymity in the report and the permission for recording. In addition, they received an information letter with general information about the interview itself (see Appendix 4). The interview consisted of 12 open-ended questions, concerning the caregiver's usage of, experience with and opinion on nutritional supplements for children with DS. The interviews were held to get a more detailed insight in their usage of nutritional supplements and their motivation behind this. After the interview was conducted, the interview answers were sent back to the person in question. In this way, the interviewed person was able to verify and approve their interview before the results were analyzed. Eventually, five caregivers of children with DS aged 0-18 with different perspectives regarding the use of nutritional supplements were interviewed.

Aside from the interviews with caregivers, experts specialized in DS were interviewed. SDS shared the contact details of two specialized experts, one of whom one was a pediatrician and one a dietician. Via their network, two other experts (again one pediatrician and one dietician) were approached, who were also willing to participate in an interview. Additionally, one interviewed caregiver provided contact details of another expert, the founder of NutriChem, a compounding pharmacy based in Canada which produces a supplement aimed at people with DS. All experts were contacted via e-mail and an appointment was made to conduct the interview via Microsoft Teams. Prior to the interview, experts were required to sign a consent form (see Appendix 3), concerning the rights of the expert, their anonymity in the report and the recording. In addition, they received an information letter with general information about the interview itself (see Appendix 4). The interview for the pediatricians and dieticians consisted of 16 open questions, concerning their advice, opinion and knowledge about nutritional supplements for children with DS. The goal of these interviews was to get a more detailed overview regarding the provision of nutritional supplements to children with DS and to determine the knowledge of experts on the available nutritional supplements for children with this condition. A separate interview was designed for the founder of NutriChem. This interview consisted of 14 questions with regard to the nutritional supplement aimed at people with DS that NutriChem developed and his opinion on nutritional supplementation for people with DS. After the interviews were conducted, the elaborated interview was sent back to the interviewee. In this way, they were able to verify and approve it before results were analyzed. In total, five experts were interviewed.

Because participation in an interview is time-consuming and takes more effort than completing a questionnaire, it was decided to send a small present to everyone who participated in an interview. However, this was also optional, as the participants had to share their home address to be able to receive the present. The small present consisted of a brownie box from Brownies&downieS and was delivered via the post.

Considering the analysis of the interview data, this process was similar for both the caregiver group and expert group, but was executed separately. Firstly, the interviews were anonymized, caregivers

were given a code 1 through 5, the four Dutch experts a code A through D. The interview of the founder of NutriChem was not anonymized as was discussed with him (see Appendix 3). Secondly, the elaborated interview has been checked for irrelevant information by the researchers. Any irrelevant information was not used in any further analyses of the interviews. Thirdly, the interviews were split into fragments based on the specific topics discussed in the interview. Subsequently, each of these fragments were labeled in which the following labels were applied: dietary pattern, nutritional-related problems (oral motor skills, tube feeding, obesity, celiac disease and lactose intolerance), nutritionals deficiencies (vitamin D and zinc), nutritional supplements (usage, supplements specialized DS, usage of brands, knowledge of caregiver and knowledge of children), recommendation (guidelines and sources), scientific evidence of effectiveness supplements (evidence-based vs practice based), necessary dietary supplements, and trust in medical profession. Afterwards, the labeled fragments were grouped according to their topic. Eventually, a summarizing text was made out of these findings.

The internal validity of the interviews was ensured by properly documenting the interviews, using both video and audio recordings. In addition, minutes were written during the interview. Afterwards, the recorded interview was revisited and the minutes were supplemented to a fully elaborated interview, which was then checked again by someone else. The external validity was warranted as the interviews included different perspectives on nutritional supplementation of both caregivers and experts specialized in people with intellectual disabilities. This contributed to creating an overview that is taking into account varying points of views of the current usage, knowledge and opinions with regard to nutritional supplementation for children with DS. Lastly, the reliability of the interviews was guaranteed by maintaining the circumstances in which the interviews were conducted as equal as possible. For instance, the questions were asked in a fixed order, all interviews were performed via Microsoft Teams and all participants received the same information beforehand.

The data obtained from the interviews with the caregivers was used in answering sub questions 1, 2 and 3. The interviews with the experts contributed to answering sub questions 1, 2 and 4 of this study. The interview with the founder of NutriChem from Canada was analyzed in a different way for two main reasons. First of all, this interview consisted of different questions than the interviews with the caregivers and experts. Moreover, this person is the only one with a pharmacological perspective that has been interviewed during this study. Therefore, these answers could not be compared with the results of the other interviewees. A summarizing text was written for this interview separately.

Market research

The market research was performed to investigate and to make an indication what supplements are currently on the market for children with DS. Information about the most commonly used supplements was obtained from the internet search in the exploration phase, the interviews and the questionnaire. The focus of the market research was on claims made by the manufacturers with regard to the specific health effects and the doses that are recommended. The different dosages were compared with the guidelines from 'Nederlandse Voedingsmiddelentabel' (Stichting Voedingscentrum Nederland, 2016). For this, the sites of the manufacturers itself were mainly consulted. Ultimately, an overview was made of the supplements that are currently on the market specifically aimed at people with DS, which ingredients these supplements contain and which health effects are claimed by the manufacturers of a particular supplement. Based on the results from the questionnaire, two commonly used multivitamins not aimed at people with DS were also included here for comparison. Market research contributes to answering sub research question 5.

Literature research

With this literature research, it was investigated what nutritional deficiencies and other nutrition-related problems are common among children with DS. Furthermore, it was explored if there is scientific evidence regarding the health effects of nutritional supplements for children with DS. Articles were searched via the free searching tools Pubmed® and Scopus®. For this, the following search terms were used: ("Down syndrome" OR "trisomy 21") AND ("nutrition* supplements" OR

"nutrition* deficiencies"). In total, Pubmed yielded 80 results and Scopus 75 results. In addition, articles from other systematic reviews and meta-analyses were found via snowballing of the literature. All these articles were checked for relevance and reliability. Duplicates across databases, articles not in English or Dutch and articles for which no full-text was available, were excluded. The quality of the relevant articles was examined by looking at the date of publication, the methods, and the type of study. There was a preference for articles published up to five year ago. However, due to a lack of (recent) articles on the topic of this report, it was decided to maintain a wider range with a maximum publication date of 1990. Articles that were published before 1990 mainly included outdated information or were of inferior quality, and were therefore of no value for this report. All relevant articles were analyzed, compiled and presented in a table that gave an overview of all included articles. In this table, the articles were split into two topics: articles on nutritional supplements and articles on nutrition-related problems and/or nutritional deficiencies. Therefore, this literature research consisted of two parts. Eventually, all available information was summarized into this report.

The validity of the literature research is determined by the relevance of the articles for answering the (sub)research question(s) and the way in which the articles have been searched. In terms of reliability, the degree of scientific nature of the articles is decisive. However, accidental mistakes made while searching, valuing and combining the findings from the available and relevant literature also affect reliability. The quality of the articles was determined by multiple team members. Therefore, the risks of accidental mistakes were minimized. In addition, attempts have been made to use recent articles as much as possible and thereby the focus was mainly on meta-analyses, systematic reviews and randomized controlled trials (RCT's). These types of articles were chosen because they have a high position in the evidence-based pyramid (Murad, Asi, Alsawas & Alahdab, 2016). This part of the study contributed to answering sub research questions 1 and 6.

Results

General information

To gain more insight into the current situation regarding the use of nutritional supplements among children with DS and to answer the sub questions that have been composed, literature research, a questionnaire and interviews were conducted. Moreover, an exploratory internet search and market research were performed. Before the sub questions will be addressed, first some baseline characteristics of the questionnaire and interviews will be presented, respectively.

Questionnaire

After leaving the questionnaire open for approximately 2.5 weeks, PAHL consultancy received 299 questionnaires in total, of which 247 were fully completed, as illustrated in Figure 1. Some of the completed questionnaires did not meet the inclusion criteria (for instance if a respondent's child was ≥18 years old), and were removed before analyzing the responses. This resulted in 234 usable questionnaires.

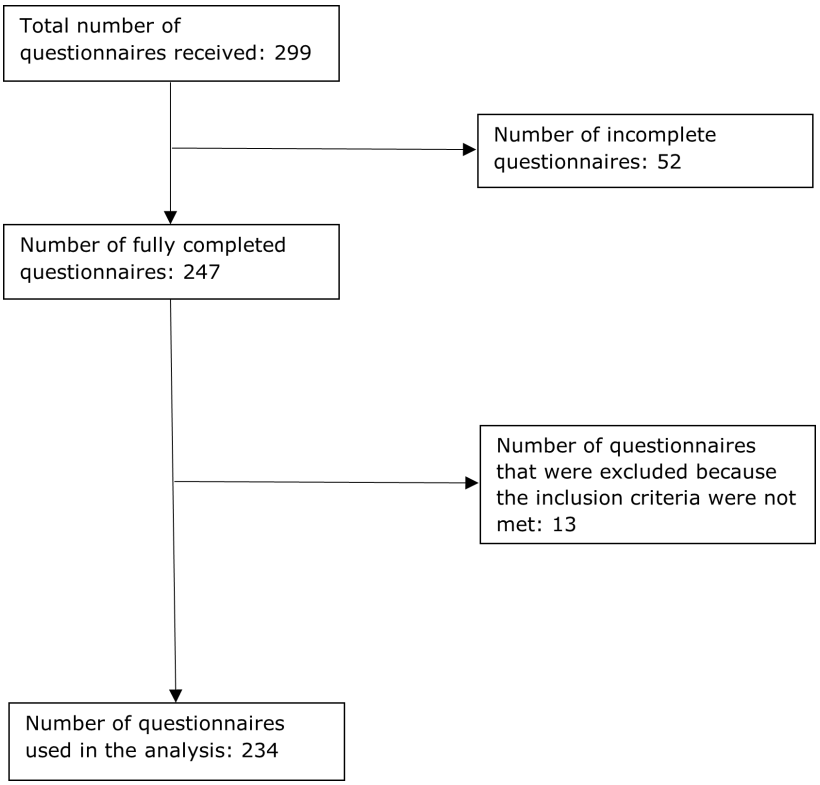

Figure 1: Flowchart of questionnaire sample size used for analysis.

The BMI's of the respondent's children with DS are depicted in Table 2 (page 16), based on age and sex. A more detailed table of results can be found in Appendix 2, Table 1. Respondents were also asked to indicate their child's physical health and eating behavior. These results were, again, split into categories based on age and sex. In most categories, the mode was 'Good' for both physical health and eating habits. However, in one category (eating habits of boys aged 6) the mode was 'Very Poor'. The mode 'Very Good' was also seen once, in the category physical health of boys aged 3. More details on these results can be found in Appendix 2, Table 2. Table 3 shows the division into a healthy, underweight or overweight range for different age categories. In all categories over 60% of children have a BMI in the healthy range.

Table 2: Average BMI ± standard deviation of respondents' children with DS for each age group and sex.

	BMI (average ± SD)	
Age	boys ♂ n= 115	girls ♀ n= 112
0 ♂n= 3, ♀n= 1	17.8 ± 5.19	16.3 ± 0.00
1 ♂n= 8, ♀n= 4	18.5 ± 7.58	15.2 ± 0.980
2 ♂n= 4, ♀n= 9	15.9 ± 1.46	15.5 ± 0.743
3 ♂n= 5, ♀n= 1	16.6 ± 2.09	13.3 ± 0.00
4 ♂n= 2, ♀n= 10	16.0 ± 0.50	16.4 ± 0.869
5 ♂n= 10, ♀n= 4	16.7 ± 2.97	16.6 ± 2.98
6 ♂n= 10, ♀n= 5	16.7 ± 1.60	15.3 ± 0.777
7 ♂n= 6, ♀n= 8	17.0 ± 2.11	17.6 ± 3.43
8 ♂n= 9, ♀n= 5	18.6 ± 3.25	17.5 ± 2.77
9 ♂n= 5, ♀n= 7	16.4 ± 0.773	18.0 ± 3.23
10 ♂n= 7, ♀n= 5	16.0 ± 2.12	22.9 ± 4.91
11 ♂n= 5 ♀n= 9	17.4 ± 1.4	20.2 ± 3.8
12 ♂n= 4, ♀n= 6	19.1 ± 4.34	20.6 ± 2.31
13 ♂n= 6, ♀n= 7	20.4 ± 3.32	16.9 ± 8.3
14 ♂n= 10, ♀n= 7	20.7 ± 2.55	18.9 ± 2.65
15 ♂n= 8, ♀n= 11	21.9 ± 3.90	23.7 ± 3.77
16 ♂n= 9, ♀n= 9	20.7 ±2.69	26.6 ± 9.7
17 ♂n= 4, ♀n= 4	24.3 ± 3.24	27.0 ± 2.27

Table 3: Division according to BMI into the ranges of severe underweight, underweight, healthy weight, overweight or obesity.

Age	**Severe underweight**	**Underweight**	**Healthy weight**	**Overweight**	**Obesity**
2-5 (n=30)	0	1 (3%)	26 (87%)	2 6%)	1 (3%)
5-9 (n=57)	3 (5%)	0	35 (61%)	9 (16%)	10 (18%)
9-13 (n=48)	0	1 (2%)	33 (69%)	11 (23%)	3 (6%)

13+ (n=74)	1 (1%)	0	49 (66%)	21 (28%)	3 (4%)

Furthermore, in Appendix 2, Table 3 the education level of the respondents and their partners and the Dutch average are displayed. This information is used to determine the representatively of the sample size.

Interviews
The interview questions of the experts are shown in Appendix 5 and the questions of the caregivers are shown in Appendix 6. The analysis of the interviews is based on the sub questions, which can be found in the methodology section. From these premises different labels have been designed and under each of these labels, the fragments of caregivers and experts are featured. For more detail regarding the different fragments, see Table 1 and 2 in Appendix 8 'Interview analysis'. In addition, Kent MacLeod of NutriChem was interviewed, the manufacturer of the supplement MSB Neuropil's. The questions of the interview of MacLeod are found in Appendix 7. The results are addressed separately and are found under the header 'NutriChem'.

Regarding the experts, two pediatricians (B, C) and two dietitians (A, D) were interviewed. Expert A has over 25 years of experience as a dietitian and specializes in people with intellectual disabilities (dietician "verstandelijk gehandicaptenzorg" VG). Expert B is a pediatrician whose career has been centered around DS. Expert B has noticed that the topic of nutritional supplements is of great interest to the caregivers. This expert treats a group of about 300 children with DS of all age groups over an extended period. Expert C has been a pediatrician for 22 years and has set up a Downpoli consisting of a multidisciplinary team. Expert C reports seeing about 70 patients currently. In total, expert C has treated approximately 125 patients with DS. Expert D has been working as a dietitian in the intellectual disability sector for eight years, providing tailored advice. Expert D sees about 15 to 20 children with DS per year. Besides these four experts, Kent MacLeod was also interviewed. Kent MacLeod is a Canadian pharmacist and founder of the company NutriChem. With this company, MacLeod aims to provide his clients with personalized health solutions. He has had an interest in DS specifically for 30-40 years.

Five caregivers of children with DS were interviewed. The ages of their children with DS ranged between 7 and 17 years old and all children have their own nutritional issues. The extent of the use of supplements varied between the interviewed caregivers.

Sub question 1

Which nutrition-related problems or nutritional deficiencies are common among children with DS?

To be able to answer the first sub question, results of the literature research, questionnaire and interviews were analyzed. These results are shown below.

First of all, the available and relevant literature regarding nutrition-related problems or nutritional deficiencies among children with DS was analyzed. In general, people with DS have specific nutritional challenges, which include nutritional deficiencies and other food-related problems (Nordstrøm et al., 2020). Furthermore, the diet of people with intellectual disabilities tends to be poor compared to the general population (Ptomey et al., 2013). These nutritional challenges are thought to contribute to the development of comorbidities often seen in people with DS, such as obesity (Ptomey et al., 2013). It is therefore important to determine which particular nutritional challenges are common among children with DS.

Food-related problems

Firstly, difficulties in chewing and swallowing during the oral phase due to the absence of teeth, extensive tooth wear or other dental abnormalities have been reported in 55-60% of children with DS (Mazurek & Wyka, 2015; Nordstrøm et al., 2020). In addition, Nordstrøm et al. (2020) found that 64% of the children with DS have oral motor difficulties. Feeding difficulties are encountered when food textures are firm, gummy and chewy or rubbery, while purée, soft and creamy textures are considered more easily consumed by people with DS (Nordstrøm et al., 2020). Furthermore, Mazurek & Wyka (2015) found that gastrointestinal tract abnormalities appear in 12% of children with DS. Examples of these gastrointestinal tract abnormalities include trachea-oesophageal fistula, duodenal atresia, pyloric stenosis, Hirsch sprung disease, annular pancreas and anal/rectal atresia (Mazurek & Wyka, 2015). Both poor chewing of foods and a dysfunctional gastrointestinal tract can contribute to suboptimal digestion and absorption of nutrients, which can in turn lead to nutritional deficiencies (Cherpak, 2019). Secondly, the development of feeding and self-feeding abilities is often delayed in children with DS (Nordstrøm et al., 2020). Pisacane et al. (2003) reported that the mean duration of breastfeeding was 54 days in children with DS compared to 165 days in controls, which was mainly due to suckling difficulties. In addition, 13-40% of children with DS aged 0-3 months require a nasogastric tube for adequate nutrition and 2-5% of these children receive a gastrostomy tube (Génova, Cerda, Correa, Vergara & Lizama, 2018).

Considering these nutritional challenges, children with DS have been reported to prefer foods that are easy to chew and swallow, which consist of mostly simple carbohydrates (Mazurek & Wyka, 2015). As a result, these children generally have a poorer diet quality compared to the general population (Ptomey et al., 2013). More precisely, on average, people with DS consume low amounts of fruit and vegetables, fish and unsaturated fatty acids (Nordstrøm et al., 2015). Nordstrøm et al. (2015) found that merely 33% of people with DS consume fruit each day. In addition, daily consumption of vegetables among people with DS was reported in only 29% of the study population (Nordstrøm et al., 2015). This low consumption of fruit and vegetables resulted in lower carotenoid plasma levels and was associated with an increased BMI (Nordstrøm et al., 2015). A high prevalence of overweight and obesity was found among participants with DS (Nordstrøm et al., 2015). Besides this, 21% of the participants with DS consumed soft drinks several times a day (Nordstrøm et al., 2015). Because soft drinks contribute to the intake of sugar, frequent consumption of these drinks is also associated with the development of overweight (Nordstrøm et al., 2015). Furthermore, children with DS have a lower energy expenditure and therefore require 500-800 fewer calories per day than controls (Polfuss et al., 2018). However, they have been reported to actually consume more calories than children without DS (Magenis et al., 2018). This overconsumption of required calories is likely to be another cause in the high prevalence of overweight and obesity in children with DS (van Gameren-Oosterom et al., 2012). The exact reason for the overconsumption of calories is not known, however, reduced cognitive abilities might influence activity levels and food choices in children with DS (Jobling & Cuskelly, 2009). Specifically, Jobling & Cuskelly (2009) reported that

children with DS aged 11-18 years usually have a poor knowledge of healthy food and this could be a factor contributing to caloric overconsumption.

Nutritional deficiencies

Aside from a caloric overconsumption, the food preferences of children with DS might contribute to the development of several nutritional deficiencies (Ptomey et al., 2013). Firstly, Mazurek & Wyka (2015) concluded that deficiencies in vitamin C occur more often in children with DS compared to their peers. Secondly, it was shown that children with DS have an increased risk of low 25-hydroxy-vitamin D levels compared to children without DS, as 77% of the children with DS had a vitamin D deficiency in a study performed by Stagi et al. (2015). Considering the musculoskeletal consequence of a vitamin D deficiency and the fact that people with DS already have a decrease in bone mass due to their genetics, Kamalakar et al. (2014) suggested that monitoring vitamin D levels is important in people with DS. Thirdly, two studies showed that children with DS had lower folate and vitamin B12 levels as compared to children without this condition (Song et al., 2015; Sukla et al., 2015). This suggests a higher risk of developing both folate and vitamin B12 deficiencies in children with DS (Song et al., 2015; Sukla et al., 2015). However, contradicting results were reported regarding these children's homocysteine levels (Song et al., 2015; Sukla et al., 2015). Vitamin B12 and homocysteine are both important biomarkers of the one-carbon unit cycle, which plays a role in the epigenetic process of DNA methylation (Song et al., 2015). Deviating homocysteine levels can therefore result in an overall change of DNA methylation (Song et al., 2015). This overall change might be involved in the degeneration of neurons, leading to the development of, for instance, Alzheimer's Disease (Song et al., 2015). This highlights the importance of further research concerning the homocysteine levels in children with DS. Finally, deficiencies in vitamin A, E and K and other B vitamins were reported (Mazurek & Wyka, 2015; Ptomey et al., 2013). All of the mentioned deficiencies can give rise to constipation and a slow intestinal peristalsis (Mazurek & Wyka, 2015). Additionally, vitamin deficiencies might contribute to the development of cardiovascular diseases, cancer, obesity and other health comorbidities (Ptomey et al., 2013).

Besides the aforementioned vitamin deficiencies, deficiencies in minerals and other trace elements were also reported by several studies. Previous studies demonstrated that hair mineral analysis can be used to measure body mineral levels (Sahin et al., 2015). Gabreklis et al. (2020) found that hair zinc levels in school-aged children with DS were 14% lower compared to controls. This finding was replicated by Józefcuk et al. (2017). In addition, Saghazadeh et al. (2017) and Lima et al. (2009) demonstrated that zinc levels were also reduced in blood samples of people with DS. Furthermore, Ram & Chinen (2011) illustrated that zinc deficiencies are common among people with DS. According to previous studies, zinc deficiencies are a result of an altered zinc metabolism in individuals with DS (Lima, Cardoso & Cozzolino, 2009). It was noticed that these people have an abnormal distribution of zinc inside the body, while consuming a sufficient amount of zinc through their diet (Lima et al., 2009). Another important finding is that zinc deficiencies can contribute to the development of immunological abnormalities (Ram & Chinen, 2011). An example of such an immunological abnormality is coeliac, of which the prevalence is higher among people with DS (Nordstrøm et al., 2020). Moreover, Gabreklis et al. (2020) showed that hair iron levels in school-aged children with DS were lower compared with the respective control values. Furthermore, two studies by Mittal et al. (2020) and Jézefcuk et al. (2017) illustrated that the rate of iron deficiencies anemia was higher in children with DS compared to children without this condition, an interesting finding as this is associated with cognitive impairment. In addition, it was demonstrated that 5% of the children with DS aged <10 years and 14% of the children aged >10 years had iron deficiency anemia (Tenenbaum et al., 2011). Finally, multiple studies found a decreased hair content of copper, cobalt, calcium, chrome, vanadium and mercury in children with DS as compared to children without this condition (Gabreklis et al., 2020; Gabreklis et al., 2019; Józefcuk et al., 2017).

Saghazadeh et al. (2017) found lowered selenium and calcium levels in the blood samples of people with DS. This finding regarding calcium levels was confirmed by multiple studies (Kamalakar et al., 2014; Mazurek & Wyka, 2015; Ptomey et al., 2013).

On the other hand, hair phosphorus, magnesium, lead, iodine and silicon levels of children with DS exceeded the control values (Gabreklis et al., 2020; Gabreklis et al., 2019). Gabreklis et al. (2020) demonstrated that the abnormal trace element and mineral status in children with DS shares certain characteristics that are similar to those of other conditions, including obesity and growth delay. Therefore, they suggest that deficiency of essential elements may predispose these children to certain syndrome comorbidities and that correction/management of this may be considered as a potential tool for managing health and improving the quality of life (Gabreklis et al., 2020).

The cause of the aforementioned deficiencies is largely unknown. However, a possible explanation for this could be an insufficient nutritional intake or an abnormal metabolism in people with DS (Lima et al., 2009; Ptomey et al., 2013). Moreover, an altered amino acid profile or high levels of the parathyroid hormone might also contribute to the development of nutritional deficiencies and a different micronutrient status in children with DS (Saghazadeh et al., 2017). In addition, because of metabolic differences often observed in people with DS as compared to the general population, it is possible that there is a different nutritional need for people with DS (Izzo et al., 2018). The extra chromosome 21 seen in people with DS causes overexpression of all the genes that are located on chromosome 21 (Izzo et al., 2018). As a result, these overexpressing genes can exert an effect on other genes, like those that are associated with mitochondrial functioning and energy conversion (Izzo et al., 2018). Because this, people with DS often experience chronic oxidative stress (Izzo et al., 2018). This could lead to a higher need for antioxidants than in people without DS (Izzo et al., 2018).

Second, the results of the questionnaire were analyzed regarding this topic. 12% of the respondents indicated that their child has at least one (tested or suspected) nutritional deficiency. In the third row of Table 4, the nutritional deficiencies are depicted for each respondent, indicating that their child was (probably) deficient in at least one nutrient. The most frequently deficiencies that were mentioned by the caregivers include a vitamin D, iron and vitamin C deficiency.

Table 4: Types of nutritional deficiencies and nutritional supplements reported by respondents who had previously indicated a nutritional deficiency in their child with DS.

	Respondent	**Type(s) of deficiencies**	**Type(s) of supplement(s)**
Does the child have nutritional deficiencies?			
Yes, I have had this tested in the past year	1	Vitamin A Vitamin D Vitamin K	None
	2	Iron	MSB NeuroPlus (contains iron) Probiotics
	3	Vitamin A Vitamin B11 Iron Zinc	Best choice Multivitamin Debar Pharma Folium Katie Vitamin B6 Vitamin B11 Vitamin B12 Vitamin D Vitamin E Selenium Zinc Probiotics Melatonin Resveratrol EGCG
	4	Vitamin C Iron	MSB NeuroPlus

	5	Vitamin D Calcium	Vitalize Multivitamin kids Viterbi Buffered vitamin C Viterbi vitamin D3 25 mcg Vitamin C Vitamin D Fish oil (EPA/DHA)
	6	Vitamin D	Vitamin D
	7	Vitamin D Calcium	MSB NeuroPlus Vitamin D Calcium Fish oil (EPA/DHA)
	8	Iron	Orthiflor orthica original Etos huismerk multivitaminen Iron Probiotics
	9	Vitamin D	Vitamin D
	10	Vitamin D	Vitamin D
	11	Vitamin D Iron	Vitamin D Iron
	12	Vitamin D Calcium	Vitamin D Melatonin
Yes, I have had this tested over a year ago	13	Vitamin D	Vitamin D
	14	Vitamin D	Kruidvat multivitaminen voor kids Vitamin D
	15	Vitamin D	Vitamin D
	16	Vitamin D	Vitamin D
	17	Vitamin D Iron*	Vitamin D Unknown supplement
	18	Vitamin D Selenium Zinc	Vitamin C Vitamin D
	19	Zinc	Vitamin C Vitamin E Calcium Magnesium Zinc Resveratrol
	20	Vitamin B1 Vitamin B2 Vitamin B5 Vitamin B6 Vitamin B11 Vitamin B12 Vitamin C Vitamin D	Vitamin B1 Vitamin B2 Vitamin B5 Vitamin B6 Vitamin B11 Vitamin B12 Vitamin C Vitamin D

			Magnesium
Probably, but I have not had this tested	21	Vitamin C	Probiotics Unknown supplement
	22	Vitamin A Vitamin B1 Vitamin B5 Vitamin B6 Vitamin B11 Vitamin C Vitamin D Vitamin E Calcium Magnesium	MSB Vitamin C Vitamin D
	23	Unknown	Vitamin D
	24	Vitamin B1 Vitamin B11 Iron Iodine	Dagravit
	25	Iron	Davitamon 3-12
	26	Vitamin B12	Vitamin B12
	27	Vitamin C	Vitamin C
	28	Vitamin B12 Vitamin C Vitamin D Magnesium	Davitamon compleet weerstand
	29	Vitamin D	Vitamin D Zinc Probiotics Unknown supplement

Third, the results of the interviews concerning food-related problems and nutritional deficiencies among children with DS were analyzed and these are shown. All the experts indicated that children with DS have a higher risk of celiac disease. According to expert A this occurs ten times more in children with DS as compared to children without DS. Experts A and D mentioned that children with DS are more prone to lactose intolerance. All caregivers indicated that their children do not face these intolerances. In fact, children 3, 4 and 5 tested negative for nutritional intolerances such as coeliac and lactose sensitivity.

Expert A indicated that people with DS have a higher risk of type 1 diabetes, osteoporosis, gastroesophageal reflux, rumination, intestinal problems (Hirsch sprung's disease), obesity, and less growth and muscle tension during infancy. Expert B also argued that children with DS have a higher chance of heart defects, which causes a lower energy balance. In addition, expert A observed lower muscle tension in children with DS, which affects their oral motor skills. Caregivers 2, 3, 4, and 5 indeed mentioned difficulties with oral motor skills, indicating a difference in the chewing pattern, which may affect the food digestion. These caregivers reported difficulties with swallowing, sucking, and drinking, which occurred mostly in the first years of life. As children 4 and 5 had difficulties with drinking breast milk, which was partly due to low muscle tone, the children were tube-fed. Expert B mentioned that 25% of the children with DS are on tube feeding in their first years of life. However,

some children are tube-fed without any good or scientific reason. The expert's A and B agreed upon the fact that tube feeding needs to be as brief as possible, as tube-fed children have a higher chance of becoming overweight.

Experts A, B and D stated that a study suggests that children with DS have a lower metabolism or higher leptin secretion. However, this evidence is insufficient, and it is still being researched. Expert B indicated that the difference in calorie intake should be around 15 to 20% less than in their peers. Based on clinical experience, this expert advises a diet with lower calories to reduce the risk of becoming overweight. In addition, expert B and D indicated that children tend to overeat. Caregivers 1, 3, and 4 confirmed this and said that their children can keep eating and that their child does not feel saturated. Another factor which increases the likelihood of obesity, mentioned by the dietitians, is the lack of nutritional knowledge and the sensitivity to environmental influence. Caregiver 3 mentioned that the child is overweight, but according to the dietician, the current diet meets the guidelines.

The nutritional-related problems may result in nutritional deficiencies. All the experts indicated that children with DS are more prone to have a vitamin D deficiency. Moreover, these children are also more likely to develop an iron deficiency, according to expert D. Experts B and D noticed that a zinc deficiency is also a well-known abnormality, however, the experts mentioned that these studies are of such poor quality that no specific advice can be given. Further, medication may also have a negative effect on the absorption of vitamin D, calcium or folic acid, argue expert A and D. Caregivers 4 and 5 mentioned that their child has been tested for nutritional deficiencies early on. Caregiver 4 implied that these tests never showed any results concerning nutritional deficiencies. Caregiver 5 stated that the child had a zinc deficiency. However, this caregiver finds it unfortunate that vitamins are measured via the blood since it does not reflect anything about the nutrient content within the cells. The zinc deficiency disappeared after starting with supplementing MSB NeuroPlus. Caregiver 5 indicated that MSB NeuroPlus is given not only to solve nutritional deficiencies, but also to counteract long-term effects, such as the aging processes.

According to MacLeod, people with DS generally have several consistent nutritional issues like malabsorption of nutrients; increased oxidative stress and, therefore, an increased need for antioxidants; altered methylation pathways that affect the way folic acid, vitamin B12 and choline are utilized and many more issues like these. In addition, people with DS also have more general issues, such as vitamin D deficiencies, which are common in the general population of Canada. Moreover, there are additional deficiencies caused by feeding challenges in individuals with DS. Thus, nutritional deficiencies are known to have a higher prevalence among people with DS, which is also observed in the lab that MacLeod built to test the nutrient levels of children with DS. Currently, when MacLeod looks at individualizing supplements, he largely focuses on the microbiome to increase the absorption of nutrients as opposed to just providing people with more nutrients when they are deficient in those.

Conclusion

To conclude, there are several nutrition-related problems and nutritional deficiencies that are common among children with DS, including a vitamin D, iron, vitamin C and zinc deficiency. Besides this, children with DS often experience problems with oral motor skills, such as chewing and suckling, especially in the first years of life. Furthermore, children with DS have an increased likelihood of developing obesity.

Sub question 2

What nutritional supplements are currently given by caregivers to their children with DS and to what extent?

To be able to answer the second sub question, results of the exploratory internet search, questionnaire and interviews were analyzed. These results are shown below.

First, the exploratory internet search indicated often-used supplements by caregivers of children with DS. The results were used to construct answer options for the questionnaire, to formulate questions to ask in the interviews with caregivers and experts and to determine which supplements would be investigated in the market research.

Second, the results from the questionnaire were analyzed regarding this sub question. Figure 2 shows the number of caregivers that provide their child with nutritional supplements. Caregivers could indicate that they did provide their child with nutritional supplements, did not, or did not but had done so in the past. It can be seen that the majority of the respondents (61%) do provide their child with supplements. For the three different responses, the mode and median of the physical health and eating behavior scores of the respondents' children were assessed, as depicted in Appendix 2, Table 4. For all groups, both the mode and the median were 'Good' on physical health as well as eating behavior. The age at which supplementation was started for people who indicated that supplementation was provided, is depicted in Appendix 2, Figure 1. Of the caregivers that provide nutritional supplements to their child, almost 50% started with this at the age of 0. For the respondents who indicated that they provided nutritional supplements to their child, it is indicated whether or not their child's physician is aware of this in Appendix 2, Figure 2. Here, it can be seen that most respondents (69%) have notified their child's physician of the use of nutritional supplements.

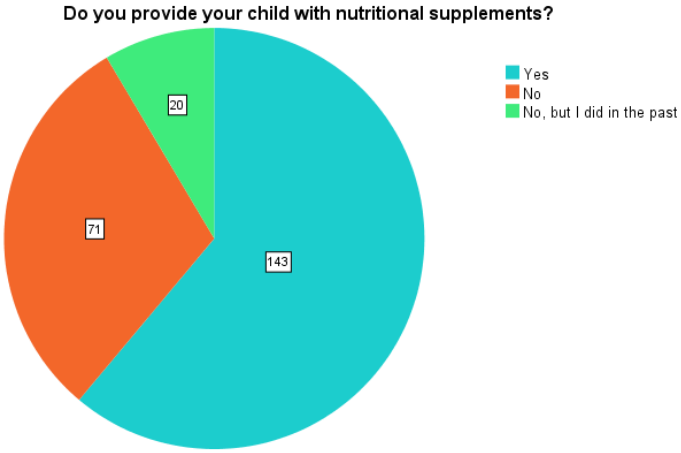

Figure 2: Number of caregivers providing their children with nutritional supplements (n=234).

The deficiencies mentioned under sub question 2, as depicted in Table 4 (page 20), were compared to the supplements that were provided by these caregivers. It can be observed, in the fourth row of Table 4, that the provided supplements often contain nutrients that the children are (probably) deficient in, sometimes in combination with other nutrients. In Figure 3, it can be seen that the most often provided nutritional supplement by caregivers is vitamin D, followed by a general multivitamin, vitamin C and multivitamins aimed at people with DS.

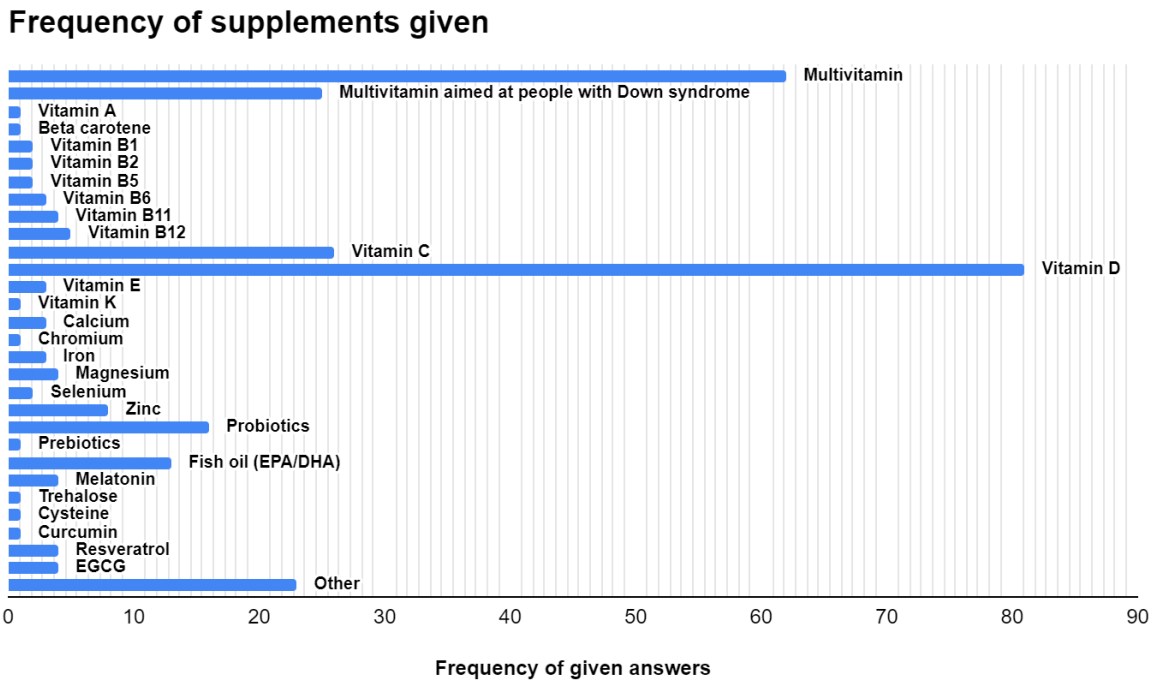

Figure 3: Frequency of the indicated types of supplements that respondents provide to their child (n=143). Respondents could select multiple types of supplements.

When looking at dosage of the most frequently supplemented nutrients, it can be seen that Vitamin D is often provided in amounts ranging from 7,5 mcg to 40 mcg, with most respondents indicating that they give 10 mcg, which is the recommended amount (Stichting Voedingscentrum Nederland, 2016). Two outliers were observed, where respondents reported to give 800 mcg or even 25 mg Vitamin D. Vitamin C is reported to be provided in amounts that vary a lot. Most respondents, however, reported vitamin C dosages ranging from 100 to 1000 mg. The recommended daily intake for vitamin C ranges from 20 to 75 mg for children aged 0-17 (Stichting Voedingscentrum Nederland, 2016). Most respondents indicated to provide more. However, there is no upper limit for vitamin C (Stichting Voedingscentrum Nederland, 2016). For the general multivitamins, the brands Davitamon and Kruidvat were most often reported. Respondents providing their children with general multivitamins from these brands mostly reported giving the multivitamin in the dosage recommended on the label or half this dosage. For both Davitamon and Kruidvat, these dosages exceed the daily value (DV) for vitamin D (Appendix 9, Figures 4, 5 & 6). For the multivitamins specifically aimed at people with DS and the general multivitamins, the ingredients and dosages can be found on the labels in Appendix 9, Figures 1 & 2. In the questionnaire, respondents indicated the amount of the multivitamin that was provided. It can be seen that children receiving MSB NeuroPlus often get higher doses of B vitamins than recommended, as these vitamins are highly concentrated in MSB NeuroPlus. When looking at the label of Nutrivene-D, which can be found in Appendix 9, Figure 2, it can be noticed that most nutrients in this supplement exceed DV's. As a result, children receiving this supplement are very likely to ingest higher amounts of these nutrients than recommended. More detailed information on this can be found under sub question 5: 'What supplements linked to nutritional deficiencies seen in children with DS are currently on the market, what do they claim and do they contain safe doses?'.

Figure 4 shows which brands are most often given by caregivers of children with DS. The brand 'Davitamon' was indicated most frequently, followed by store brands and NutriChem, the producer of MSB NeuroPlus. Most of the caregivers indicated that they bought their supplements at the drugstore, followed by purchases online, inside the European Union (EU) as depicted in Appendix 2, Figure 3.

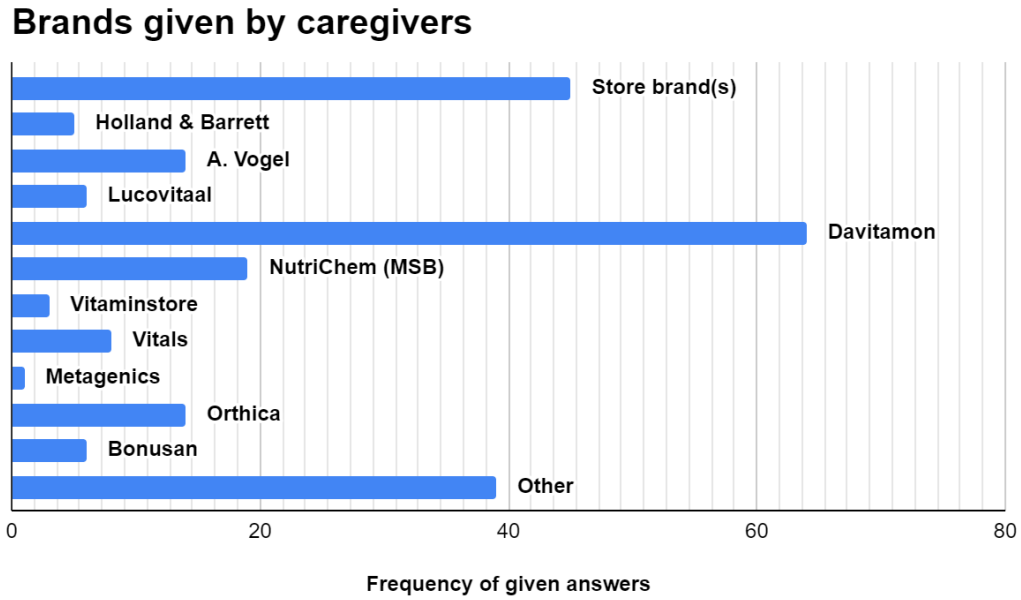

Figure 4: Frequency with which respondents indicated certain brands (n=143). Respondents could select multiple brands.

Third, the results from the interviews were collected to answer the second sub question. Caregiver 1 reported to provide vitamin C and Davitamon to their child, which is more implemented in the winter months. Caregiver 2 provides the child with the following supplements; NuTriVene-D, omega-3 with the DHA enriched, Huperzine A, occasionally Probiotics, Choline and Lutein. In the evening, polyphenol and Hesperidin are given. Besides the standard protocol, caregiver 2 indicated they also follow the detox protocol, which is advised to follow once a week or once a month. This protocol consists of the following supplements; Lycopene, Glutathione, Vitamin C, Melatonin, Blueberry or Raspberry Polyphenols, Omega-3 and Alpha Lipoic Acid. Finally, caregiver 2 mentioned that she occasionally stops giving Huperzine A to the child, as this accumulates in the body. This caregiver spends around 100 euros a month on these supplements. Caregiver 3 provides a multivitamin in the form of gummies during the winter. Caregiver 4 indicated that their child uses Vitalize complete A till Z. Caregiver 4 has switched to Vitalize, due to the high prices of MSB NeuroPlus and NuTriVene-D. Caregiver 5 mentioned that they use half of the recommended dose of MSB NeuroPlus, so the child experiences the positive effects of the supplements, alertness, with a good skin, good stools, etc., without becoming hyper. This caregiver gives vitamin D, extra vitamin C, omega-3 fatty acids (krill oil, EPA and DHA) and probiotics. Caregiver 5 indicated spending 30 euros a month on supplements (MSB NeuroPlus and some separate vitamins/minerals) and values natural origin over price. However, price will become important if supplements become too expensive, such as the customized MSB NeuroPlus supplement.

Conclusion

All in all, it can be concluded that vitamin D, general multivitamins (Davitamon, Vitalize), vitamin C, multivitamins aimed at people with DS (NuTriVene-D, MSB NeuroPlus), probiotics and fish oil are the most provided nutritional supplements by caregivers to their children with DS. Regarding the dosages of these supplements, different conclusions can be drawn. Vitamin D is often provided in the recommended amount, whereas most caregivers provide their children with more vitamin C than is advised. Concerning the general multivitamins, most caregivers reported to give the dosage recommended on the label or half this dosage. However, most multivitamins exceed the DV for vitamin D. Additionally, with regard to the multivitamins aimed for people with DS, many nutrients in these supplements exceed DV's.

Sub question 3

What is the motivation of caregivers of children with DS to provide nutritional supplements to their children and based on what information do they do this?

To be able to answer the third sub question, results of the exploratory internet search, questionnaire and interviews were analysed. These results are displayed below.

First, the exploratory internet search provided a first impression on where caregivers found the information that motivated their choice regarding the use of nutritional supplements. The Facebook pages of SDS and the caregivers groups provided advice from different caregivers. On the SDS page, in the main posts, no claims were made on nutritional supplements, while in the comments on these posts, people showed to be interested in this, or already provided their opinions on this subject. These opinions vary from people who are scared of what some others provide their children with, to people who share their positive experience with supplements and actively recommend them. On the Facebook pages that focus on one nutritional supplement, most users seem to be pro-supplement use. In some of the posts, advice is asked about for example dosage, and in some posts orders for the supplement are combined.

Second, the results of the questionnaire were analysed. In Table 5 it is shown how many caregivers reported nutritional deficiencies for each answer option to the question 'Do you provide your child with nutritional supplements?'. Across all three groups, most caregivers indicated that they were uncertain of the nutritional status of their child as they had not had this tested recently.

Table 5: Number of caregivers reporting nutritional deficiencies across the three groups of nutritional supplementation. For each of these three groups of nutritional supplementation, percentages are indicated for whether they know or suspect their children have nutritional deficiencies or not.

Does your child have nutritional deficiencies?	**I give my child nutritional supplements**	**I do not give my child nutritional supplements**	**I do not give my child nutritional supplements, but I did in the past**
Yes, I have had this tested in the past year (5%)	11 (8%)		1 (5%)
Yes, I have had this tested over a year ago (3%)	8 (6%)		
Probably, I assume this based on my child's diet (4%)	9 (6%)		
No, I have had this tested in the past year (9%)	10 (7%)	12 (17%)	
No, I have had this tested over a year ago (4%)	6 (4%)	3 (4%)	1 (5%)
I am not sure, I have never had this tested (72%)	**96 (67%)**	**55 (77%)**	**18 (90%)**
Other (2%)	3 (2%)	1 (1%)	

Figure 5 shows the different motivations for providing nutritional supplements by respondents who are currently providing these to their child. Most frequently, respondents indicated that they did this to enhance their child's immune system, followed by recommendations from their child's physician. Figure 6 presents the motivation to stop providing nutritional supplements by respondents who provided them in the past, but not anymore. For this question, it can be noticed that the motivation 'I don't have a specific reason for this' was most frequently indicated, as was the option 'other'. For this option, most respondents indicated that they felt that their child did not need supplementation. Respondents could also choose the option 'I observed adverse effects' for this question, but this was never indicated. Finally, Figure 7 shows what motivates respondents who do not provide supplements at all, for which it can be observed that most respondents do not think that this is necessary, or they have never thought about providing nutritional supplements.

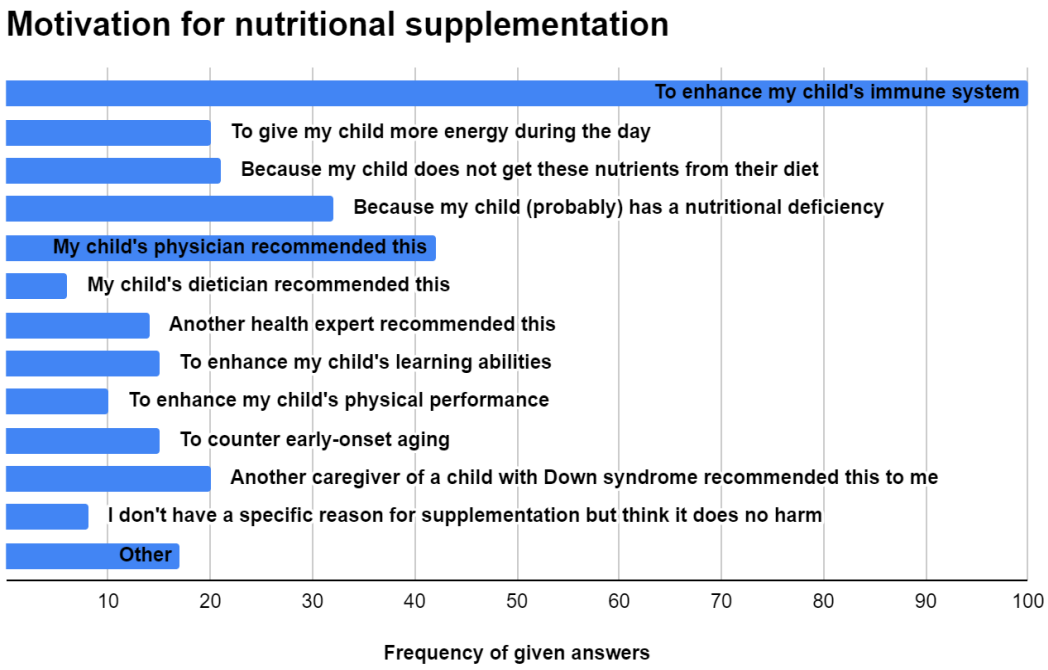

Figure 5: Frequency of motivations for giving nutritional supplements given by respondents who are currently providing their child with nutritional supplements (n=143). Respondents could indicate multiple motivations.

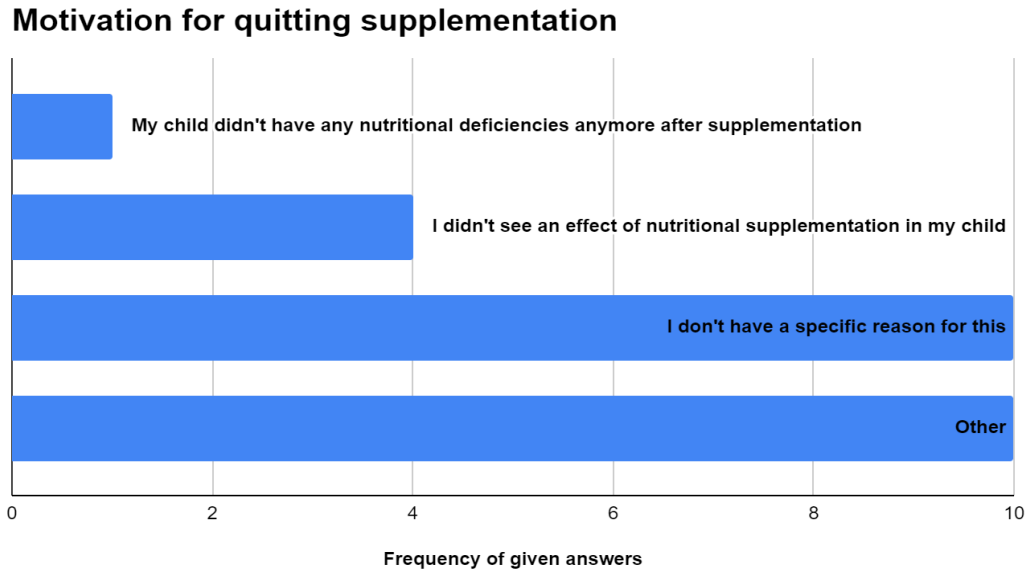

Figure 6: Frequency of motivations given for quitting nutritional supplementation by respondents who provided their child with supplements in the past (n=20). Respondents could indicate multiple motivations.

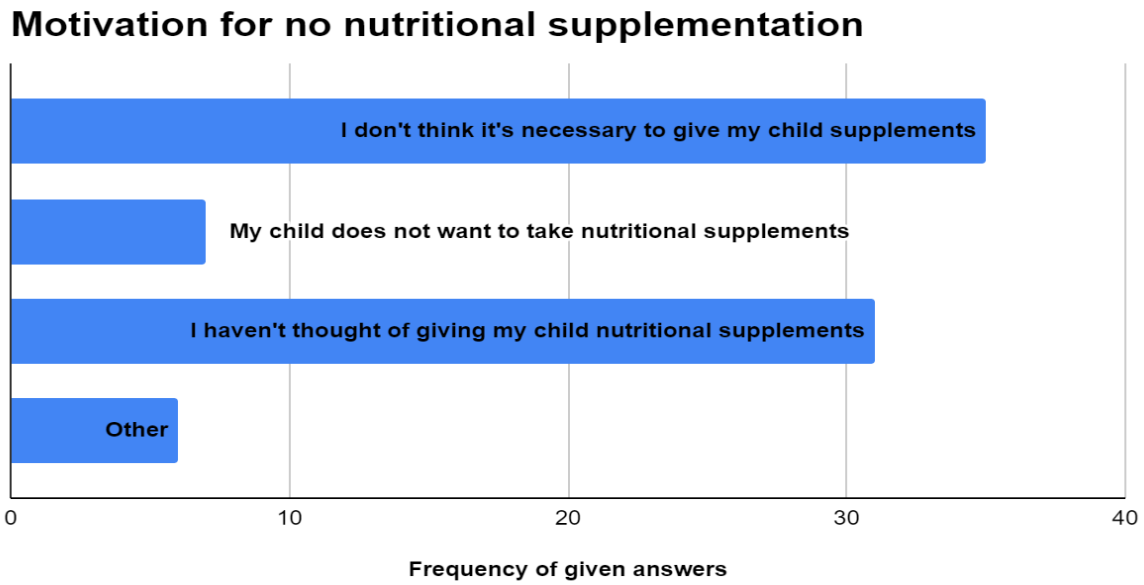

Figure 7: Frequency of motivations for not giving nutritional supplements by respondents who do not provide their child with nutritional supplements (n=71). Respondents could indicate multiple motivations.

Figure 8 shows the source from which the caregivers required information regarding (the use of) nutritional supplements. It can be seen that most caregivers did not require any information regarding nutritional supplements. Most caregivers that did require information, required this via a physician, the internet, social media or people in their network.

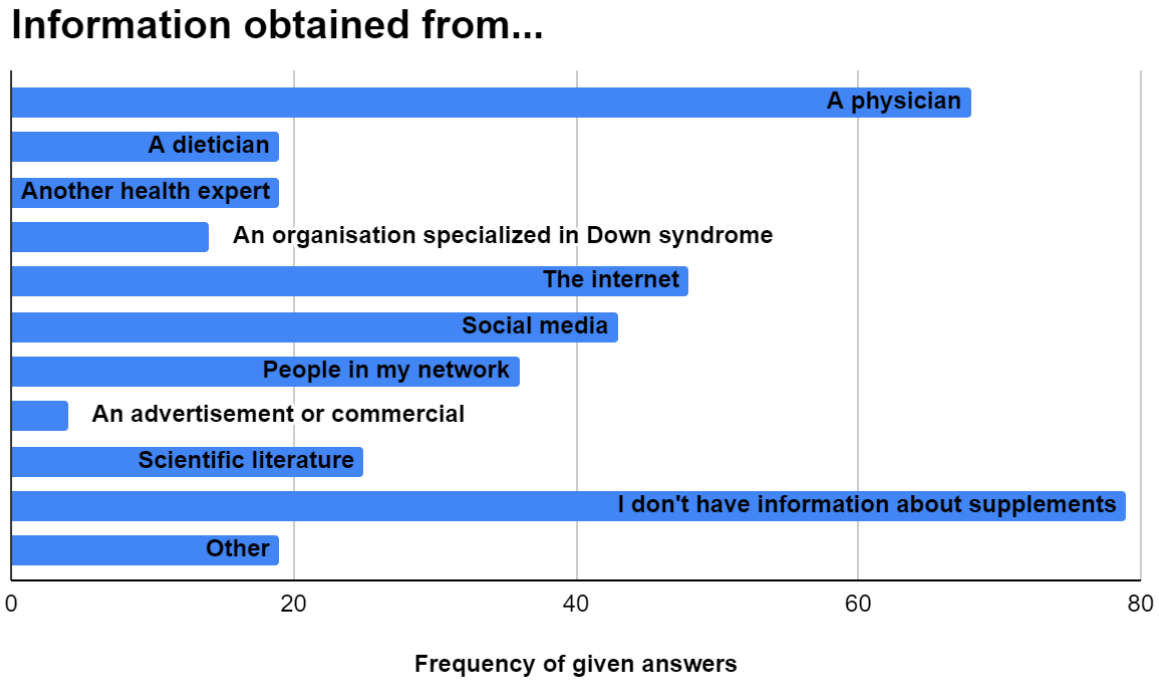

Figure 8: Source from which the caregivers required information regarding nutritional supplements (n = 234). Respondents could indicate multiple sources.

Caregivers were asked about their experience with nutritional supplements. This question was asked to both caregivers still providing their child with nutritional supplements and to caregivers who have stopped providing their child with nutritional supplements. Of the first group, the majority reported a good experience. Of the second group, the majority reported a neutral experience. This last group also indicated a poor experience more often than the first group. These results can be seen in Appendix 2, Figure 4.

Third, the results from the interviews were examined. The caregivers, motives for the use (or not) of supplements are strongly divided. Caregivers 1, 2, 4, and 5 indicated that supplements have a positive effect on the development and overall health of their child. It is incredibly valuable, according to caregiver 2, to be able to help the child with cognitive development utilizing supplementation. Caregivers 2 and 5 have searched a long time for supplements and finally chose NuTriVene-D (caregiver 2) and MSB NeuroPlus from NutriChem in Canada (caregiver 5). Caregiver 1 is rather neutral, and says that using supplements might be beneficial, but nutrients should be mainly obtained from basic nutrition. And, this caregiver mentioned that conversations concerning supplement usage are rare in their environment. In addition, this caregiver argued that no exception is made for the child with DS regarding supplement use. However, the caregiver noticed that the child with DS is more affected by the nutritional supplements, because the child has a weaker health in comparison with the siblings. Nevertheless, this caregiver believes that the effort involved with utilizing supplementation outweighs the pros of supplement use. Caregiver 3 indicated to be somewhat old-fashioned and thinks that children do not need nutritional supplements and therefore excludes the opinions of other caregivers regarding nutritional supplements. Caregiver 4 indicated that every doctor mentions that vitamins are not necessary, but caregiver 4 disagrees. Caregiver 4 did research and discussed the topic of supplements with fellow caregivers, and is convinced that supplements are beneficial.

All but one of the caregivers were familiar with NuTriVene-D and MSB NeuroPlus. Caregiver 2 uses NuTriVene-D, which is a conscious choice. This caregiver indicated that NuTriVene-D was more attractive, as they conduct more consistent studies and understand more about performing high-quality research. However, caregiver 2 thinks MSB NeuroPlus is more often used due to the greater awareness and says that using MSB NeuroPlus is still more beneficial than using no supplements. This caregiver indicated that it is impossible to say something about the effect of supplements based on one person. However, caregiver 2 is convinced that nutritional supplements have a positive effect on the development of the child and tries to focus on these positive developments. This caregiver noticed for example that the child had a growth spurt because of Huperzine A and another antioxidant, which was also confirmed by many other caregivers from a Facebook group. In contrast, caregiver 4 indicated that their child uses Vitalize complete A till Z, which contains a lower dose of nutrients compared to MSB NeuroPlus or NuTriVene-D. This caregiver currently uses Vitalize due to the lower costs and because this caregiver is curious about the effect of this lower dose of vitamins/minerals. This caregiver preferred NuTriVene-D, as this supplement led to the best effect on bowel movement. Caregiver 5 chooses MSB NeuroPlus over NuTriVene-D, due to the fact that NuTriVene-D had to be given more often during the day and contained an excessively high dose of vitamin A. In addition, the formula contains zinc but not copper, while these two nutrients stimulate each other. Caregiver 5 mentioned that the previous version of MSB NeuroPlus entailed very high levels of B vitamins, which shocked a lot of caregivers. However, in the new formula of MSB NeuroPlus, vitamin B6 is replaced by the active form, namely P5P because research showed that children with DS lacked a compound to convert B6 to its active form. Caregiver 3 once saw a Facebook post about a caregiver who gave their child MSB NeuroPlus supplements and their child turned yellow and the urine turned brown, so this caregiver is rather skeptical. This caregiver made the deliberate decision not to give the child any nutritional supplements, due to the fact that the doctor of this child explained that there are no scientifically proven benefits.

Caregiver 2 and 4 indicated that the evidence based information about supplement usages among children with DS is still very limited in the Netherlands, caregiver 4 pointed out that in the United

States and Canada, there is more evidence-based information. Caregiver 4 specifically mentioned paying attention to the RDA of different supplements. However, this caregiver also mentioned the uncertainty that prevails in regard to the use and dosages of the supplements, that is why this caregiver sometimes stops for a week or three. Caregiver 2 indicated that there is not much hope for extensive research due to decreasing numbers of newborns with DS. This makes children with DS a rather uninteresting target group for research. Unless there is a linkage to Alzheimer's research, argued caregiver 2. If Alzheimer's research continues to advance, DS research can also benefit from this. Caregiver 5 indicated that pediatricians do not recommend supplements, because there is no scientific evidence for it. However, this caregiver still uses MSB NeuroPlus, because the caregiver noticed positive effects in the child. Occasionally caregiver 5 stops giving MSB NeuroPlus, but within a week, the child was already more tired, less alert and got poorer skin. According to caregiver 5, caregivers should do more research into the causes of higher values of vitamins or minerals in the blood of their children. This caregiver indicated that, when looking for the cause of higher values of nutrients in blood, most of the high values have a clear solution, for example due to the intestinal function. Caregiver 4 conducted her own research, after doctors recommended not to give supplements. Caregiver 2 mentioned a feeling of neglect by the medical experts, as these professionals mentioned they don't prescribe nutritional supplements. She concluded that the medical protocols are more focused on treatment rather than on the prevention of certain diseases. This is something expert B also struggles with. This expert is often asked for advice about whether caregivers should give their children multivitamins. This expert does, based on scientific evidence, not subscribe supplements to children with DS. Nevertheless, he still noticed caregivers giving the supplement anyways. On the contrary, caregiver 3 indicates to have complete trust in the medical specialist of the child.

Conclusion

To summarize, most caregivers (initially) provide their DS children with nutritional supplements to enhance their immune system, to follow the recommendations from their child's physician and to improve the development and overall health of their child. Subsequently, these caregivers continue providing supplements to their DS children because they mention observing positive effects. The sources from which most caregivers require information regarding the use of nutritional supplements are a physician, the internet, social media or people in their network (e.g. fellow caregivers).

Sub question 4

What is the opinion and advice of doctors, dietitians and (another expert(s) on the provision of nutritional supplements to children with DS?

To be able to answer the third sub question, results of the interviews were analysed. All the experts were critical on the usage of supplements; experts A and D indicate a clear preference for obtaining nutrients from basic foods, and if necessary, supplements may be used to replenish for any deficiencies. Expert B stated to have a more positive perspective on supplements if the labels were more realistic, as frequently claims are stated which are unproven. Next to that, expert C considered supplementation from a different perspective; caregivers with a child with DS shouldn't endlessly search for a new way to learn their child more than they are capable of, instead caregivers should accept and enjoy their peculiarities. Expert A stated that practice-based proven theory is sometimes taken into account, as the expert mentioned not to immediately disapprove a supplement if a caregiver is interested in giving it to their child. However, the expert will always search for information about the concerned supplement. The supplement should, by all means, not cause any damage to health. Expert D indicated that caregiver reasoning for giving supplements is often "no harm, no foul", however, supplements can certainly cause damage to one' s health.

Experts A en D indicated that they haven't heard about supplements that are specifically developed for people with DS. However, MSB NeuroPlus and NuTriVene-D sounded familiar to expert D. Expert B knew MSB NeuroPlus and NuTriVene-D, but indicated that MSB NeuroPlus entails high levels of B1, B6 and B12, which is alarming. Expert C knew NuTriVene-D, but mentioned that only a few clients mention it. Experts B and C state that there are fashion trends visible in providing nutritional supplements for children with DS.

All experts implied that there is nothing included within the DS treatment guidelines about the use of dietary supplements. The treatment guidelines only refer to the guidelines of healthy nutrition, as these guidelines are no different for children with DS. All experts agree that nutrients should come mainly from the basic diet. However, expert C specifically points out that vitamin D can be taken in addition. Expert D advises to recommend supplements based on individual needs, as it is too difficult to prove anything scientifically about nutrition in general, given the wide diversity. Expert C agreed and indicated that as a pediatrician, global nutritional advice is given, but when a detailed advice is needed this is forwarded to a dietician. Expert B mentioned that the dosages for children with DS should be different than for children without DS. A child with DS needs about 1/10 melatonin of what a child without DS would need, the expert mentioned as an example. This may also apply to other supplements, however expert B is not aware of studies confirming this hypothesis. Therefore, expert B only recommends supplements that contain less than 100% of the Recommended Dietary Allowances (RDA).

Expert B, C and D give advice that is only based on evidence. They implied that giving advice concerning supplements based on other caregivers' experiences is not reliable. All experts indicated that the level of knowledge in general varies a lot among caregivers. Expert B and C mentioned that the level of knowledge is mostly superficial. Expert D also mentioned that most of the caregivers often do not realize that more than 100% RDA is not conducive to health. In addition, expert A and B indicated that there is not enough scientific evidence for the effectiveness of nutritional supplements for children with DS. This subject is interesting for experts in the field, as expert C conducted research on NuTriVene-D and expert B conducted a study about MSB NeuroPlus. However both experts have not found significant evidence regarding the effectiveness of supplement in children with DS. Expert B will prescribe supplements when there is enough scientific evidence backing effectiveness. Expert A indicates that scientific evidence is of most importance, but also provides practice-based advice.

According to MacLeod, it is reasonable to provide multivitamins to children with DS, based on the observation that most individuals do not obtain sufficient nutrients from their diet. Moreover, he mentioned that there are studies in which the effectiveness of multivitamins is shown in children

without DS, but not in children with DS. MacLeod finds it strange that you would give a child without DS a supplement as it has beneficial effects but then withhold this from a child with DS. According to MacLeod, using a multivitamin can cover a lot of issues.

Conclusion

To conclude, pediatricians and dieticians have a clear preference for obtaining nutrients from the basic diet. However, MacLeod does find it reasonable to provide multivitamins to DS children, because it is observed that most individuals do not obtain sufficient nutrients from their diet. Therefore, MacLeod suggested that using a multivitamin can cover a lot of issues. In contrast, the interviewed pediatricians and dieticians only give advice when it is based on evidence, which still lacks in their opinion. As a result, it can be concluded that the pediatricians and dieticians are critical concerning the use of nutritional supplements for people with DS.

Sub question 5

What supplements linked to nutritional deficiencies seen in children with DS are currently on the market, what do they claim, and do they contain safe doses?

To be able to answer the fifth sub question, results of the exploratory internet search and market research were analysed. These results are shown below.

First, the results of the exploratory internet search served as a foundation to conduct the market research as it indicated supplements (specific for people with DS), such as MSB NeuroPlus and NuTriVene-D, that are on the market and commonly used.

In this chapter, a few of the most frequently used supplements for people with DS are described. The supplements described here are mostly from manufacturers in the USA or Canada, and not from the Netherlands or other EU countries. This is because the European Food Safety Authority (EFSA) has specific rules concerning claims made about supplements (Pronk, 2005). EFSA distinguishes between health claims and medical claims. According to EFSA guidelines, health products, like nutritional supplements, may only claim to maintain normal health, while medical products like drugs may also claim to prevent, treat or cure diseases. In addition, EFSA guidelines state that information about health products cannot refer to specific diseases with the claims on their product (Pronk, 2005). For this reason, it is not allowed that Dutch or European supplement providers aim their product at people with DS, or claim that their supplements will help prevent concomitant issues of DS. Therefore, no Dutch supplements specifically aimed at people with DS were found. In countries outside the European Union these claims are sometimes allowed, which is why some supplements from Canada or the United States supplements aimed at people with DS have been found. These are discussed below. The labels of all the supplements mentioned in this chapter are included in Appendix 9.

Multivitamins aimed at people with DS

In this subchapter, the nutritional supplements MSB NeuroPlus, NuTriVene-D and LTO3 are further explained.

- MSB NeuroPlus (Nutrichem Pharmacy, Ottowa, ON, Canada)
Price: $59 for 50 gram
Intake recommended by supplier: ½ - 4 scoops, depending on age and weight.

NutriChem is a Canadian company that specializes in personalized health solutions. They offer tailored supplements, based on a "body chemistry balancing test". However, they also provide a standard MSB NeuroPlus supplement, which is commonly used in the Netherlands by caregivers of children with DS, as was seen in the results of our questionnaire. MSB NeuroPlus is a supplement that is created and produced by NutriChem. It is a supplement in powder or capsule form. On the NutriChem webpage about MSB NeuroPlus it says: "*NutriChem has been supporting the nutritional needs of individuals with Down Syndrome for over 30 years.*". This supplement also forms the basis for the personalized supplements for people with DS that NutriChem also produces (NutriChem, n.d.).

When looking at the ingredients of MSB NeuroPlus, several things can be noticed. Firstly, this supplement is rich in ingredients, with 36 ingredients listed on the label (Appendix 9, Figure 1). According to NutriChem, this combination of ingredients will provide better vitamin absorption, neuroprotection against Alzheimer's, anti-inflammatory functions, and improves mood and cognitive functioning. Nutrichem also claims that MSB NeuroPlus promotes microbiome health and that they only use high-quality ingredients. "*As with all of NutriChem's products, all of the ingredients in MSB NeuroPlus are high-quality pharmaceutical grade, meeting or exceeding all U.S. Pharmacopeial Convention (USP) Reference Standards*" (NutriChem, n.d.). Compared to some of the more common multivitamins in the Netherlands (Kruidvat and Davitamon multivitamin for children were used for comparison), this multivitamin is especially unique in the addition of botanicals like resveratrol, lutein or curcumin (NutriChem, n.d.; Davitamon, n.d.; Kruidvat, n.d.). The second thing that can be noticed, is that when comparing the amounts of the different ingredients present in MSB NeuroPlus

to the Dutch recommended DV's, some of the micronutrients well exceed recommendations. For example, the B vitamins (B1, B2, B5, B6, B12) are in higher dosage than the recommended amounts. About the composition of their MSB NeuroPlus supplement, NutriChem states that "*Research in Trisomy 21 is continuously evolving and so does the MSB NeuroPlus formula.*", which is why "research-driven reformulations" have taken place already a few times (NutriChem, n.d.).

- NuTriVene-D (International Nutrition, Middle River, MD, USA)
Price: $58 for 153 gram (294 capsules)
Intake recommended by supplier: 2-14 capsules, depending on weight.
The NuTriVene-D line of multivitamin supplements is available in tablets or powdered form and contains over 40 vitamins, minerals, and other nutrients. In its name or on its label, people with DS are not mentioned as the target group, but the description on the website states that some of the ingredients may aid in the metabolic disturbances that are observed in DS (NuTriVene, n.d., a). These claims are based on the literature available on some of the ingredients in NuTriVene-D and, according to the information on the website, a case study that is performed with NuTriVene supplements specifically. However, when checking the case study report that is referred to on the site, this is a reference to a more general review and not a case study with NuTriVene as was reported (Lubec & Engidawork, 2002). Therefore, it remains uncertain what the specific effects of NuTriVene are, as PAHL consultancy could not find an article in their cited sources that supported their claims.

From the label of the NuTriVene Daily supplement powder it can be observed that the DV is surpassed by many nutrients present in the supplement (Appendix 9, Figure 2) (NuTriVene, n.d., b). Moreover, some ingredients even exceed the upper limit, like vitamin B6 and zinc. Like in NutriChems MSB NeuroPlus, this supplement also contains some ingredients that are not commonly present in general multivitamins that can be purchased in the Netherlands. For example, specific amino acids are included, as well as some botanicals like lutein, lycopene or silica.

NuTriVene offers the NuTriVene-D supplementation program, which includes daily supplements, daily enzymes and a night time formula. According to their website, it includes minerals, amino acids, and other nutrients children with DS may require during the day (NuTriVene, n.d., c). NuTriVene claims that children with DS may have a deficit in digestive enzymes and therefore they might encounter some problems with the absorption of nutrients. The Daily Enzyme-product consists of digestive enzymes, that help with better absorption of nutrients from the diet and dietary supplement. NuTriVene states that the Night-Time formula has an effect on physiological functions between diner and breakfast. The company implies that the supplements help with sleep disturbance, premature aging, and growth (NuTriVene, n.d., c).

- LTO 3 (SmartVital, Maastricht, The Netherlands)
Price: €39,50 for 90 capsules
Intake recommended by supplier: 2-3 capsules daily, depending on weight.
LTO3, L-Theanine Omega 3, is a supplement, mostly seen in tablet-form. It is available from multiple brands, e.g. Herb-e-Concept, Lucovitaal, Vitaplanet, Nova Vitae and Natuurlijk presteren. However, most LTO3 supplements contain similar ingredients. Here, information was obtained from the informational website 'LTO3.org' and the website of distributor SmartVital, which sells the brand Herb-e-Concept. LTO3 typically consists of L-Theanine, Sementis complex (fish roe), and Blue Mugwort (LTO3, n.d., a) (Appendix 9, Figure 3). According to the LTO3 site, this combination of ingredients works synergistically, if combined in the correct dose (LTO3, n.d., a). L-Theanine is claimed to increase dopamine levels, ability to concentrate, relaxation, and to protect the brain from neurotoxins. Sementis is said to contain a high amount of antioxidants that are effective in reducing stress and fatigue. Lastly, the site claims that the Blue Glide herb serves to support the nervous system and has a calming effect on physical restlessness (LTO, n.d., b). LTO3 is originally Canadian, but it is also available in the Netherlands (LTO3, n.d., a). Besides this, LTO3 is a supplement that is 100% natural, and according to the LTO3 site, it consists of very pure and high-quality ecological ingredients (LTO3, n.d., a).

The ingredients in the LTO3 supplement from SmartVital are all botanicals, which is why no recommended DV is available for these bioactives. In the Netherlands, due to regulations, it is not legal to be more specific about the diagnosis and symptoms for which LTO3 has a positive effect. No claims are made on the working mechanisms, effectiveness or specific target groups that could benefit from this LTO3 supplement on the SmartVital website (SmartVital, n.d.). However, on the Canadian Herb-e-concept site also selling LTO3, it is claimed that LTO3 promotes concentration ability, improves sleep condition, and helps with relaxation (Herb-e-concept, n.d.). By this, it is claimed to help with the reduction of panic, stress, anxiety, and with symptoms which are associated with ADD and ADHD (Herb-e-concept, n.d.).

General multivitamins

Davitamon multivitamins and Kruidvat multivitamins are general multivitamins not aimed at people with DS. These multivitamins were both mentioned frequently in the questionnaire that was conducted, which is why it was decided to provide some information on these supplements here. Due to the aforementioned EFSA regulations on health claims, Dutch nutritional supplements usually only have EFSA approved health claims on their webpages or labels.

- Davitamon Junior 3-12 Gummies (Omega Pharma Nederland B.V., Rotterdam, The Netherlands)
Price: €19.99 for 60 tablets
Intake recommended by supplier: 1 tablet daily.

The approved EFSA claims on the Davitamon website are that the Junior supplement supports the immune system, aids in bone growth and helps to maintain strong teeth. It is further mentioned that the Junior 3-12 supplement is adapted to the specific needs of children aged 3 and older, and that this supplement is a good addition to a normal diet. The supplement contains several B vitamins, vitamin C, D3, E and Zinc (Appendix 9, Figure 4). Only vitamin D3 exceeds the recommended intake value (200%), which is something that is also advertised on the bottle as "met extra vitamine D" (Davitamon, n.d., a).

- Davitamon Junior 3+ Kauwtabletten (Omega Pharma Nederland B.V., Rotterdam, The Netherlands)
Price: €17.99 for 120 tablets
Intake recommended by supplier: 1-2 tablets daily, depending on age.

Like the Davitamon Junior Gummies, the Davitamon website only states EFSA approved claims about their ingredients (Davitamon, n.d., b). The Davitamon Kauwtabletten contain more ingredients than the Gummies, as they contain more trace elements, and are more similar in composition to the Kruidvat Multi A-Z (Appendix 9, Figure 5). The vitamins and trace elements are provided in amounts below the recommended intake value, except vitamin D, which is present in 100% of the recommended value, meaning that 2 tablets would lead to 200% of the recommended vitamin D intake (Davitamon, n.d., b).

- Kruidvat multi A-Z tuttifrutti kauwtabletten voor kinderen 4+ (Kruidvat, Renswoude, The Netherlands)
Price: €3.19 for 60 tablets
Intake recommended by supplier: 2 tablets daily.

The information on the webpage of this multivitamin tells us that the supplement contains "important vitamins and minerals". It is mentioned that calcium and vitamin D are needed for the normal growth of bones and that iron and zinc support the immune system, conform to EFSA regulations. The multivitamin contains vitamin A, several B vitamins, vitamin C, D, E, K and several trace elements like iron and magnesium (Appendix 9, Figure 6). One chewable tablet contains all ingredients in amounts below the recommended DV, except for vitamin D and calcium, which were added in 200% or 160% respectively (Kruidvat, n.d.).

Conclusion

Altogether, some multivitamins aimed for people with DS that are currently on the market are MSB NeuroPlus, NuTriVene-D and LTO3. The claims on their websites are differential and not always backed with the right scientific evidence. Regarding the safe doses, MSB NeuroPlus contains higher values of vitamin B than recommended. For NuTriVene-D the DV is surpassed by many nutrients present in the supplement. Additionally, some ingredients even exceed the upper limit. Regarding LTO3, DV's are not available as the ingredients of the supplement are not essential nutrients. Besides this, some general multivitamins that are currently on the market include Davitamon Junior 3-12 Gummies, Davitamon Junior 3+ Kauwtabletten and Kruidvat multi A-Z tutti-frutti kauwtabletten voor kinderen 4+. Their websites only contain EFSA approved claims. All multivitamins exceed the recommended DV of vitamin D and, only, the Kruidvat multi A-Z kauwtabletten also exceeds this value for calcium.

Sub question 6

Is there scientific evidence for the health effects of the available supplements for children with DS?

To be able to answer the sixth sub question, results of the exploratory internet search, literature research and interviews were examined. These results are displayed below.

First, the exploratory internet search, both in Dutch and English and in different internet browsers and search engines, resulted in scientific papers, informational web pages, web pages from non-profit organizations and web pages from commercial companies. The scientific papers that were found, displayed a similar perspective as our literature research showed, and concluded that supplement use should be handled with great care (Buckley & Sacks, 1998). Furthermore, no concrete evidence for a beneficial effect of a particular supplement had been found (Blair et al., 2008; Ellis et al., 2008). Another article that came up during the internet search explained that many of the studies done on nutritional supplements and DS had methodological shortcomings and were not able to detect differences in, for instance, IQ (Ani et al., 2000). The authors also indicated that still no evidence for a beneficial effect of supplements was found, and that not all supplements used in trials had a theoretical rationale backing them. Non-scientific websites reported both similar and contradicting results. Some webpages strongly advised to provide children with DS with supplements (MacLeod, 2014), whereas others (mostly non-profit organizations) were more reserved in recommending supplements to people with DS (Coleman, 1997; Leshin, 1998). An interesting result is that not many recent publications or recently written web pages came up in doing the internet search.

Second, the available and relevant literature regarding scientific evidence for the health effects of the available supplements for children with DS was analysed. As mentioned in the previous section, children with DS are more likely to consume inadequate amounts of particular nutrients and, subsequently, develop several nutritional deficiencies more often. Therefore, nutritional supplements could be considered as an effective way to supplement the daily diet (Ibrahim & El-Sayed, 2013). Moreover, several manufacturers claim that nutritional supplements have beneficial health effects on, for instance the cognitive abilities of children with DS (Blair et al., 2008). It is important to investigate if there is actually scientific evidence that supports the health claims of manufacturers, before these supplements are used by children with DS. The information and evidence that is currently available regarding the health effects of nutritional supplements for people with DS is reviewed below.

Vitamins

Firstly, Ani et al. (2000) reviewed an article that demonstrated that vitamin A supplementation resulted in an improved immunity in people with DS, compared to their untreated siblings. On the other hand, no evidence regarding the efficacy of vitamin A supplementation for people with DS was found by Roizen (2005). Secondly, Salman et al. (2002) reviewed eleven RCTs that evaluated the effects of nutritional supplements on cognitive functioning in children with DS. None of these trials were able to reveal an enhanced effect of vitamin B1 on the cognitive abilities of children with DS (Salman, 2002). This finding was replicated by Roizen (2005). Furthermore, Roizen (2005) found similar results regarding the use of vitamin B3 and B6 for people with DS. Several other studies also evaluated the use of vitamin B6 supplementation for people with DS, as it was speculated to slow down the development of dementia in these people (Thiel, 2005). However, Kozlowski (1992), Ani et al. (2000) and Salman (2002) could not provide any evidence to support this. Thirdly, Pogribna et al. (2001) demonstrated that nutritional intervention with folinic acid can possibly result in an improved metabolic profile in vitro. In line with this research, Schaevitz et al. (2014) reviewed several articles regarding supplementation of folinic acid in people with DS. They concluded that there is little evidence that folinic acid is able to reverse or prevent language and cognitive dysfunction in people with DS (Schaevitz, Berger-Sweeney & Ricceri, 2014). Moreover, a RCT performed by Ellis et al. (2008) observed that daily oral supplementation with folinic acid did not result in an improved psychomotor and language development in infants with DS. Conversely,

Ibrahim & Sayed (2013) summarized the findings derived from several studies and reported that both folic acid and vitamin B12 supplementation are proved to be successful clinical interventions for children with DS. Considering vitamin B12 supplementation, this finding was confirmed by Pogribna et al. (2001) for methyl-B12, an active form of vitamin B12. Fourthly, a study conducted by Thiel (2005) hypothesized that vitamin C and E might be able to delay neurodegeneration in people with DS, as these vitamins contain anti-glycation agents. Moreover, Parisotto et al. (2014) also proposed that antioxidant therapy with vitamins C and E might be beneficial for children with DS as they showed that six months of therapy attenuated the systemic oxidative damage present in people with DS. These findings were replicated by Mustafa et al. (2014) for supplementation with α-tocopherol, which is the most active type of vitamin E. Oxidative stress levels were also normalized in mice treated with vitamin E in an animal study performed by Lockrow et al. (2009). In addition, they demonstrated that long-term supplementation with vitamin E sustains hippocampal morphology, preserves markers of cholinergic cell survival and delays cognitive impairment in a mouse model for DS (Lockrow et al., 2009). Finally, multiple studies investigated the use of multivitamins for people with DS. Salman (2002) and Ani et al. (2000) did not find an improvement in the cognitive abilities of children and adults with DS. On the other hand, Ibrahim & El-Sayed (2013) illustrated that multivitamin supplements were able to decrease the levels of oxidative stress in people with DS. However, supplementation of multivitamins in children with DS might also have negative health effects. For instance, Blair et al. (2008) suggested that multivitamin and/or herbal supplement-use possibly increases the risk for developing acute myeloid leukemia.

Minerals and trace elements

Besides the vitamins, there is also some scientific evidence available regarding the supplementation of minerals and trace elements for people with DS. Firstly, several studies investigated the health effects of zinc supplementation for people with DS. Multiple positive health effects were found, for example Lakshmi et al. (2008) found an increased activity of serum cholinesterase's after six months of zinc supplementation in combination with minerals and antioxidant vitamins. Ultimately, this resulted in an improved cholinergic activity of the neurons in the brain and an improvement in cognitive skills and behavioral patterns (Lakshmi, Surekha, Srikanth & Jyothy, 2008). Additionally, Ibrahim & El-Sayed (2013) demonstrated that zinc supplementation resulted in an improved thyroid function and increased growth in children with DS. Moreover, Soto-Quintana et al. (2013) proposed that supplementation in case of a deficiency might lead to less immune abnormalities. Furthermore, Thiel (2005) suggested that zinc supplementation might attenuate neurodegeneration. Chiricolo et al. (1993) exposed cells derived from children with DS and their matched controls to a genotoxic agent. After exposure, the rate of DNA repair was higher in the cells from children with DS compared to the cells from controls, which contributes to neurodegeneration and advanced aging (Chiricolo, Musa, Monti, Zannotti & Franceschi, 1993). However, they observed that 4 months of oral zinc supplementation resulted in a controlled DNA repair rate (Chiricolo et al., 1993). Despite this, supplementation with zinc had no effect on the amount of DNA damage caused by the genotoxic agent (Chiricolo et al., 1993). Although most studies found positive health effects of zinc supplementation, Mazurek & Wyka (2015) found that supplementation with zinc increased the appetite in children with DS, which might result in an increased risk of overweight and obesity. Besides the studies that found either positive or negative health effects, three studies executed by Marreiro et al. (2009), Roizen (2005) and Ani et al. (2000) did not find consistent evidence regarding the health effect of zinc supplementation in children with DS. Secondly, Ani et al. (2000) reviewed articles that illustrated improved immunity and reduced oxidative stress in people with DS after supplementation with selenium. In accordance with this, Ibrahim & El-Sayed (2013) also found a decrease in oxidative stress after supplementation with selenium. Besides, Thiel (2005) hypothesized that supplementation with selenium might result in reduced development of dementia in people with DS, as selenium contains anti-glycation agents. Nevertheless, Roizen (2005) did not deliver scientific evidence regarding the health effects of selenium supplements in children with DS.

Other

Finally, there is some evidence available for other nutritional supplements, which cannot be categorized into either vitamins or minerals and trace elements. To start, recent studies focused mainly on the potential health effects of epigallocatechin gallate (EGCG) in people with DS, which is among other things, found in green tea. Xicota et al. (2020) demonstrated a trend for less body weight gain and lower BMI increase in young adult males with DS supplemented with EGCG compared to those receiving a placebo. EGCG seems to ameliorate mitochondrial functioning and energy metabolism, resulting in an increased metabolic rate and to a decrease in the absorption of proteins and fat, resulting in a reduced caloric uptake (Xicota et al., 2020). In addition, de la Torre et al. (2016) reported an improvement in memory and executive function deficits after 12 months of treatment with EGCG in combination with cognitive training in young adolescents with DS. Another study, performed in mouse models for DS, found that treatment with EGCG increased neural progenitor cell proliferation and countered mitochondrial dysfunction (Valenti et al., 2016). Both these processes promote an improved nervous system development (Valenti et al., 2016). Furthermore, Gu et al. (2020) suggested that supplementation with green tea extract, consisting of 94% EGCG, might be able to delay cognitive impairment in people with DS. Finally, Long et al. (2019) reported that individuals with DS, whose caregivers indicated that they use EGCG supplements, were generally characterized as less seriously disabled. Moreover, the authors stated that EGCG is a potential candidate to improve developmental and cognitive phenotypes that are reported in people with DS. However, some individuals that participated in this research did not experience any improvements upon EGCG use (Long et al., 2019). More importantly, some persons even experienced negative side effects of EGCG, as it caused sleep disturbances, more aggressiveness and lethargy (Long et al., 2019).

Zmijewski et al. (2015) illustrated that omega-3 fatty acids, present in fish oil, represent a potential treatment option for people with DS, and perhaps also for the associated early-onset Alzheimer's disease, as omega-3 fatty acids are able to modestly suppress the overexpressed RCAN1 gene. Moreover, research has been conducted regarding the use of amino acids as nutritional supplements for people with DS. Ibrahim & El-Sayed (2013), Ani et al. (2000) and Salman (2002) investigated the health effects of 5-HTP supplements. 5-HTP is a precursor of the neurotransmitter acetylcholine. Ibrahim & El-Sayed (2013) showed that 5-HTP supplementation resulted in an improved memory, while the other two studies did not find any evidence regarding this nutritional supplement (Ani et al., 2000; Salman, 2002). Besides this, Livingstone et al. (2015) reviewed several articles that investigated the effects of acetyl-L-carnitine supplements on cognitive functioning in people with DS. Afterwards, they concluded that there is currently not enough evidence to determine whether acetyl-L-carnitine supplements are effective (Livingstone, Hanratty, McShane & Macdonald, 2015). Another study demonstrated that addition of methionine and dimethylglycine to cultured trisomy 21 lymphoblastoid cells might result in an enhanced metabolic profile in vitro (Pogribna et al., 2001). They found the same effect for thymidine, which is one of the nucleobases for DNA (Pogribna et al., 2001). Finally, the health effects of antioxidants for people with DS were investigated. A RCT performed by Ellis et al. (2008) did not observe any improvement in psychomotor and language development in children with DS who received antioxidant supplements. Additionally, Livingstone et al. (2015) summarized the findings of multiple studies and stated that there currently is not an adequate amount of evidence available to conclude that antioxidant supplements lead to health benefits in people with DS.

Third, the result of the interview with Kent MacLeod also contributed to answering this sub question. According to MacLeod, people generally report benefits from nutritional supplementation. MacLeod said that based on diet and specific genetic or biochemical issues, there is sufficient evidence for children with DS to take a nutritional supplement or multivitamin. He sees reports from caregivers who see changes in their child's health, cognition and ability to perform tasks, after which he states: "Why not give a supplement to a child with DS if there is no risk?". MacLeod has also observed shifts in the way people with DS are treated, and observes that caregivers that provide supplements often also create a more nurturing environment and provide healthier diets. MacLeod cannot claim an effect of supplements on cognition, as many other factors also influence cognition. Another reason

for this, is that the methodology of most studies investigating the effect of nutritional supplements on cognition in DS was not validated. Most of these studies used IQ tests that were unsuitable to assess changes in cognitive functioning in people with DS, which created a bias against beneficial effects of nutrients in the scientific world. According to MacLeod, the effects of a given supplement depend on the individual's microbiome, which should be considered as an effector for any type of diet. MacLeod believes that the composition of MSB NeuroPlus is very science-based. The dosages used in MSB NeuroPlus are safe, effective and approved by Health Canada under the Natural Health Product Directorate.

Conclusion

All in all, a lot of research has been conducted to investigate the (possible) health effects of nutritional supplements for people with DS. However, it stands out that many results of different studies are contradicting. Some studies report no health benefits and remain hesitant regarding the use of nutritional supplements, whilst other studies and MacLeod emphasize that there is sufficient evidence for children with DS to take a nutritional supplement or multivitamin. Therefore, the results of these studies should be interpreted with caution. Besides this, further research with larger sample sizes and a longer follow-up time is urgently needed, as is also mentioned in the articles themselves, because the available studies have major methodological shortcomings.

Discussion

The discussion first states a summary of findings. The second part of the discussion consists of a methodological part and an ethical part. In the methodological part the limitations of the research methods are discussed, while in the ethical part the implications and suggestions for the future are considered.

Summary of findings

To summarize, the literature showed that nutritional challenges are common among children with DS. For instance, children with DS often have food-related problems, such as difficulties with chewing and swallowing. Moreover, children with DS have a higher probability of developing several nutritional deficiencies, due to an insufficient nutritional intake or an abnormal metabolism. These findings correspond to the results of the questionnaire and interviews with both caregivers and experts. Many caregivers mentioned in the interviews that their child has difficulties with oral motor skills. Moreover, both caregivers and experts stated, in the interviews as well as in the questionnaire, that deficiencies in zinc, vitamin D and the B-vitamins are often seen in children with DS. Because nutritional supplements might be a way to treat these deficiencies, and many manufacturers claim that supplementation can lead to health benefits, many caregivers provide nutritional supplements to their children with DS. This was confirmed in the current study, as 61% of the caregivers indicated in the questionnaire to provide nutritional supplements to their children. The most frequently provided supplements by caregivers include vitamin D, general multivitamins, vitamin C and multivitamins specifically aimed at people with DS. Their motivation behind this is diverse and included solving nutritional deficiencies, improving cognitive development, counteracting long-term effects of DS, and enhancing a child's immune system. Most caregivers provide supplements with the idea "no harm, no foul". However, most experts that were interviewed emphasized that supplements can certainly cause damage to one's health and find some high levels of particular vitamins in supplements alarming. As regards nutritional supplements, except for vitamin D, there are no recommendations included in the DS treatment guidelines, due to the lack of evidence-based research. The guidelines state that, in case of deficiencies, it first must be considered whether the diet is complete. Only if the diet has been optimized, but deficiencies are still observed, nutritional supplements can be prescribed. Diametrically opposed to this is the view of Kent MacLeod, the founder of NutriChem, who states that most individuals do not obtain sufficient nutrients from their diet and therefore believes that everyone needs extra supplements for optimal cognitive performances.

Caregivers indicated to gather information about nutritional supplements mainly via Facebook groups and websites. This information was used to conduct a market research in this study. From this market research it can be concluded that due to EFSA regulations, no nutritional supplements specifically aimed for people with DS can be found in the EU. Outside of the EU, the two biggest brands NutriChem and NuTriVene provide multivitamins and make several claims on their website about the effects of these supplements on people with DS. However, if it is desired to provide nutritional supplements, it is preferable to buy these in the Netherlands, as these supplements, in contrast to the supplements of NutriChem and NuTriVene, do not exceed DV's. Before the use of nutritional supplements by children with DS can be recommended by experts, more scientific evidence regarding the health benefits of nutritional supplements is needed. A lot of research has already been conducted to investigate the (possible) health effects of nutritional supplements for children with DS. However, as these studies show contradictory results, there is currently not a sufficient amount of consistent scientific evidence concerning this topic. Therefore, the need for further research with larger and longer trials should be emphasized.

Ethical discussion

Knowledge in the form of scientific research is valued the highest in the Western world. However, knowledge gained through experience might also be very valuable. Expertise gained by experience consists of coping with a certain condition, dealing with health care providers and organizations, handling social reactions, relating to peers aiming to facilitate empowerment, and to enhance quality

of life and care. It appears that caregivers attach great value to other people's experiences. Research findings mention that caregivers, who use supplementation, obtain knowledge from Facebook-groups. This can be seen as peer-support, as caregivers share their impressions regarding suppletion based on experiential knowledge. However, it is important that the usage of supplements contain safe dosages and a balance must be struck between the experts who focus on evidence-based knowledge and some caregivers who are more focused on knowledge gained from practical experience. Moreover, it is also important to consider the placebo-effect. It appears from the interviews that supporters of nutritional supplements actually do notice improvements in their child's cognitive and physical health after the use of supplements. Furthermore, Kent MacLeod suggests that caregivers who give nutritional supplements to their children may create a more nurturing environment than those who do not, which may also have an effect on a child's health. For this research, the focus was mainly on the improvement of children's health by using supplements. Due to this focus, alternative options for improving children's health were not studied. For example, a study showed that cognitive therapy was very effective to improve cognitive health. However, PAHL consultancy did not include these results as they were outside the scope of the research. Moreover, PAHL consultancy did not include the perspectives and influences of marketing, commerce and legislation concerning nutritional supplements. So, for the example of legislation, when conducting the market research, certain claims of manufactures in Canada and the USA about the improving health effects of supplements, aimed for people with DS, were found. However, these claims cannot be made in Europe, because of different regulations. All in all, these topics exceed the limits of this research and could be interesting topics to include in a follow-up study.

Methodological discussion

Literature research

The study consisted of a limited literature search. The focus of this research was mainly on field research, as the follow-up study will consist of a deeper literature search. PAHL consultancy only used PubMed and Scopus as searching tools, but in an ideal situation, more searching tools would be used to get a more broad overview of the available literature (Ovid, Web of Science, etc.). Also, it should be noticed that some studies targeted older individuals with DS, because in the search query, PAHL consultancy did not include age or mentioned anything about the fact that children <18 are the target group. Furthermore, cultural differences have not been taken into account by PAHL consultancy. In addition, the quality of most of the studies was poor, due to major methodological shortcomings. For instance, many studies had small sample sizes, lacked control subjects, or the duration of the studies was too short. Moreover, some studies used relatively low doses of supplements. This might contribute to the fact that no consistent supportive evidence was found regarding the health effects of nutritional supplements.

Questionnaire

Because the program logic8 EyeQuestion version 4.11 was used for this questionnaire, many people could participate, because people can complete the questionnaire from home. Moreover, it is a reliable and approved program as it is positioned on the whitelist of the WUR. Besides this, conducting online questionnaires also leads to fast results and a wide range of respondents. However, PAHL consultancy was aware of the possible disadvantages that might arise when conducting online questionnaires. For example, people could interpret the questions differently than they were actually intended or socially desirable answers might play a role. Some of the respondents indicated in the comments of the questionnaire that they missed certain questions or answer options, even though these were included in the questionnaire, indicating the possibility that some respondents overlooked or misinterpreted certain questions or answer options. However, as indicated in Methods, this was corrected for when possible. The questionnaire helps to gain insight into the current knowledge and use of nutritional supplements. However, it is not always clear whether nutritional supplementation is related to the fact that the child has DS, or whether this is because of other factors. For example, some caregivers indicated in the comments that they only give vitamin K as this is recommended for all babies, or that they supplemented all of their children, also children without DS, temporarily due to the COVID-19 pandemic. These are all good remarks for factors that cannot be observed in the results of our questionnaire. Moreover, respondents could

only indicate their reasons for providing supplements in one question, while it was sometimes indicated in the comments that respondents sometimes had different motivations for the different supplements they provided.

In order to guarantee the internal validity of the questionnaire, it was important that the sample size was large enough. As mentioned earlier, PAHL consultancy eventually included 234 completed questionnaires in the analysis of this study. When writing the proposal for this research, it was discussed that 100 completed questionnaires would be sufficient to make an initial inventory of the current status regarding nutritional supplementation among children with DS. Moreover, the study population included a similar amount of children across all ages, with only age groups 0 and 3 being somewhat underrepresented, and had a representative gender distribution.

The respondents were asked to fill in their own and their partner's highest level of education to assess whether this study population was representative of the general population. This can be seen in Appendix 2, Table 3. The percentage of respondents with a degree from a university (of applied science) was much higher compared to the general population (obtained from CBS). However, PAHL consultancy did not split the results concerning education level in male and females. In addition, respondents were asked to indicate whether they were a member of SDS or not. Of the respondents, 80.8% indicated to be a member of the SDS. An interviewed expert shared that, in her experience, caregivers with a lower level of education were less likely to be affiliated with SDS. This could also have contributed to a selection bias for the questionnaire. Another factor to consider is that this questionnaire was shared among members of a Facebook group dedicated to the MSB NeuroPlus supplement. PAHL consultancy does not have any knowledge of this questionnaire being shared in other dedicated groups. It should therefore be taken into consideration that there might be an overrepresentation of respondents providing their child with MSB NeuroPlus. All these factors lead us to believe that the results of this questionnaire may not completely be generalizable to all caregivers of children with DS in the Netherlands.

Some respondents indicated that they provided their child with (extra) nutritional supplements because of CoVid-19 but that they will stop doing this when the pandemic is over. This could mean that there is a slight overrepresentation of caregivers providing their children with nutritional supplements or an overrepresentation of certain types of supplements that are given. Additionally, the standard in the Netherlands is to provide children aged 0-4 with vitamin D and vitamin K. This could be a reason why the age at which nutritional supplementation was started is reported as 0 by most caregivers. The age at which caregivers started additional supplementation may be higher in reality. Moreover, there might be a bias for younger starting ages of supplementation, because there are younger children in the study population. Finally, not all dosages of supplements were reported properly by the respondents. For example, the amounts of vitamin C reported varied greatly. These amounts ranged from 10 mcg to 500 g. This last number is certainly an outlier as it is impossible to consume this much vitamin C in one day.

Interviews

This research consisted of semi-structured interviews. Three different interviews were divided over the caregivers, experts, and Kent MacLeod. As only a relatively small population was included in the interviews, the interviews are not generalizable to the whole population. The reader should bear in mind that the interviews are based on the questions and execution by PAHL consultancy and not by professionals. This could imply biases, as PAHL consultancy consists of a team of students who did not have much experience with designing questions, conducting interviews, elaborating and processing the results from the interview. It was noticed that some information remained superficial and more in-depth questions could have been asked. PAHL consultancy interviewed dietitians, however, no orthomolecular dieticians were interviewed. Including orthomolecular dietitians in the study might have led to a more complete result regarding different ideologies on supplement usage. In the informed consent, the importance of the anonymization of interviews was emphasized. Therefore, much important information about their careers had to be left out. However, the credibility of the conducted interviews decreased as the experts could not be traceable. Therefore,

for the interview of Kent MacLeod, the informed consent was changed, so he could be named. PAHL consultancy interviewed Kent MacLeod. However, to take a more neutral point of view, it would have been beneficial to interview someone from Nutrivene as well. The interview of MacLeod could be easily arranged because of a caregiver that introduced PAHL consultancy to MacLeod, whereas arranging an interview with a spokesman of Nutrive-D would have been very time-consuming. It was not deemed realistic to succeed in this before the end date of this project.

Market research
With regard to the reliability of the market research, only the websites of the manufacturers themselves have been used to gather information regarding the ingredients and claims about a specific supplement. The supplements incorporated in the market research are specifically aimed at people with DS and were most frequently mentioned in the questionnaires and/or came up during the exploratory internet search. There might be other supplements on the market aimed at people with DS, but these were not mentioned by caregivers and did not come up in the internet search. Therefore, it is likely that the most often used supplements aimed at people with DS were included. In addition, not all general multivitamins were included, but only the two brands that were most mentioned most frequently in the questionnaire. It is possible that conclusions that were drawn based on these two are not representative for all multivitamins available in the Netherlands as dosages might vary.

Conclusion

The aim of this research was to get insight into the current situation concerning nutritional supplement usage among Dutch children aged 0-18 with DS. 61% of the caregivers in the current study provided nutritional supplements to their children with DS. The most common nutritional deficiency was vitamin D, and this supplement was also the one most frequently provided. Caregivers have multiple motivations to provide supplements to their children, most often based on information acquired from their child's physician, and they continue doing this because they have mentioned observing positive effects. However, Dutch pediatricians and dieticians are critical and do not generally prescribe nutritional supplements other than vitamin D to children with DS. Conversely, Kent MacLeod of NutriChem finds it reasonable to provide nutritional supplements, especially multivitamins, to children with DS. There are some general multivitamins as well as multivitamins specifically aimed at people with DS currently on the market. However, the use of general multivitamins is preferable, because the claims of the multivitamins aimed for people with DS would not be EFSA approved and the DV's, or sometimes even the upper limits, of some ingredients are exceeded. The available scientific evidence concerning the health effects of nutritional supplements for people with DS is contradicting. Therefore, further research with improved methodologies is urgently needed.

Advice

Based on the information obtained in the different elements of this study, PAHL consultancy would like to provide the following advice to SDS.

Most importantly, more research with validated methodology needs to be performed to elucidate the health effects of nutritional supplements in children with DS.

- In the literature search, nutritional deficiencies are often suggested to occur more frequently in children with DS. However, there is no consistent scientific evidence yet for beneficial health effects of nutritional supplements. This could be due to methodological shortcomings of the currently published studies.

For now, caregivers should be advised to follow the guidelines for good nutrition (richtlijnen goede voeding) for their child, as provided by the Dutch Health council.

- According to the experts that were interviewed and the Dutch Health council, it should be possible to obtain all necessary nutrients from the diet, with the exception of vitamin D (10 mcg for children aged 0-4) and vitamin K (150 mcg in the first 12 weeks of breastfeeding).

Caregivers should be advised that if they suspect that their child has a nutritional deficiency, they should consult a dietician or physician.

- The dietician gives specific nutritional advice, where a physician only gives global advice. However, the dietician can refer a child to a physician to take a blood test or the other way around.
- If a nutritional deficiency is found in a child with DS because of any nutrition-related issues, which cannot be solved through nutrition, it is advised to supplement this.

Caregivers that still want to provide their child with multivitamins, are advised to use a general multivitamin.

- The nutrients in the general multivitamins PAHL consultancy looked into contained nutrients below the upper limits. An additional benefit of these supplements is that they can be purchased in the Netherlands and are generally cheaper than supplements specific for people with DS. While caregivers have reported positive effects of multivitamins aimed at people with DS, it cannot be generally recommended to use multivitamins specifically aimed at people with DS based on the scientific literature currently available.
- It is important that experts are understanding and engaging in conversations with caregivers that provide supplements that are specialized for DS, even though they cannot recommend these specific remedies. In order to prevent over dosage in supplement usage and to make the caregivers opinion feel heard.

Keep the dialogue alive about nutritional supplement usage

- The task of SDS is to raise awareness among caregivers on the usage of supplements and to create a dialogue between the proponents and opponents, in which people do not feel judged on their choices. The most important thing is to put the interests of the child first, therefore it is important for both sides to listen to each other to prevent polarization.
    - For instance, by interviewing experts and caregivers, to create a dialogue between these two groups and publish this interview in the Down+up magazine.

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Appendices

Appendix 1: Questionnaire

Beste ouder/verzorger,

Bedankt dat u wilt meewerken aan ons onderzoek! Wij zijn studenten van zowel de masteropleiding Nutrition and Health als de masteropleiding Communication, Health and Life Sciences. Wij voeren dit onderzoek uit in opdracht van Wageningen University and Research (WUR), in samenwerking met Stichting Downsyndroom (SDS). Dit onderzoek wordt uitgevoerd onder ouders en verzorgers van kinderen met Downsyndroom in de leeftijd van 0 t/m 17 jaar.

De volgende enquête heeft betrekking op het gebruik van voedingssupplementen voor kinderen met het syndroom van Down. Het doel van deze enquête is om een beeld te schetsen van de huidige situatie omtrent het gebruik van voedingssupplementen. Om een zo compleet mogelijk beeld te krijgen, zijn we zowel geïnteresseerd in ouders die hun kinderen wel voedingssupplementen geven als in ouders die dit niet doen.

De enquête bestaat uit gesloten vragen, waarbij er soms ook een optie is om zelf een ander antwoord in te vullen dat niet tussen de antwoordmogelijkheden vermeld staat. Formuleer uw antwoord alstublieft zo duidelijk en helder mogelijk.

Voordat u start met het invullen van de enquête willen wij u graag op het volgende attenderen:
o U dient een ouder of verzorger te zijn van een kind met het syndroom van Down.
o Deelname aan dit onderzoek is geheel vrijwillig en volledig anoniem.
o U kunt op elk moment uw deelname aan het onderzoek stopzetten.
o U dient ouder dan 18 jaar te zijn.

De onderzoeksgegevens worden op een vertrouwelijke manier bewerkt. Na afloop van het onderzoek worden deze geanonimiseerde gegevens - volgens wettelijke bewaartermijn - 10 jaar bewaard.

Indien u meer wilt weten over dit onderzoek, verwijzen wij u door naar de website van het onderzoek: https://www.wur.nl/nl/show/Voedingssupplementen-bij-kinderen-met Downsyndroom.htm

Bij voorbaat dank voor uw deelname.

Voordat u start met de enquête, vragen wij u hieronder toestemming te geven voor deelname aan dit onderzoek:
o Ik ga akkoord met deelname aan dit onderzoek.

1. Wat is uw geslacht?
o Man
o Vrouw
o Anders/wil ik niet zeggen

2. Wat is de relatie met uw kind?
o Ik ben vader (biologisch/stief/pleeg)
o Ik ben moeder (biologisch/stief/pleeg)
o Andere primaire verzorger
o Anders, namelijk: …

3. Wat is het geslacht van uw kind?
o Jongen
o Meisje
o Anders/wil ik niet zeggen

4. Hoe oud is uw kind?

5. Wat is de lengte van uw kind? (in centimeters, cm)

6. Wat is het gewicht van uw kind? (in kilogrammen, kg)

7. Hoe zou u de algemene fysieke gezondheid en algemene eetgewoontes van uw kind omschrijven?

	1. slecht	2. matig	3. neutraal	4. goed	5. Uitmuntend
7.1. Algemene fysieke gezondheid	◯	◯	◯	◯	◯
7.2. Algemene eetgewoontes	◯	◯	◯	◯	◯

De volgende vragen hebben betrekking op het al dan niet geven van voedingssupplementen aan uw kind met het syndroom van Down. Onder voedingssupplementen worden alle pillen, poeders, druppels, capsules of drankjes die extra vitamines, mineralen en/of bioactieve stoffen bevatten verstaan.

8. Heeft uw kind voor zover u weet, zonder supplementen, tekorten aan bepaalde voedingsstoffen?
o Ja, dat heb ik in het afgelopen jaar laten testen.
o Ja, dat heb ik meer dan een jaar geleden laten testen.
o Waarschijnlijk, dat baseer ik op het dieet van mijn kind.
o Nee, mijn kind heeft geen tekorten. Dat heb ik in het afgelopen jaar laten testen.
o Nee, mijn kind heeft geen tekorten. Dat heb ik meer dan een jaar geleden laten testen.
o Dit weet ik niet zeker, ik heb dit nooit laten testen.
o Anders, namelijk …

8.1. Aan welke voedingsstof(fen) heeft uw kind tekorten? Er zijn meerdere antwoorden mogelijk.
o Vitamine A
o Bèta-caroteen
o Vitamine B1 (thiamine)
o Vitamine B2 (riboflavine)
o Vitamine B5 (pantotheenzuur)

o Vitamine B6 (pyridoxine)
o Vitamine B11 (foliumzuur)
o Vitamine B12 (cobalamine)
o Vitamine C
o Vitamine D
o Vitamine E
o Vitamine K
o Calcium
o Chromium
o IJzer
o Jodium
o Kalium
o Magnesium
o Selenium
o Zink
o Anders, namelijk ...

8.1. Aan welke voedingsstof(fen) heeft uw kind waarschijnlijk tekorten? Er zijn meerdere antwoorden mogelijk.
o Vitamine A
o Bèta-caroteen
o Vitamine B1 (thiamine)
o Vitamine B2 (riboflavine)
o Vitamine B5 (pantotheenzuur)
o Vitamine B6 (pyridoxine)
o Vitamine B11 (foliumzuur)
o Vitamine B12 (cobalamine)
o Vitamine C
o Vitamine D
o Vitamine E
o Vitamine K
o Calcium
o Chromium
o IJzer
o Jodium
o Kalium
o Magnesium
o Selenium
o Zink
o Anders, namelijk ...

9. Geeft u uw kind op dit moment wel eens voedingssupplementen?
o Ja
o Op dit moment niet, ik heb dit in het verleden ook niet gedaan.
o Op dit moment niet, maar dit heb ik in het verleden wel gedaan.

9.1. Welke voedingsstoffen, vitamines, mineralen, bioactieve stoffen etc. geeft u aan uw kind in de vorm van een supplement? Deze informatie kunt u vinden op de verpakking van het voedingssupplement. Er zijn meerdere antwoorden mogelijk. Indien u een multivitamine geeft, hoeft u bij deze vraag niet alle losse voedingsstoffen in de multivitamine aan te geven.
o Multivitamine(n)
o Multivitamine(n) specifiek voor Downsyndroom (Bijvoorbeeld MSB Neuro plus/MSB-methyl)
o Vitamine A
o Bèta-carotenen
o Vitamine B1 (thiamine)

o Vitamine B2 (riboflavine)
o Vitamine B5 (pantotheenzuur)
o Vitamine B6 (pyridoxine)
o Vitamine B11 (foliumzuur)
o Vitamine B12 (cobalamine)
o Vitamine C
o Vitamine D
o Vitamine E
o Vitamine K
o Calcium
o Chromium
o IJzer
o Jodium
o Kalium
o Magnesium
o Selenium
o Zink
o Probiotica
o Prebiotica
o Visolie (EPA/DHA)
o Melatonine
o Trehalose
o Cysteïne
o Kurkuma
o Resveratrol
o EGCG (epigallocatechinegallaat/groene thee extract)
o Anders, namelijk …

9.2. Hoe heet/heten de multivitamine(n) die u geeft aan uw kind? Denk hierbij aan de naam van het supplement en het merk.

9.2. Hoe heet/heten de multivitamine(n) specifiek voor het Downsyndroom die u geeft aan uw kind? Denk hierbij aan de naam van het supplement en het merk.

10.1. Deze vraag gaat over het voedingssupplement 'multivitamine'. Welke dosering van dit supplement geeft u aan uw kind? Denk hierbij aan het aantal pillen/schepjes poeder, en indien vermeld op het potje/doosje, de grootte of het gewicht van de pil/schepjes poeder).

10.2. Deze vraag gaat over het voedingssupplement 'multivitamine specifiek voor Downsyndroom'. Welke dosering van dit supplement geeft u aan uw kind? Denk hierbij aan het aantal pillen/schepjes poeder, en indien vermeld op het potje/doosje, de grootte of het gewicht van de pil/schepjes poeder).

10.3. Deze vraag gaat over het voedingssupplement 'vitamine A'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.4. Deze vraag gaat over het voedingssupplement 'bèta-carotenen'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.5. Deze vraag gaat over het voedingssupplement 'vitamine B1 (thiamine)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.6. Deze vraag gaat over het voedingssupplement 'vitamine B2 (riboflavine)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.7. Deze vraag gaat over het voedingssupplement 'vitamine B5 (pantotheenzuur)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.8. Deze vraag gaat over het voedingssupplement 'vitamine B6 (pyridoxine)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.9. Deze vraag gaat over het voedingssupplement 'vitamine B11 (foliumzuur)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.10. Deze vraag gaat over het voedingssupplement 'vitamine B12 (cobalamine)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.11. Deze vraag gaat over het voedingssupplement 'vitamine C'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.12. Deze vraag gaat over het voedingssupplement 'vitamine D'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.13. Deze vraag gaat over het voedingssupplement 'vitamine E'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.14. Deze vraag gaat over het voedingssupplement 'vitamine K'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.15. Deze vraag gaat over het voedingssupplement 'calcium'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.16. Deze vraag gaat over het voedingssupplement 'chromium'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.17. Deze vraag gaat over het voedingssupplement 'ijzer'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.18. Deze vraag gaat over het voedingssupplement 'jodium'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.19. Deze vraag gaat over het voedingssupplement 'kalium'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.20. Deze vraag gaat over het voedingssupplement 'magnesium'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.21. Deze vraag gaat over het voedingssupplement 'selenium'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.22. Deze vraag gaat over het voedingssupplement 'zink'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.23. Deze vraag gaat over het voedingssupplement 'probiotica'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.24. Deze vraag gaat over het voedingssupplement 'prebiotica'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.25. Deze vraag gaat over het voedingssupplement 'visolie (EPA/DHA)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.26. Deze vraag gaat over het voedingssupplement 'melatonine'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.27. Deze vraag gaat over het voedingssupplement 'trehalose'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.28. Deze vraag gaat over het voedingssupplement 'cysteïne'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.29. Deze vraag gaat over het voedingssupplement 'kurkuma'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.30. Deze vraag gaat over het voedingssupplement 'resveratrol'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.31. Deze vraag gaat over het voedingssupplement 'EGCG (epigallocatechinegallaat/groene thee extract)'. Welke dosering van dit supplement geeft u aan uw kind? **Vermeld hierbij ook de**

eenheid die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

10.32. U heeft bij de vraag over de soort voedingssupplementen die u aan uw kind geeft ' anders' aangegeven. Wat voor supplement(en) geeft u aan uw kind en in welke dosering? **Vermeld hierbij ook de eenheid** die op het potje/doosje vermeld staat (bijvoorbeeld microgram, µg of mcg, milligram/mg, gram/g, colony-forming units/cfu).

11. Van welke merken koopt u voedingssupplementen? Er zijn meerdere antwoorden mogelijk.
o Huismerk(en)
o Holland & Barrett
o A. Vogel
o Lucovitaal
o Davitamon
o NutriChem (DSM)
o Vitaminstore
o Vitals
o Melvita
o Nutramin
o Royal Green
o Metagenics
o Anders, namelijk …

12. Waar koopt u voedingssupplementen? Er zijn meerdere antwoorden mogelijk.
o Supermarkt
o Drogisterij
o Apotheek
o Online (binnen de Europese Unie)
o Online (buiten de Europese Unie)
o Anders, namelijk …

13. Vanaf welke leeftijd bent u begonnen met het geven van voedingssupplementen aan uw kind?

14. Wat is de reden dat u uw kind deze voedingssupplement(en) geeft?
o Om de weerstand van mijn kind te verhogen
o Om mijn kind meer energie te geven gedurende de dag
o Omdat mijn kind via voeding deze stoffen niet binnenkrijgt
o Omdat mijn kind(waarschijnlijk) een tekort aan deze voedingsstof(fen) heeft
o Op aanraden van een arts
o Op aanraden van een diëtist
o Op aanraden van een andere expert
o Om de leerprestaties van mijn kind te verbeteren
o Om vroegtijdige veroudering tegen te gaan
o Op aanraden van andere ouders/verzorgers van kinderen met Downsyndroom
o Ik heb hier geen specifieke reden voor, maar denk dat het in ieder geval geen kwaad kan
o Anders, namelijk …

14.1. Om wat voor/welke expert gaat dit (bijvoorbeeld fysiotherapeut)

15. Hoe vaak geeft u deze supplementen aan uw kind?
o (Bijna dagelijk)
o Een aantal keer per week
o 1 keer per week
o 1 keer per 2 weken
o 1 keer per maand

o Een paar keer per jaar
o Soms een periode wel en soms een periode niet
o Anders, namelijk …

16. Is de huidige huisarts/kinderarts van uw kind op de hoogte van het supplementengebruik?
o Ja
o nee

10. Wat is de reden dat u uw kind geen voedingssupplementen geeft?
o Ik vind het niet nodig om mijn kind voedingssupplementen te geven.
o Ik vertrouw voedingssupplementen niet.
o Mijn kind wilt geen voedingssupplementen slikken.
o Ik vind voedingssupplementen te duur.
o Ik heb nog nooit nagedacht over het geven van voedingssupplementen aan mijn kind.
o Anders, namelijk …

10. Wat is de reden dat u bent gestopt met het geven van voedingssupplementen aan uw kind?
o Mijn kind had geen voedingstekorten meer na het gebruik van voedingssupplementen.
o Ik zag geen effect bij mijn kind na het gebruik van voedingssupplementen.
o Ik zag negatieve effecten bij mijn kind na het gebruik van voedingssupplementen.
o Ik heb hier geen specifieke reden voor.
o Anders, namelijk …

10.1 Wat voor negatieve effecten ervaarde u bij uw kind?
o Negatieve gedragsverandering(en)
o Fysieke klachten
o Verminderde leerprestaties
o Anders, namelijk ...

17. Wat is uw ervaring met betrekking tot het geven van voedingssupplementen aan uw kind?

	1. slecht	2. matig	3. neutraal	4. goed	5. Uitmuntend
Ervaring	○	○	○	○	○

11. Wat is uw ervaring in het verleden met betrekking tot het geven van voedingssupplementen aan uw kind?

	1. slecht	2. matig	3. neutraal	4. goed	5. Uitmuntend
Ervaring	○	○	○	○	○

18. Waar heeft u de informatie over het wel of niet geven van voedingssupplementen aan uw kind verkregen? Er zijn meerdere antwoorden mogelijk.
o Via een arts
o Via een diëtist
o Via een andere gezondheidsspecialist
o Via een organisatie gespecialiseerd in Downsyndroom
o Via informatie op internet
o Via sociale media (fora, facebook-groepen, etc.)
o Via mensen in uw omgeving
o Via een advertentie of andere reclame-uiting
o Via wetenschappelijke literatuur
o Ik heb geen informatie over het geven van voedingssupplementen
o Anders, namelijk …

18.1 Om wat voor/welke gezondheidsspecialist gaat dit?

18.1 Om welke organisatie gaat dit?

Als laatste willen we u nog wat vragen stellen omtrent u en uw eventuele partner en uw relatie tot de Stichting Downsyndroom. Dit doen we om te kijken hoe representatief onze steekproef is.

19. Wat is uw hoogst genoten opleiding?
o Lagere school (en LAVO, VGLO)
o VMBO (en voormalige MAVO, LBO vormen) + eerste drie jaar Havo/VWO
o Havo/VWO (afgerond), Atheneum, Gymnasium, NMS, HBS, Lyceum
o MBO (MTS, UTS, MEAO)
o HBO en universiteit
o PhD/promotie
o Niet van toepassing
o Dat zeg ik liever niet

20. Wat is de hoogst genoten opleiding van de eventuele andere ouder/verzorger van uw kind?
o Lagere school (en LAVO, VGLO)
o VMBO (en voormalige MAVO, LBO vormen) + eerste drie jaar Havo/VWO
o Havo/VWO (afgerond), Atheneum, Gymnasium, NMS, HBS, Lyceum
o MBO (MTS, UTS, MEAO)
o HBO en universiteit
o PhD/promotie
o Niet van toepassing
o Dat zeg ik liever niet

21. Bent u donateur van Stichting Downsyndroom?
o Ja
o Nee

22. Wilt u kans maken op één van de bol.com cadeaubonnen die wij verloten? Vul dan hieronder uw mailadres in. Dit is niet verplicht. Uw e-mailadres wordt apart van uw overige antwoorden opgeslagen en na verloting van de cadeaubonnen weer verwijderd.

23. Heeft u nog opmerkingen naar aanleiding van deze enquête?

Wij danken u voor uw deelname aan deze enquête. Ons onderzoek zal bijdragen aan een toepasbaar advies omtrent het geven van voedingssupplementen aan kinderen met Downsyndroom. Dit advies zal in het najaar uitgebracht en met u gedeeld worden via Stichting Downsyndroom.

Heeft u vragen over het gebruik van voedingssupplementen, neem dan contact op met uw arts of diëtist.

Klik nu op ‘verzenden’.

Appendix 2: Questionnaire results

Table 1: Height, weight and BMI values of the children with DS whose caregivers participated in the questionnaire. Average value ± standard deviation is given.

Age		boys ♂ n= 122*	girls ♀ n= 121*	other n=1*
0 ♂n= 3 ♀n= 1	Height	71 ± 8.2	70.0 ± 0.00	
	Weight	8.67 ± 0.577	8.00 ± 0.00	
	BMI	17.8 ± 5.19	16.3 ± 0.00	
1 ♂n= 8 ♀n= 4	Height	77.8 ± 10.3	75.8 ± 4.35	
	Weight	10.5 ± 1.54	8.70 ± 0.945	
	BMI	18.5 ± 7.58	15.2 ± 0.980	
2 ♂n= 4 ♀n= 11	Height	86.8 ± 2.22	82.3 ± 2.45	
	Weight	12.0 ± 1.63	10.6 ± 0.929	
	BMI	15.9 ± 1.46	15.5 ± 0.743	
3 ♂n= 5 ♀n= 1	Height	93.4 ± 3,72	95.0 ± 0.00	
	Weight	14.6 ± 3.13	12.0 ± 0.00	
	BMI	16.6 ± 2.09	13.3 ± 0.00	
4 ♂n= 2 ♀n= 10	Height	102 ± 4.95	98.0 ± 4.47	
	Weight	16.5 ± 2.12	15.8 ± 1.98	
	BMI	16.0 ± 0.50	16.4 ± 0.869	
5 ♂n= 10 ♀n= 4	Height	103 ± 3.20	99.5 ± 1.29	
	Weight	17.7 ± 3.77	16.5 ± 3.11	
	BMI	16.7 ± 2.97	16.6 ±2.98	
6 ♂n= 10 ♀n= 5	Height	113 ± 8.76	108 ± 9.21	
	Weight	21.4 ± 5.20	18.1 ± 2.79	
	BMI	16.7 ± 1.60	15.3 ± 0.777	
7 ♂n= 6 ♀n= 8	Height	120 ± 8.29	118 ± 8.21	
	Weight	24.8 ± 4.62	24.8 ± 5.85	
	BMI	17.0 ± 2.11	17.6 ± 3.43	
8 ♂n= 9 ♀n= 5	Height	119 ± 7.76	122 ± 3.36	132 ± 0
	Weight	26.9 ± 7.18	26.4 ± 5.37	not known

other = 1	BMI	18.6 ± 3.25	17.5 ± 2.77	not known
9 ♂n= 5 ♀n= 7	Height	125 ± 5.07	126 ± 5.59	
	Weight	25.6 ± 2.34	29.1 ± 7.36	
	BMI	16.4 ± 0.773	18.0 ± 3.23	
10 ♂n= 7 ♀n= 5	Height	129 ± 5.65	133 ± 8.74	
	Weight	26.8 ± 3.95	41.2 ± 10.8	
	BMI	16.0 ± 2.12	22.9 ± 4.91	
12 ♂n= 4 ♀n= 6	Height	150 ± 3.86	140 ± 9.13	
	Weight	43.5 ± 11.8	40.8 ± 6.31	
	BMI	19.1 ± 4.34	20.6 ± 2.31	
13 ♂n= 6 ♀n= 7	Height	152 ± 2.45	144 ± 9.74	
	Weight	47.3 ± 8.45	41.8 ± 12.5	
	BMI	20.4 ± 3.32	16.9 ± 8.3	
14 ♂n= 10 ♀n= 8	Height	157 ± 8.92	148 ± 7.03	
	Weight	51.6 ± 10.0	42.3 ± 7.41	
	BMI	20.7 ± 2.55	18.9 ± 2.65	
15 ♂n= 8 ♀n= 11	Height	162.1 ± 6.18	148 ± 7.21	
	Weight	57.9 ± 12.6	52.1 ± 11.2	
	BMI	21.9 ± 3.90	23.7 ± 3.77	
16 ♂n= 10 ♀n= 9	Height	141 ± 50.3	149 ± 5.94	
	Weight	46.5 ± 18.9	58.3 ± 17.1	
	BMI	20.7 ±2.69	26.6 ± 9.7	
17 ♂n= 4 ♀n= 4	Height	163 ± 5.83	157 ± 4.24	
	Weight	65.0 ± 11.9	66.5 ± 5.80	
	BMI	24.3 ± 3.24	27.0 ± 2.27	

**For some questions there was some missing data. This means that the n was sometimes smaller for one of the characteristics depicted.*

Table 2: Scores for self-reported physical health and eating behaviour given by caregivers. The mode of the category is depicted in bold. In the case of multiple modes, they are all depicted in bold and the smallest is indicated with an asterix.

	Age		**Very poor**	**Poor**	**Neutral**	**Good**	**Very good**
0	♂n= 3	Physical Health			1	**2**	
		Eating Behaviour				**2**	1
	♀n= 1	Physical Health				**1**	
		Eating Behaviour				**1**	
1	♂n= 8	Physical Health		1		**6**	1
		Eating Behaviour			1	**5**	2
	♀n= 4	Physical Health			1	**2**	1
		Eating Behaviour			**2**	1	1
2	♂n= 4	Physical Health		1	1	**2**	
		Eating Behaviour	**1***	**1**	**1**	**1**	
	♀n= 11	Physical Health			3	**8**	
		Eating Behaviour		3	2	**4**	1
3	♂n= 5	Physical Health				2	**3**
		Eating Behaviour		1		**4**	
	♀n= 1	Physical Health				**1**	
		Eating Behaviour				**1**	
4	♂n= 2	Physical Health		**1**		1	
		Eating Behaviour		**1**		1	

	♀n= 10	Physical Health			2	**8**	
		Eating Behaviour			4	**6**	
5	♂n= 10	Physical Health		1	1	**5**	3
		Eating Behaviour	1	2	**6**	1	
	♀n= 4	Physical Health				**4**	
		Eating Behaviour		1	1	**2**	
6	♂n= 10	Physical Health			4	**6**	
		Eating Behaviour	**3**	2	1	2	1
	♀n= 5	Physical Health				**5**	
		Eating Behaviour	1	1	1	1	1
7	♂n= 6	Physical Health			2	**4**	
		Eating Behaviour		1	**3**	2	
	♀n= 8	Physical Health			**4**	3	1
		Eating Behaviour	1		1	**5**	1
8	♂n= 9	Physical Health			4	**5**	
		Eating Behaviour		2	**3**	3	1
	♀n= 5	Physical Health		2		**3**	
		Eating Behaviour	1	1	**2**	1	
	Not applicable n=1	Physical Health			**1**		
		Eating Behaviour			**1**		
9	♂n= 5	Physical Health	1			**4**	

		Eating Behaviour			1	**3**	1
	♀n= 7	Physical Health				**7**	
		Eating Behaviour		1		**6**	
10	♂n= 7	Physical Health			1	**4**	2
		Eating Behaviour			2	**4**	1
	♀n= 5	Physical Health				**4**	1
		Eating Behaviour			1	**4**	
11	♂n= 5	Physical Health			**2***	**2**	1
		Eating Behaviour		2		**4**	
	♀n= 9	Physical Health		2	1	**4**	2
		Eating Behaviour			1	**7**	1
12	♂n= 4	Physical Health			**3**	2	
		Eating Behaviour		1	1	**3**	
	♀n= 6	Physical Health		**3**	2	1	
		Eating Behaviour		1	1	**3**	1
13	♂n= 6	Physical Health			2	**4**	
		Eating Behaviour			2	**4**	
	♀n= 7	Physical Health			2	**5**	
		Eating Behaviour				**7**	
14	♂n= 10	Physical Health			3	**6**	1
		Eating Behaviour			3	**6**	1

	♀n= 8	Physical Health			2	**6**	
		Eating Behaviour			**4***	**4**	
15	♂n= 8	Physical Health		2	1	**5**	
		Eating Behaviour		2	2	**3**	1
	♀n= 11	Physical Health		1	3	**7**	
		Eating Behaviour	1		3	**6**	1
16	♂n= 10	Physical Health		2		**6**	2
		Eating Behaviour			2	**7**	1
	♀n= 9	Physical Health			**5**	4	
		Eating Behaviour			**5**	3	1
17	♂n= 4	Physical Health				**4**	
		Eating Behaviour		1	1	1	1
	♀n= 5	Physical Health			**3**	2	
		Eating Behaviour				**5**	

Table 3: Highest education level of respondents and their partners and the Dutch average.

Education level	**Respondent (n=234)**	**Respondent's partner (n=234)**	**Dutch average (CBS, 2018)**
Primary school (including LAVO and VGLO	0%	0.4%	9.0%
VMBO (or MAVO and LBO) or the first 3 years Havo/VWO	4.3%	6.0%	20%
Havo/VWO	3.8%	1.7%	40%
MBO	21.4%	32.5%	
HBO and university	67.5%	52.1%	19%
PhD	1.7%	1.7%	1%
Not applicable	0.9%	5.1%	-
I'm not comfortable stating this	0.4%	0.4%	-

Table 4: Physical health and eating habits compared to providing or not providing nutritional supplements. Percentages shown in the table are based on the three groups regarding the provision of supplements: yes, no or no. but I did in the past.

Nutritional supplements			**Very poor**	**Poor**	**Neutral**	**Good**	**Very good**
Yes	n= 143, 100%	Physical Health	1 (0.7%)	12 (8.4%)	41 (28.7%)	**79*** (55.2%)	10 (7.0%)
		Eating Behaviour	3 (2.1%)	16 (11.2%)	34 (23.8%)	**78*** (54.5%)	12 (8.4%)
No	n= 71, 100%	Physical Health		4 (5.6%)	9 (12.7%)	**50*** (70.4%)	8 (11.3%)
		Eating Behaviour	5 (7.0%)	4 (5.6%)	16 (22.5%)	**39*** (54.9%)	7 (9.9%)
No, but I did in the past	n= 20, 100%	Physical Health			4 (20%)	**16*** (80%)	
		Eating Behaviour	1 (5.0%)	2 (10.0%)	4 20.0%)	**10*** (50.0%)	3 (15.0%)

*Modus is depicted in bold, * marks the median.*

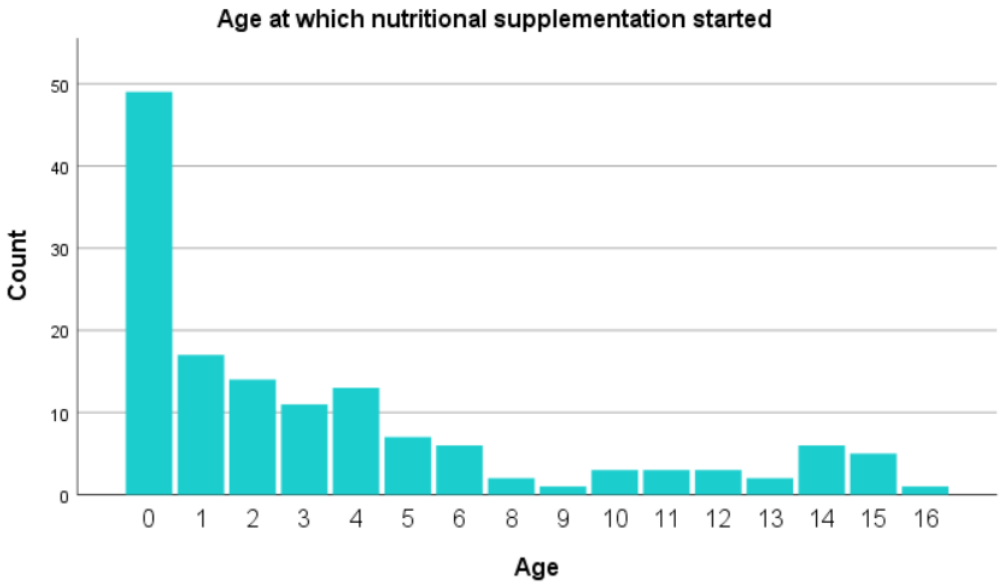


Figure 1: Age at which nutritional supplementation started as indicated by caregivers who provide their child with nutritional supplements (n=143).

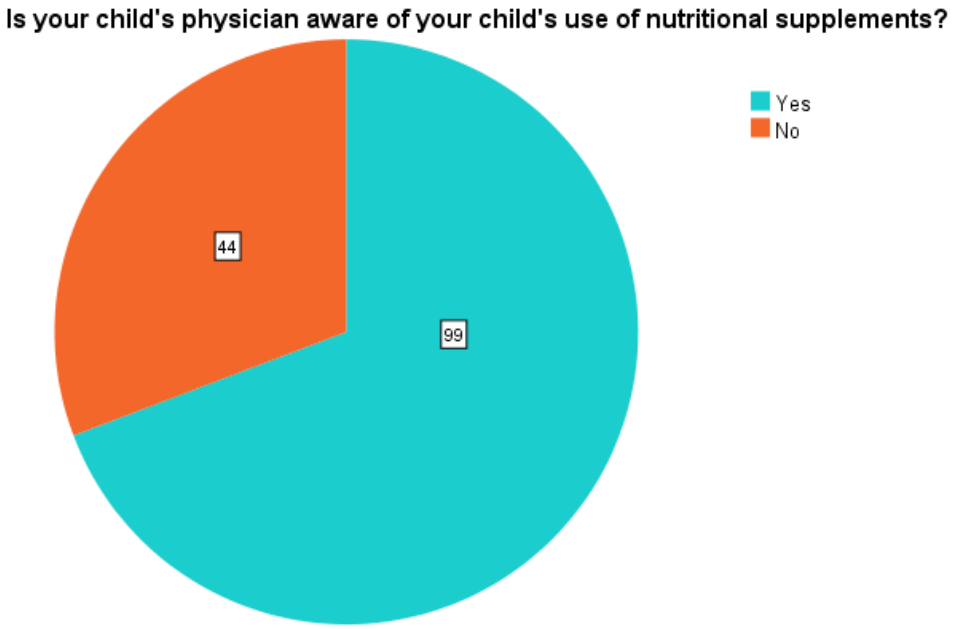


Figure 2: Number of caregivers that notified their child's physician of supplement use (n=143).

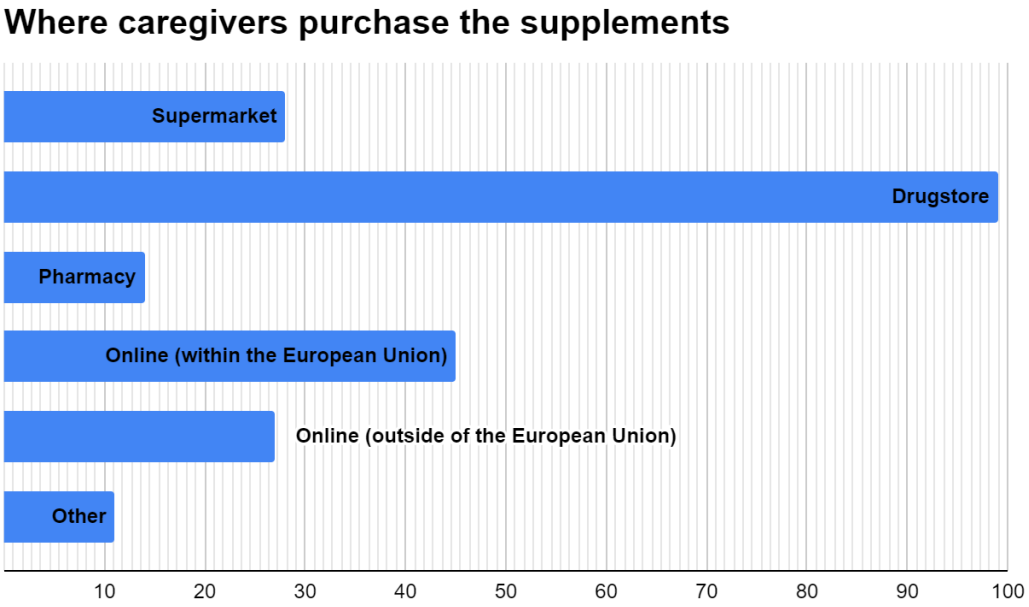


Figure 3: Frequency with which respondents indicated the location of purchase of nutritional supplements (n=143). Respondents could indicate multiple locations of purchase.

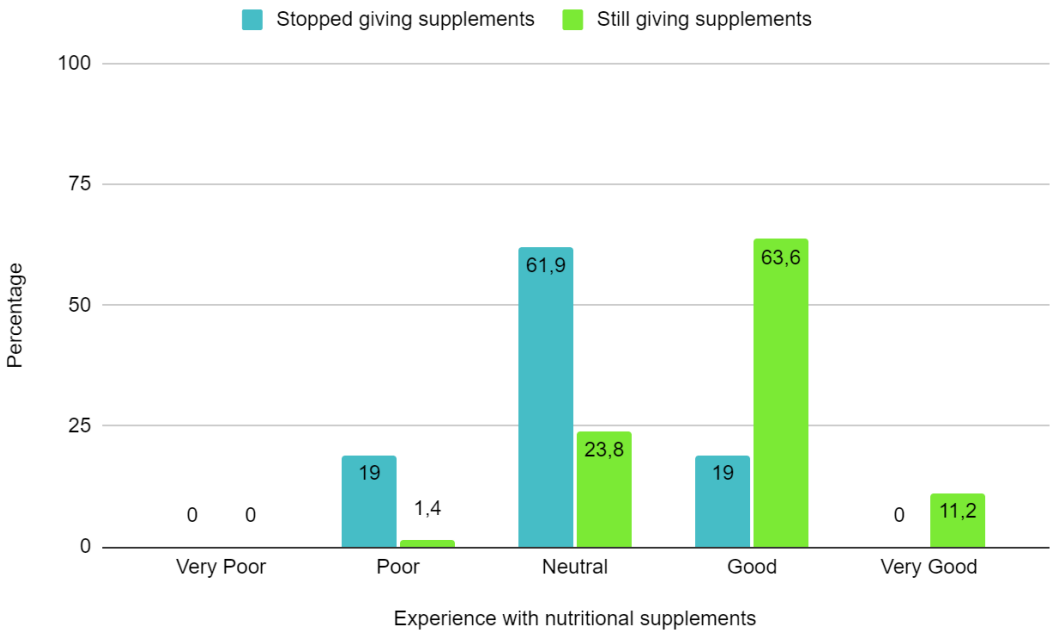


Figure 4: Experience with nutritional supplements of caregivers who provide, or have provided their child with nutritional supplements (n=214). Depicted as a percentage of the whole.

Appendix 3: Consent form for the interviews

Consent form for caregivers and Dutch experts

Toestemmingsverklaring voor interview "Voedingssupplementen voor kinderen met Downsyndroom"

Wij zijn studenten van de WUR (Wageningen University and Research) en we voeren een ACT-onderzoeksproject uit voor Stichting Down Syndroom. Academic Consultancy Training (ACT) biedt WUR-studenten een mogelijkheid om in teamverband te werken aan een onderzoeksproject voor een externe opdrachtgever. Voor dit ACT-onderzoeksproject 'Voedingssupplementen voor kinderen met Downsyndroom' houden wij een aantal interviews met ouders en voogden van kinderen met Downsyndroom. In het gesprek gaan we in op het gebruik van voedingssupplementen voor uw kind met Downsyndroom en de effecten die u al dan niet waarneemt na het geven van voedingssupplementen. Tot slot, zullen we dieper ingaan op uw redenen voor het wel of niet geven van voedingssupplementen. Het doel van het project is om uiteindelijk een advies uit te brengen aan de Stichting van Down dat betrekking heeft op de effecten van voedingssupplementen op de gezondheidsbevordering van kinderen met Downsyndroom.

We registreren uw naam en e-mailadres deze hebben we nodig om contact met u op te nemen voor het plannen van een afspraak en het houden van het interview. Deze persoonsgegevens zijn alleen inzichtelijk voor de betrokken onderzoekers en worden na afronding van het onderzoek verwijderd. We zouden het gesprek graag opnemen, zodat we de opname nog eens terug kunnen luisteren voor de uitwerking van het interview. Deze opnames worden alleen beluisterd door de onderzoekers, en niet gedeeld met anderen.

Toestemmingsverklaring

- Ik ben voldoende geïnformeerd over het vraaggesprek.
- Ik weet dat de onderzoeksgegevens anoniem verwerkt worden voor het doel van het project.
- Ik weet dat de onderzoeksgegevens niet met derden gedeeld worden.
- Ik weet dat de geanonimiseerde onderzoeksgegevens - volgens de wettelijke bewaartermijn - tot 10 jaar na dit onderzoek bewaard worden.
- Ik weet dat meedoen vrijwillig is, en dat ik altijd kan stoppen zonder opgaaf van reden.

Kruis aan waarvoor u toestemming wilt geven:

o Ik geef toestemming voor het verwerken van de antwoorden voor ons onderzoek.

o Ik geef toestemming voor een geluidsopname van het gesprek.

Naam: .....
Email-adres: .....
Telefoonnummer: .....
Handtekening: .....
Datum: .....

Hieronder kunt u lezen hoe Wageningen University & Research omgaat met persoonsgegevens:
**Met het geven van uw toestemming verklaart u uw persoonsgegevens vrijwillig te hebben verstrekt. De door u verstrekte persoonsgegevens zullen uitsluitend voor het doel worden gebruikt waarvoor u deze heeft verstrekt.*

Consent form for founder of NutriChem

Declaration of Consent for interview "Nutritional supplement use among children with Down syndrome"

We are MSc students of Wageningen University & Research (WUR) and who are conducting an ACT-research project for 'Stichting Downsyndroom'. For this research project "Nutritional supplements for people with Down syndrome, do they have beneficial effects?", we are conducting interviews with caregivers, health experts and manufacturers of nutritional supplements. These interviews help us map the current situation regarding supplement use and scientific evidence for this. In this interview, we will address the composition of the supplements aimed at people with Down syndrome, dosages of vitamins, minerals and other bioactive substances in the supplement and the current state of research on this subject. The goal of this project is to provide 'Stichting Downsyndroom' an applicable advice regarding the effects of nutritional supplements on the health of children with Down syndrome.

We will register your e-mail address. We need this information to be able to contact you to schedule and conduct the interview. This contact information is only accessible to the researchers involved and will be deleted after the research is completed. We would like to record the interview to facilitate the transcription of the interview. These recordings will only be accessible to the researchers and will not be shared with third parties. The answers given during the interview will be incorporated in the final report.

Declaration of Consent

- I have sufficient information on the content of the interview;
- I am aware that research data will not be shared with third parties;
- I am aware that the research data -according to the Dutch legal retention period- will be saved up to 10 years after completion of this research;
- I am aware that participation in this interview is completely voluntary and that I can quit at any time, without providing a reason.

Please check the boxes applicable to you:

[ ] I give consent for processing the answers given by me in this interview for research purposes

[ ] I give consent the recording of my interview

Name: .....

E-mail address: .....

Phone Number: .....

Date: .....

Signature: .....

By giving consent, you declare that you have voluntarily provided your personal data. Personal data provided by you will be used exclusively for research purposes

Appendix 4: Information letter for the interviews

Informatiebrief interview

Achtergrond
Bedankt voor uw interesse in dit online interview! Wij zijn studenten van Wageningen University & Research van de masteropleidingen Nutrition & Health en Communication, Health & Life Sciences. We volgen op dit moment gezamenlijk het vak Academic Consultancy Training waarvoor wij het adviesteam PAHL consultancy vormen. In opdracht van Stichting Downsyndroom en de Wetenschapswinkel gaan wij uitzoeken wat de huidige situatie is betreffende het gebruik van en kennis over voedingssupplementen bij kinderen van 0-18 jaar met het syndroom van Down. Door middel van dit online interview via Microsoft Teams willen wij meer te weten komen over hoe u als ouder/verzorger van een kind met het syndroom van Down denkt over het geven van voedingssupplementen, en waarom u ze wel of niet geeft. Via de begeleidingscommissie van het overkoepelende project hebben we vernomen dat u geïnteresseerd bent om deel te nemen aan dit interview.

Algemeen doel
Met dit project zullen wij als academisch adviesteam de huidige situatie met betrekking tot het gebruik van voedingssupplementen bij kinderen met het syndroom van Down schetsen en onderzoeken of er voldoende wetenschappelijk bewijs is voor de mogelijke gezondheidsvoordelen van voedingssupplementen. Het uiteindelijke doel is om Stichting Downsyndroom van een toepasbaar advies te voorzien over het gebruik van voedingssupplementen. De stichting zal de opgedane kennis uiteindelijk overbrengen aan de ouders en verzorgers van kinderen met Downsyndroom. Omdat dit een zeer breed en uitgebreid onderwerp is, zal ons onderzoek zich vooral richten op de huidige situatie met betrekking tot het gebruik van voedingssupplementen bij kinderen met het Downsyndroom en wat specialisten hierover adviseren. De informatie die wordt verzameld, vormt de basis voor verder literatuuronderzoek, dat later dit jaar door een scriptiestudent zal worden uitgevoerd. Ons onderzoek zal uiteindelijk bijdragen aan de ontwikkeling van het advies over voedingssupplementen voor verzorgers van kinderen met het syndroom van Down dat Stichting Downsyndroom zal uitbrengen in het najaar van 2021.

Anonimiteit & verwerking gegevens
Dit interview zal geanonimiseerd worden, waardoor uw antwoorden niet te herleiden zijn naar u of uw werkplek. Om het uitwerken van dit interview te vergemakkelijken, willen we dit interview graag opnemen. Uw persoonsgegevens worden gelijk na afronding van het onderzoek verwijderd. De opnames van uw interview worden beschouwd als onderzoeksgegevens en blijven bewaard. Als u hiermee akkoord gaat, vragen wij u om de bijgevoegde toestemmingsverklaring ingevuld naar ons terug te sturen voor de start van het interview. Nadat uw interview uitgewerkt en geanonimiseerd, sturen wij u uw resultaten op. Wij vragen u om deze door te lezen en goed te keuren. Mocht u hier onjuistheden in zien, dan kunt u dit altijd aangeven. Als u verder nog vragen heeft over het opnemen van het interview of de verwerking van de resultaten, dan kunt u altijd contact met ons opnemen.

Resultaten
Uw deelname aan dit interview helpt ons onderzoek en draagt bij aan de uitkomsten van dit project. Wij hopen het advies over voedingssupplementen dat Stichting Downsyndroom aan ouders van kinderen met het syndroom van Down verstrekt te verbeteren en de nieuwste wetenschappelijke kennis hier in op te nemen.

Tijdsduur & locatie
We verwachten dat het interview ongeveer een uur zal duren. Het interview zal in verband met de huidige corona maatregelen worden gehouden via het gratis programma Microsoft Teams. U ontvangt een mail met daarin een link voor een vergadering in Microsoft Teams.

Structuur
We zullen beginnen met wat meer algemene vragen en gedurende het interview zal dit steeds specifieker worden. Mocht u vragen of opmerkingen hebben gedurende of na dit interview, kunt u deze altijd aan ons stellen.

Appendix 5: Interview questions for the caregivers

Beste ouder,

Bedankt dat u mee wilt werken aan ons onderzoek naar het gebruik van voedingssupplementen bij kinderen met het syndroom van Down. Met behulp van dit interview willen we inzicht krijgen in de huidige situatie omtrent het gebruik van voedingssupplementen door kinderen van 0-18 jaar met het syndroom van Down. Uiteindelijk zal Stichting Downsyndroom in het najaar van 2021 een toepasbaar advies uitbrengen aan ouders en verzorgers van kinderen met het syndroom van Down over gezondheidseffecten van voedingssupplementen.

Wij zullen u het komende uur een aantal vragen stellen met betrekking tot het voedingsgedrag van uw kind, het gebruik van wel of geen voedingssupplementen en uw motivatie hierachter. Mocht u ergens geen antwoord op willen geven of willen stoppen met het interview, dan kan dit altijd.

We hebben uw toestemmingsverklaring in goede orde ontvangen. Had u daar nog eventuele vragen over?

We hopen dat u net zo veel zin heeft in dit interview als wij en dat dit tot een mooi resultaat leidt.

1. Kunt u kort iets meer vertellen over uw kind met het syndroom van Down?
   Geslacht, lengte, gewicht, leeftijd, eventuele beperkingen die uw kind ondervindt door het syndroom van Down.

2. In hoeverre krijgt u begeleiding bij de opvoeding van uw kind?
   Sociale kring, loopt u bij een arts/diëtist o.i.d.

3. Kunt u iets meer vertellen over het voedingspatroon van uw kind?
   Schijf van 5, vlees/vis, groenten/fruit, vochtinname (zoete dranken/frisdrank), gezond gewicht.

4. Ervaart uw kind voedingsgerelateerde problemen?
   Problemen met slikken, kauwen, afkeer tegen voedsel, intolerantie/allergieën.

5. Heeft u uw kind ooit laten testen op voedingstekorten?
   Zo ja, wanneer heeft u uw kind laten testen en welke voedingstekorten kwamen naar voren?
   Zo nee, verwacht u op basis van het voedingspatroon of andere kenmerken van uw kind dat uw kind voedingstekorten heeft?

6. Weet u wat voedingssupplementen zijn?
   Definitie van het voedingscentrum: voedingssupplementen zijn producten in de vorm van pillen, poeders, druppels, capsules of drankjes en zijn bedoeld als aanvulling op de dagelijkse voeding. Ze bevatten vitamines, mineralen of bioactieve stoffen, zowel apart, zoals in een vitamine C pil, of als combinatie, zoals in een multivitaminepil.

7. Leest u of hoort u veel over voedingssupplementen in uw omgeving/andere ouders van kinderen met het syndroom van Down?

8. Geeft u voedingssupplementen aan uw kind?
   Zo ja, welke en in welke mate (dosis, frequentie etc.)

9. Waarom geeft u uw kind wel/geen voedingssupplementen?
   Waar haalt u deze informatie vandaan (wetenschappelijke artikelen, internet, sociale media, arts/diëtist, ervaring van mensen uit de omgeving)?

Zo nee, maar in het verleden wel: heeft u in het verleden negatieve effecten ondervonden van het gebruik van voedingssupplementen of heeft u andere redenen voor het stoppen (geld, geen tekorten meer etc.)?

10. (WEL voedingssupplementen) Wat is uw ervaring met het geven van voedingssupplementen? Merkt u positieve/negatieve effecten?
    Lichamelijke effecten, stemming, gedrag.

11. (WEL voedingssupplementen) Van welk(e) merk(en) en waar koopt u voedingssupplementen?
    Waar let u op (mark, branding, prijs etc.)? Waarom koopt u specifiek dit merk? Waarom koopt u de supplementen hier?
    a. Hoeveel geld geeft u maandelijks uit aan supplementen?
       In hoeverre speelt geld een rol?

12. Weet u of er specifieke voedingssupplementen voor kinderen met het syndroom van Down op de markt zijn?
    Motivatie waarom hier wel of geen gebruik van gemaakt wordt.

Dit was de laatste vraag van het interview. Is er nog iets wat u wilt toevoegen, vragen of opmerken?

Bedankt voor uw deelname aan dit interview! Wij zullen het interview gaan uitwerken en naar u opsturen. We willen u vragen om dit door te nemen en ons nogmaals toestemming te geven. Om u te bedanken willen wij u een presentje opsturen. Wilt u daarvoor uw adres opgeven? Uw email adres zal uitsluitend hiervoor gebruikt worden.

Nogmaals bedankt voor uw deelname en nog een fijne dag gewenst!

Appendix 6: Interview questions for the experts

Beste expert,

Bedankt dat u mee wilt werken aan ons onderzoek over het gebruik van voedingssupplementen bij kinderen met het syndroom van Down. Met behulp van dit interview willen we inzicht krijgen in de huidige kennis en adviezen van gezondheidsexperts gespecialiseerd in het syndroom van Down omtrent voedingssupplementen. Uiteindelijk zal Stichting Downsyndroom in het najaar van 2021 een toepasbaar advies uitbrengen aan ouders en verzorgers van kinderen met het syndroom van Down over de gezondheidseffecten van voedingssupplementen.

Wij zullen u het komende uur een aantal vragen stellen over het huidige gebruik van en advies over voedingssupplementen in de gezondheidszorg. Mocht u ergens geen antwoord op willen geven of willen stoppen met het interview, dan kan dit altijd.

We hebben uw toestemmingsverklaring in goede orde ontvangen. Had u daar nog eventuele vragen over?

We hopen dat u net zo veel zin heeft in dit interview als wij en dat dit tot een mooi resultaat leidt.

1. Wat is uw beroep en hoe lang voert u dit beroep al uit?

2. Op wat voor manier bent u gespecialiseerd in/heeft u te maken met het syndroom van Down in uw werk en hoe lang al?

3. Hoeveel kinderen met het syndroom van Down behandelt/ziet u ongeveer?

4. Zijn er voedingsdeficiënties of voedingsgerelateerde problemen die u in de praktijk vaak ziet bij kinderen met het syndroom van Down?

5. Zijn er specifieke gevolgen van deze voedingsdeficiënties zichtbaar bij kinderen met het syndroom van Down?

6. (DIËTISTEN) Wat adviseert u aan (verzorgers van) kinderen met het syndroom van Down met betrekking tot hun dieet?

7. Ziet u veel ouders die hun kinderen met het syndroom van Down voedingssupplementen geven?

8. Heeft u een idee of er veel supplementen specifiek voor het syndroom van Down op de markt zijn?
   Zo ja, welke supplementen zijn dit?

9. Hoe schat u over het algemeen de kennis in van ouders met kinderen met het syndroom van Down met betrekking tot voedingssupplementen?

10. Is er iets opgenomen in de behandelingsrichtlijnen over het gebruik van voedingssupplementen bij het syndroom van Down?

11. Is er, naar uw weten, wetenschappelijk bewijs voor de effectiviteit van voedingssupplementen op de mentale en fysieke gezondheid van kinderen met het syndroom van Down?

12. Wat is uw mening over het gebruik van voedingssupplementen voor kinderen met het syndroom van Down? Denkt u dat voedingssupplementen positieve (of zelfs negatieve) effecten kunnen hebben op het leven van kinderen met het syndroom van Down?

13. Geeft u wel eens een advies aan verzorgers van kinderen met het syndroom van Down met betrekking tot voedingssupplementen of verstrekt u slechts informatie hierover?

14. Zijn er specifieke voedingssupplementen die u (altijd) adviseert aan (verzorgers van) kinderen met het syndroom van Down?

15. Waarop baseert u uw advies aan ouders met betrekking tot voedingssupplementen? Wetenschappelijke inzichten, ervaringen van ouders, combinatie hiervan etc.

16. Denkt u dat voedingssupplementen nodig zijn voor kinderen met het syndroom van Down om voedingsdeficiënties te voorkomen of om de algemene gezondheid te verbeteren?

Dit was de laatste vraag van het interview. Is er nog iets wat u wilt toevoegen, vragen of opmerken?

Bedankt voor uw deelname aan dit interview! Wij zullen het interview gaan uitwerken en naar u opsturen. We willen u vragen om dit door te nemen en ons nogmaals toestemming te geven. Om u te bedanken willen wij u een presentje opsturen. Wilt u daarvoor uw adres opgeven? Uw email adres zal uitsluitend hiervoor gebruikt worden.

Aan het einde van dit project zullen wij de gevonden resultaten presenteren. Deze presentatie zal online plaatsvinden op 10 maart om 12:00 uur. Mocht u hierbij aanwezig willen zijn, dan bent u van harte welkom!

Nogmaals bedankt voor uw deelname en nog een fijne dag gewenst!

Appendix 7: Interview questions for the founder of NutriChem

Dear founder,

Thank you very much for taking the time to do this interview with us and for participating in our research on nutritional supplements among children with Down syndrome. By having this interview, we want to gain a deeper understanding of the current knowledge of and advice on the use of nutritional supplements among health experts. The overarching outcome of our research and research being done later this year, is an applicable advice in the fall of 2021 from Stichting Downsyndroom to caregivers of children with Down syndrome on the health effects of nutritional supplements.

In this coming hour, we will ask some questions about supplement use specifically for people with Down syndrome. If you do not want to answer a question or if you want to stop the interview at any point, you are free to do so.

We have received your signed consent, thank you for this. Do you have any additional questions about this?

We are looking forward to this interview and hope it will help us reach a nice result.

1. Can you tell us something about yourself, your education and your career?

2. Can you tell us something about NutriChem?
    a. What type of service do you provide to your customers/clients?
    b. How big a role does Down syndrome play in your organisation?

3. What supplements aimed at people with Down syndrome does NutriChem produce?

4. What is it that MSB does in people with Down syndrome? Which nutrients play what role?
   What effects can people expect after taking the supplement?
   Some parents reported a high or low energy level upon consumption of MSB, do you have an explanation for this?

5. Can you tell us more about the scientific basis behind MSB?

6. How did you develop the composition of MSB?
    a. Do the nutrients in the supplement meet recommended daily intakes?
    b. We saw that some of the ingredients exceed the (Dutch) daily recommended intake. We saw that mainly multiple B vitamins (B1, B2, B5, B6, B12) are higher than the RDA. Why is this?

7. On what do you base the dosages of MSB?
    a. Do you think that parents generally stick to the dosages on the label? Or do they give more or less? How do you feel about this?

8. We read on your site that the composition of MSB has been altered a few times already. Which changes were made and based on which insights?

9. Do you assess the efficacy/effectiveness of MSB?
   If yes, how?

10. Of course, NutriChem, is specialised in personalised health solutions. However, we have found that many Dutch parents order the 'standard' MSB formula. What is the difference in composition and effect between the standard MSB supplement and a personalised supplement?

11. Are you aware of Dutch parents who order personalised supplements from NutriChem?
    a. When do you advise people to order personalised supplements?
    b. On what do you base the composition of the supplements?
    c. How often do you reassess the composition?
    d. Is it possible to perform the analyses used in the Netherlands (or somewhere else) or do people have to go to Canada for this?

12. Does your company collaborate with first-line health experts, like doctors or dieticians?

13. What is your opinion about the use of nutritional supplements among people with Down syndrome?
    Is the current use sufficient? Does your opinion on supplements differ for people with Down syndrome and people without Down syndrome?

This was your final question. Do you have any questions, remarks or anything else you would like to tell us?

Thank you very much for taking the time to participate in this interview! We will process your interview and send the results back to you to read and approve. If there are any inaccuracies or other remarks, you can notify us and we will change this.

Thanks again and have a nice day!

Appendix 8: Interview analysis

Table 1: Interview caregivers

Labels	Caregiver	Fragments
Dietary pattern	Caregiver 1	indicated that the child eats a lot of vegetables and sugar-intake is limited. The child can deal well with the boundaries regarding eating patterns.
	Caregiver 2	tries to minimize sugar intake. Also, an attempt was made to implement a gluten- and dairy-free diet, but in practice, this was too hard to combine with the current lifestyle.
	Caregiver 3	indicated that the child is overweight, but the dietician also indicates that the diet (on paper) is a healthy one.
	Caregiver 4	indicated that sugar is limited, as it makes the child hyper, but otherwise, the child eats according to a normal eating pattern.
	Caregiver 5	indicated that the child stopped eating warm food after 2.5 years, the child eats along with the rest of the family as much as possible.
Nutrition-related problems	Caregiver 1	indicated that the child does not have any nutritional-problems. Thyroid hormones were discussed with the paediatrician but the caregiver decided not to do this.
	Caregiver 2	is convinced that adopting a gluten-free diet has a positive influence on the gut and brain connection ('Gut-Brain Axis').
	Caregiver 3	indicated that the child was tested for celiac disease and lactose allergy, but nothing came out of the test. Implemented a low lactose diet, due to suffering from gastroesophageal reflux.
- Oral motor skills	Caregiver 4	indicated that the child has no food allergies or intolerances.
	Caregiver 5	indicated that the child stopped eating warm after 2,5 years. So, caregiver 5 started looking for nutritional supplements because they felt that the child was not getting enough nutrients. The child has tested negative for gluten and other food allergies.
	Caregiver 2	indicated that the child has a different chewing pattern because the front teeth come through earlier than the molars, which may affect food digestion (this is more common in children with DS).
	Caregiver 3	indicated that the child had difficulty swallowing at 4 months.
	Caregiver 4	indicated that the child had a very low muscle tone from birth (hypotonia). Because of this, the child was

		unable to swallow/suckle/drink etc properly until the age of 3.
- Tube feeding	Caregiver 4	indicated that the child was tube fed after birth. Eventually, family 3 gave the child both breastfeeding and tube feeding. After 10 months, caregiver 4 stopped tube feeding, however, the breastfeeding had to be thickened with locust bean gum.
- Obesity	Caregiver 5	indicated that the child was tube fed for the first 2,5 months and after these months, family 5 gave breastfeeding. Caregiver 5 is happy that the child was breastfed, this in connection with the development of oral motor skills.
	Caregiver 1	indicated that the child is somewhat firmly built, but not fat.
	Caregiver 3	indicated that the child eats everything, the problem here is that the child can keep eating and that the child does not feel saturated.
	Caregiver 4	had to make sure that the child does not overeat.
- Celiac disease	Caregiver 2	is convinced that adopting a gluten-free diet has a positive influence on the gut and brain connection ('Gut-Brain Axis').
Nutritional deficiency	Caregiver 1	has never had the child tested for a nutritional deficiency. However, one caregiver of the family is a nurse, who keeps an alert eye.
	Caregiver 2	has never had the child tested for nutritional deficiencies, but the paediatrician performs annual blood tests.
	Caregiver 4	indicated that the child has been tested for nutritional deficiencies, especially when the child was just born, but these tests never revealed anything. Caregiver 4 states that this is strange since the child actually lost weight, so the caregiver would expect to see certain deficiencies.
	Caregiver 4	takes into account the child's iodine content since they hardly use salt at home.
	Caregiver 5	indicated that blood will be drawn at the Down poli.
- Zinc	Caregiver 5	indicated that when the child was 3 years old, the child had a zinc deficiency. After giving MSB NeuroPlus, the zinc level was back to normal.
Nutritional supplements - Opinion → Pro	Caregiver 2	gives nutritional supplements, to help the cognitive development of the child and to support the child as much as possible. "I can do something about my child's cognitive development by giving my child supplements."

	Caregiver 4	indicated that, when using nutritional supplements, the child seems more himself, the child sits still longer, makes more contact, as if the child is more comfortable. Thereby, caregiver 2 does not experience negative effects.
	Caregiver 5	has heard many good stories and is convinced that giving MSB NeuroPlus has benefits for the child.
→ Neutral	Caregiver 1	is neutral and prefers old-fashioned parenting, indicating that vitamins are always a good thing, but caregiver 1 indicated that one should get nutrients mainly from nutrition.
→ Con	Caregiver 3	mentioned being still quite old-fashioned in this: as in if a child plays outside and for the rest just eats well (fruit, potatoes, vegetables, and meat) with the right portions, the opinion is that no supplementation is needed regarding vitamins. As long as children are healthy, they do not need supplements.
	Caregiver 3	is skeptical of MSB NeuroPlus because the effect of the supplement is difficult to measure and does not understand what these mothers are doing. Caregiver 3 does not think this is responsible.
	Caregiver 1	indicated that nutritional supplements can help but finding out is too much trouble. Therefore, there is not a sense that the benefits outweigh the drawbacks.
- Usage	Caregiver 1	gives Vitamin C and Davitamon (multivitamin for children) to the child. This is more adequately implemented during the winter months. Gives this to all children.
	Caregiver 2	provides Nutrivene-D, omega-3 with the DHA enriched, Huperzine A, Probiotics (somewhat sporadic with these), Choline and Lutein to the child. In the evening polyphenol and in connection with the Coronavirus Hesperidin are given. Besides the standard protocol, caregiver 2 indicated the detox protocol is also followed. It is advised to follow this once a week or once a month. The supplements used in this are: Lycopene, Glutathione, Vitamin C, Melatonin, Blueberry or Raspberry Polyphenols, Omega-3 and Alpha Lipoic Acid.
	Caregiver 2	first considered using MSB NeuroPlus, as this supplement is easier to use, but chose to use the Nutrivene-D supplements. They conduct more constant studies and in addition, NutriVene knows more about conducting a good quality study.
	Caregiver 2	stopped giving Huperzine A for a while because this drug can accumulate in the body.

	Caregiver 3	gives the child multivitamin in the form of gummies during the winter months.
	Caregiver 3	indicated that she gave the child a strip of probiotics because the child was having trouble with the intestines after using co-trimoxazole.
	Caregiver 4	indicated that the child used MSB NeuroPlus and Nutrivene D, but currently caregiver 4 gives Vitalize (A till Z) to the child (Vitalize contains a lower dose compared to MSB NeuroPlus and Nutrivene-D).
	Caregiver 5	gives half of the recommended dose of MSB NeuroPlus, (caregiver 5 experiences the positive effects; an alert child, with a good skin, good stools, etc., without the child becoming hyper) and vitamin D to the child. During the corona period she also gives the child extra vitamin C and omega-3 fatty acids (krill oil, EPA and DHA). Also, recently started giving probiotics.
	Caregiver 5	is very much into natural remedies, vitamins and minerals that fit your body.
- Supplements specialized for DS	Caregiver 5	chose MSB NeuroPlus over Nutrivene-D, since Nutrivene-D had to be given often during the day and also contained a high dose of vitamin A. Also, it contained zinc but no copper, while zinc and copper work together.
	Caregiver 2	uses Nutrivene-D and mentioned that on the Facebook page of Nutritional Targeted Intervention, a protocol was set up for caregivers.
	Caregiver 2	mentioned that Nutrivene-D is not for sale in the Netherlands, and therefore it must be imported from the USA. Brexit makes the import even more complicated, since the deliveries go via England (Longer waiting time and extra costs for import rights).
	Caregiver 2	thinks that the appeal of MSB NeuroPlus is greater than Nutrivene-D. Also, she indicated that it is better to give MSB NeuroPlus than no supplements.
	Caregiver 3	once saw a Facebook post about a parent who gave their child an MSB NeuroPlus supplement and the child turned yellow and urinated brown.
	Caregiver 4	indicated a preference for Nutrivene-D, as this supplement had the best effect on the child's stool. However, the parent is familiar with MSB NeuroPlus and Nutrivene-D.
	Caregiver 5	is familiar with Nutrivene-D and MSB NeuroPlus.

	Caregiver 5	indicated that the previous version of MSB NeuroPlus had very high values of vitamins and which shocked many caregivers.
	Caregiver 5	asked NutriChem about hyperactivity as a result when taking the full dose of MSB NeuroPlus. They replied that the absorption of the supplements may vary from person to person, for example, there may be too little of one vitamin, which may prevent another vitamin from being absorbed properly. Also, there may still be something in the child's intestines, causing a build-up of vitamins to take place.
- Usage of brands	Caregiver 1	indicated they always buy Vitamin C from the Roter brand, along with Davitamon they get this from the Kruitvat.
	Caregiver 2	indicated that they are not brand oriented, except for Nutrivene-D, and spends 100 euros per month on supplements. Caregiver 2 indicated that they are aware of the fact that not everyone can afford supplements. Especially since these supplements are not covered by insurance.
	Caregiver 4	uses Vitalize multivitamins, and mentioned price plays a large role regarding the purchase of supplements, which is why caregiver 4 stopped giving Nutrivene-D and MSB NeuroPlus.
	Caregiver 5	spends about €30 per month on all supplements together, and values more that the supplements are of natural and physical origin, rather than the price. Caregiver 5 indicates that price will come into play if supplements become too expensive, such as the personalized MSB NeuroPlus supplement.
- Knowledge caregiver	Caregiver 4	pays attention to the RI% of different supplements.
	Caregiver 4	stops giving supplements after about a 3 month period, and then often 2 to 3 weeks. Caregiver 4 does this by feeling, since caregiver 4 does not know how much the child stores in the body or how much the child needs to use. Says that MSB NeuroPlus is easy to use and that is why this caregiver thinks more caregivers give it to their children.
	Caregiver 5	knows that some caregivers give their children lose vitamins, such as vitamin C, vitamin D and omega 3 and other caregivers also just give basic multivitamin preparation.
	Caregiver 5	would have liked caregivers to do more research into the cause of the high values of vitamins in the blood (due to the high B values of MSB NeuroPlus)

Recommendations	Caregiver 5	indicated the use of the MSB NeuroPlus supplement discussed with the pediatrician, but was neutral about it.
- Guidelines	Caregiver 5	indicated that when the child gets the full dose, the child becomes almost hyperactive.
	Caregiver 5	indicated that the previous version of MSB NeuroPlus contained high amounts of vitamin B6 and B12, the advice was "stop taking the supplements".
- Sources	Caregiver 1	indicated that they know other caregivers with children with DS, but don't have conversations concerning supplement usage.
	Caregiver 2	learned about giving supplements to children with DS through the DS conference. Another mother pointed to supplements for children with DS out. She mentioned Nutricia supplement, developed for Alzheimer's, but it is also sometimes used for people with DS. Caregiver 2 started by googling the Nutricia supplement, and so she ended up (the Nutritional Targeted Intervention/ Nutrivene-D group) and Canadian manufacturers (MSB NeuroPlus) of supplements specifically for DS.
	Caregiver 3	indicated excluding itself from what other caregivers say regarding nutritional supplements.
	Caregiver 4	indicated that there are several Facebook groups for Nutrivene-D and for MSB NeuroPlus and that many caregivers are affiliated with these.
	Caregiver 5	searched for a long time for supplements and finally arrived at MSB NeuroPlus from NutriChem in Canada.
	Caregiver 5	mentioned is familiar with the Facebook group MSB NeuroPlus and Nutrivene-D and D mama's (mentions once or twice a year something about nutritional supplements).
Scientific evidence of effectiveness supplements	Caregiver 2	wonders why there is so little knowledge in the Netherlands about supplements for people with DS.
	Caregiver 2	cites information about nutritional supplements from scientific articles and from Facebook groups
	Caregiver 2	says if Alzheimer's research continues to advance, DS research will be able to hitch a ride.
	Caregiver 2	indicated having no hope for extensive research, especially because of the decreasing incidence of DS. But caregiver 2 will regret not using the knowledge that is currently available.
	Caregiver 5	finds it unfortunate that vitamins are measured through the blood, as this does not tell them as much about how much goes into the cells.

- Evidence-based v.s. practice-based	Caregiver 2	indicated that it is impossible to say about one person whether there were clear differences seen after giving the supplements to the child, however caregiver 2 is convinced that nutritional supplements have a positive effect on the development/health of the child. Therefore, caregiver 2 focuses on positivity.
	Caregiver 2	indicated, in addition, certainty that the child had a growth spurt because of the Huperzine A and another antioxidant (this is confirmed in a specific FB group of caregivers who also give Huperzine A and the other antioxidant to their child.
	Caregiver 5	indicated that the pediatrician does not recommend the supplement because there is no scientific evidence for it.
	Caregiver 5	indicated that it matters less to them if there is scientific evidence for the effectiveness of MSB NeuroPlus, since supplementing works well for the child. MSB NeuroPlus is always adapting the formula to new developments and new research.
	Caregiver 5	indicated to have stopped giving MSB NeuroPlus to the child on occasion, however, caregiver 5 noticed that the child was less alert, more tired, and had bumps on the skin again.
Necessary dietary supplements	Caregiver 1	does notice that the DS child is more affected by the nutritional supplements, because this child has less resistance and weaker health.
	Caregiver 4	mentioned that every doctor that was spoken to has mentioned that vitamins are not necessary.
	Caregiver 5	indicated that MSB NeuroPlus is given as a counteract for long-term effects, such as the aging process, and therefore not just to counteract nutritional deficiencies.
Trust in the medical profession	Caregiver 3	has complete trust in the medical specialists and fully trusts the doctors, therefore does not practice self-doctoring.
	Caregiver 3	mentioned that the child's doctors do not recommend multivitamins aimed at people with DS.
	Caregiver 4	has done own research, noticed a difference in the child and has discussed the topic of supplements with fellow caregivers, hence the reason to start using supplements for the child.

Table 2: Interview experts

Labels	Expert	Fragments
Nutrition-related problems	Expert A	indicated that people with DS have a higher risk of celiac disease, type 1 diabetes, osteoporosis, lactose intolerance and intestinal problems (Hirschsprung), obesity and a lower growth curve and muscle tension during infancy. Furthermore, gastroesophageal reflux and rumination is more common and can cause feeding problems.
	Expert B	indicated a higher risk of celiac disease. Furthermore, DS children have a higher chance of a heart defect.
	Expert C	indicated a higher risk of celiac disease, but are less sensitive for allergies.
- Oral motor skills	Expert D	indicated that celiac disease and lactose intolerance occur more often in clients with DS.
	Expert A	said that chewing food is also different because of this lower muscle tension, the teeth and the motor system of the mouth are often abnormal.
	Expert B	noticed that sometimes energy levels are too low to chew, manly when having a heart defect.
	Expert C	indicated that DS children are more likely to have difficulty eating, given their delay in oral motor skills and often different tooth development.
• Tube feeding	Expert A	recommends tube feeding as short as possible → evidence-based.
	Expert B	indicated that about 25% of the children with DS are on tube feeding in their first years of life.
- Obesity	Expert B	indicated that children proceed with tube feeding for no good reason, which can eventually cause symptoms (more likely to become overfed).
	Expert A	indicated that studies suggest it is linked to lower basal metabolism or higher leptin secretion but the evidence is insufficient. Therefore, gives dietary advice with a lower number of calories than normal people to reduce risk.
	Expert B	indicated that children with DS need fewer calories than peers. The difference between groups is still being researched → about 15 to 20%.
	Expert B	indicated that children with DS are not able to indicate when they are satiated. So they tend to overeat. Food is often used in social life to "appease" children.
	Expert D	indicated that practical experience shows that people with DS have a lower metabolism, so if you advise the same amounts, the weight will increase.

	Expert D	indicated that a large group within DS children are very focused on eating and can also eat uninhibitedly, which increases the risk of obesity.
- Celiac disease	Expert A	indicated that celiac disease is common in children with DS. This occurs 10 times more in children with DS compared to the total population.
	Expert B	indicated that celiac disease is more common in DS children and that nutritional deficiencies can occur as a result.
	Expert C	indicated that children with DS have a greater risk of celiac disease.
	Expert D	indicated that when seeing the diet, the shortcomings due to a celiac disease become visible.
- Lactose intolerance	Expert A	indicated a lactose intolerance.
	Expert D	indicated that when seeing the diet, the shortcomings due to a lactose intolerance become visible.
Nutritional deficiency	Expert A	indicated that with anti-epileptic medication additional nutrients such as vitamin D, calcium or folic acid are advised. When suffering from delayed thyroid functions, iodine supplements are often advised. Often gives advice to use fiber preparations, specifically Nutricia (Stimulance multi fibre, this contains six types of fibre) or Nestlé Health (Optifibre, this is partially hydrolyzed guar gum).
	Expert B	indicated that a zinc deficiency is a well-known abnormality, also vitamin D deficiency is more common in children with DS.
	Expert C	indicates a vitamin D deficiency.
	Expert D	is not aware of a greater risk for nutritional deficiencies in children with DS other than the iron content might be quite low. Medication use sometimes causes a negative effect on calcium and vitamin D.
- vitamin D	Expert A	*In practice, every client within the care center is given vitamin D supplementation. Vitamin D is routinely prescribed for people with DS over the age of 50, with darker skin tones, and people who do not often get outside.*
	Expert B	indicated that vitamin D deficiency is more common in children with DS.
	Expert C	indicated a vitamin D deficiency. Vitamine D is tested more often because a deficiency is more common.
	Expert D	indicated a vitamin D deficiency.

- Zinc	Expert B	indicated that a zinc deficiency is a well-known abnormality.
	Expert D	indicated that a zinc deficiency is often mentioned in the literature, but that these studies are of such poor quality that no specific advice can be given.
Nutritional supplements		
- Opinion → Pro	Expert A	indicated sometimes looking at practice-based proven theory, for example, Floradix at low HB level and indicates not to cut off supplements directly because there is no scientific evidence for it if the supplement does not cause any damage.
→ Con	Expert A	prefered basal nutrition, supplementation comes in second place.
	Expert B	indicated to have a more positive outlook on supplements, if the labels of supplements were more realistic. The claims of dietary supplements are often unproven.
	Expert C	indicated that supplements are not necessary. "You should not endlessly search for a way to make your child learn more than they can, but you should accept that this is what your child can do and you should enjoy that."
	Expert C	indicated that supplements are very expensive. There are better ways for caregivers to spend their money, f.e. to do something fun with their child.
	Expert D	prefered basal nutrition, supplementation comes in second place.
- Usage	Expert A	indicated that caregivers take the initiative to give their child supplements. However, this mainly concerns children who still live with their caregivers.
	Expert B	indicated that caregivers give supplements to their children with DS. A large number of caregivers give fish oil, to improve cognitive development, MSB NeuroPlus or different kinds of vitamins to their child, however, the expert sees different trends in supplements.
	Expert C	regularly sees caregivers giving their children with DS nutritional supplements but does not ask about it. “Caregivers tend to follow the trend”
	Expert C	indicated that caregivers often ask if they should give a multivitamin, Expert C often advises against it but notice that caregivers often do it anyway.

	Expert D	indicated that doctors advise that "wanneer de r in de maand zit" a multivitamin can be given but disagrees with that.
- Supplements specialized for DS	Expert D	indicated that the reasoning "baat het niet dan schaadt het niet" is often used, but it can still hurt.
	Expert A	indicated that expert A has no idea what nutritional supplements are on the market for children with DS.
	Expert B	mainly knows MSB NeuroPlus, but sometimes is Nutrivene-D also mentioned but much less. However, indicated high levels of B1, B6 and B12 in the MSB NeuroPlus supplement, which is alarming.
	Expert C	says to know Nutrivene-D.
	Expert D	has heard of MSB NeuroPlus but cannot place it. Expert D has not heard caregivers talk about MSB NeuroPlus or anything else.
- Knowledge caregiver	Expert A	indicated that this is very different among caregivers.
	Expert B	indicated that caregivers of children with DS have somewhat more knowledge of nutritional supplements than caregivers of children without DS. Although the knowledge is often superficial.
	Expert C	indicated that caregivers often search for information, however, the research they conduct is often not that deep.
	Expert D	indicated that caregivers often do not realize that more than 100% RDA is not healthy.
- Knowledge children with DS	Expert A	indicated to set small goals (for example, not: you have to lose 10 kilos, but: Christmas is coming again, how will we handle this).
	Expert A	says that children with DS are generally more sensitive to advertising on TV.
	Expert D	indicated that their knowledge in the area of nutrition is often a problem for example, a brown egg can be seen as healthier than a white egg. Children with DS are also more sensitive to environmental influences as a result, according to Expert D.
Recommendations	Expert A	gives advice, if necessary, regarding food supplements, and if it concerns an alternative food

		supplement this expert will always look for information about it.
- Guidelines	Expert B	indicated the dosages of medication for children with DS should be different than for children without DS. "A child with DS needs about 1/10 melatonin of what a child without DS would need. This may also apply to other supplements however, the expert is not aware of this.
	Expert C	indicated giving global nutritional advice, but refers to a dietitian who discusses the diet in detail (the dietitian also takes dietary samples). Gives supplement advice based on lab results.
	Expert D	gives advice based on which preparation suits an individual the best.
	Expert A	said that there is no dietary supplement specifically included for children with DS.
	Expert B	indicated that there is no reason to include supplements in the treatment guidelines.
	Expert B	recommends preparations that contain less than 100% of the RDA. Preparations with more than the RDA, are a no-go.
	Expert C	said there is nothing included within the DS treatment guidelines about the use of dietary supplements and recommends to look on the 'Voedingscentrum' website.
	Expert D	said that there are nutrition guidelines designed and they all refer to the guidelines of good nutrition and literature, as these guidelines are not different for children with DS.
Scientific evidence of effectiveness supplements	Expert A	indicated that many things have not been proven specifically for people with DS, but simply for the general population to which people with DS belong. Does not follow the orthomolecular nutrition guidelines, but follows the guidelines of the Health Council (Guidelines Healthy Food) and "Voedingscentrum".
	Expert B	indicated that there is no evidence for the effectiveness of nutritional supplements however when there is enough scientific evidence expert B will be the first to prescribe supplements.
	Expert C	did research on Nutrivene-D but has found no evidence for it.

	Expert C	indicated that "Voedingscentrum" does not recommend supplements for children with DS, with the exception of vitamin D.
	Expert D	calculates the levels of vitamins/minerals, if there are shortages, then supplements can be advised.
- Evidence-based v.s. practice-based	Expert A	indicated that scientific insight is at the top and insights obtained through practice-based methods follow.
	Expert B	gives advice concerning supplements based on other caregivers experiences, because this is not reliable. Advice is only based on evidence-based information.
	Expert C	gives advice based on blood results and on the guidelines of "Voedingscentrum". → evidence-based
	Expert D	gives advice only based on scientific evidence concerning the effectiveness of supplements.
Necessary dietary supplements	Expert A	will never say that every child with DS needs a particular nutritional supplement. This is entirely dependent on the individual and what issues are involved.
	Expert B	indicated to be interested in nutritional supplements if the effectiveness is scientifically substantiated. Currently, expert B follows the research of galantamine, which may reduce Alzheimer's disease.
	Expert C	said that nutrients should come mainly from the basal diet, vitamin D can be taken in addition.
	Expert D	said that the nutritional deficiencies can be solved mostly with the basal diet. "It is difficult to prove anything scientifically about nutrition, given the wide diversity."

Appendix 9: Labels of nutritional supplements

MSB Neuro Plus 5th Generation

DAILY DOSAGE

2-3 years (12-14 kg)	4-8 years (15-31 kg)	9-13 years (32-50 kg)	14+ years (>50 kg)
1/2 scoop	**1 scoop**	**2 scoops**	**4 scoops / 4 caps**

INGREDIENTS

(per 1 scoop or 1 capsule)

Acetyl - L - Carnitine	**12.5mg**	L-Methylfolate (L-5-methyltetrahydrofolate)	**150mcg**	B6 (Pyridoxal-5-Phosphate P5P)	**6.25mg**
B1 (Benfotiamine)	**11.25mg**		**-**	Resveratrol	**12.5mg**
Biotin	**30mcg**	Alpha Lipoic Acid	**2.5mg**	B2 (Riboflavin HCl)	**7.5mg**
Calcium (Calcium Chelate)	**31.25mg**	Lutein	**0.5mg**	Selenium (Selenomethionine)	**25mcg**
Vitamin C (Calcium Ascorbate)	**150mg**	Lycopene	**2.5mg**	Glutathione (Setria Glutathione)	**7.5mg**
B5 (Calcium Pantothenate)	**37.5mg**	Magnesium (Magnesium Glycinate)	**45mg**	Betaine (Trimethylglycine)	**25mg**
Choline (Choline Citrate)	**18.75mg**	B12 (Methylcobalamin)	**75mcg**	Vitamin A (Acetate)	**375IU**
Chromium (Chromium Chelate)	**25mcg**	Molybdenum	**25mcg**	Vitamin D3 (Cholecalciferol)	**250IU**
CoQ10 (PureSorb Q40)	**7.5mg**	N-Acetyl-Cysteine	**18.75mg**	Alpha Tocopherol (Succinate)	**25IU**
Copper (Copper sulfate)	**0.2mg**	B3 (Niacin)	**1.25mg**	Gamma Tocopherol	**3.75mg**
Curcumin	**5mg**	B3 (Niacinamide)	**17.25mg**	Vitamin K2 (Menaquinone)	**3.75mcg**
Inositol	**6.25mg**	Iodine (Potassium Iodide)	**25mcg**	Zinc (Zinc Glycinate)	**5mg**
L- Methionine	**25mg**				

NON MEDICINAL INGREDIENTS

Tropical Breeze	**Fruit Medley**	**Orange Burst**	**Unflavoured**
natural flavouring, monk fruit	natural flavouring, monk fruit	natural flavouring, monk fruit	pure vitamins

All non-medicinal ingredients are Gluten Free
*Flavours are produced in a facility containing nuts

Figure 1: Label of MSB NeuroPlus.

Figure 2: Label of NuTriVene-D.

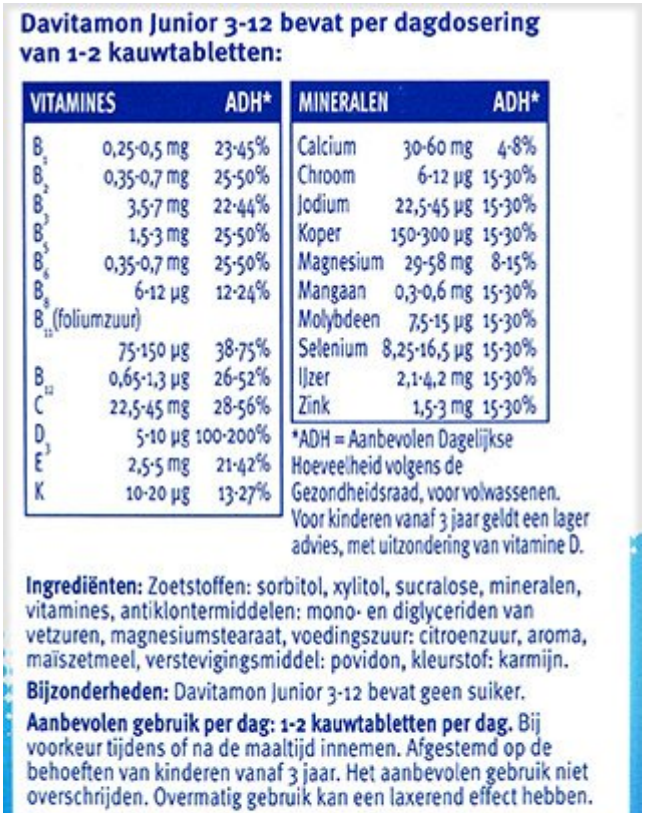
Productbeschrijving: Uniek, natuurlijk ingrediëntencomplex met Sementis*, Scutellaria Lateriflora en 5-N-ethyl-L-glutamine (L-Theanine).
Ingrediënten: Sementis* (bevat o.a. oceanisch DNA, polynucleotide, Omega-3/-6 EPA & DHA, arginine, fosfolipide, selenium, zink, vitamine C), Scutellaria Lateriflora – alleen bovengrondse delen (bevat o.a. bio-flavonoid scutellarin en andere flavonoïden, harsen, tannines en etherische oliën), 5-N-ethyl-L-glutamine (L-Theanine), scheidingsmiddel magnesiumstearaat, capsule van Pullulan.

Figure 3: Product description of SmartVital LTO3.

VITAMINES & MINERAAL Dagdosering: 1 gummie		ADH*
B_3	7 mg	44%
B_6	0,7 mg	50%
B_8	12 µg	24%
B_{12}	1,3 µg	52%
C	45 mg	56%
D_3	10 µg	200%
E	5 mg	42%
Zink	3 mg	30%

*ADH = Aanbevolen Dagelijkse Hoeveelheid volgens de Gezondheidsraad voor volwassenen. Voor kinderen vanaf 3 jaar geldt een lager advies, met uitzondering van vitamine D.

Figure 4: Label of Davitamon Junior 3-12 Gummies.



Davitamon Junior 3-12 bevat per dagdosering van 1-2 kauwtabletten:

VITAMINES		ADH*
B_1	0,25-0,5 mg	23-45%
B_2	0,35-0,7 mg	25-50%
B_3	3,5-7 mg	22-44%
B_5	1,5-3 mg	25-50%
B_6	0,35-0,7 mg	25-50%
B_8	6-12 µg	12-24%
B_{11} (foliumzuur)	75-150 µg	38-75%
B_{12}	0,65-1,3 µg	26-52%
C	22,5-45 mg	28-56%
D_3	5-10 µg	100-200%
E	2,5-5 mg	21-42%
K	10-20 µg	13-27%

MINERALEN		ADH*
Calcium	30-60 mg	4-8%
Chroom	6-12 µg	15-30%
Jodium	22,5-45 µg	15-30%
Koper	150-300 µg	15-30%
Magnesium	29-58 mg	8-15%
Mangaan	0,3-0,6 mg	15-30%
Molybdeen	7,5-15 µg	15-30%
Selenium	8,25-16,5 µg	15-30%
IJzer	2,1-4,2 mg	15-30%
Zink	1,5-3 mg	15-30%

*ADH = Aanbevolen Dagelijkse Hoeveelheid volgens de Gezondheidsraad, voor volwassenen. Voor kinderen vanaf 3 jaar geldt een lager advies, met uitzondering van vitamine D.

Ingrediënten: Zoetstoffen: sorbitol, xylitol, sucralose, mineralen, vitamines, antiklontermiddelen: mono- en diglyceriden van vetzuren, magnesiumstearaat, voedingszuur: citroenzuur, aroma, maïszetmeel, verstevigingsmiddel: povidon, kleurstof: karmijn.

Bijzonderheden: Davitamon Junior 3-12 bevat geen suiker.

Aanbevolen gebruik per dag: 1-2 kauwtabletten per dag. Bij voorkeur tijdens of na de maaltijd innemen. Afgestemd op de behoeften van kinderen vanaf 3 jaar. Het aanbevolen gebruik niet overschrijden. Overmatig gebruik kan een laxerend effect hebben.

Figure 5: Label of Davitamon Junior 3+ Kauwtabletten.

Verplichte algemene verme

Overmatig gebruik kan een laxerend effect hebben. Een gevarieerde, evenwichtige voeding en een gezonde levensstijl zijn belangrijk. Voedingssupplementen zijn geen vervanging van een gevarieerde voeding. Buiten bereik van kinderen houden.

Doseringrestrictie

2 x daags 1 kauwtablet innemen. Aanbevolen dagelijkse dosering niet overschrijden.

Samenstelling

Samenstelling: Samenstelling ; per dagdosering (2 kauwtabletten) ; ; %RI* #
Vitamine A (retinylacetaat ; 600 ; µg ; 75% #
Vitamine B1 (thiaminemononitraat) ; 0,6 ; mg ; 50% #
Vitamine B2 (riboflavine) ; 0,6 ; mg ; 40% #
Vitamine B3 (niacine (nicotinamide)) ; 10,6 ; mg ; 66% #
Vitamine B5 (pantotheenzuur (calcium-d-pantothenaat)) ; 3 ; mg ; 50% #
Vitamine B6 (pyridoxinehydrochloride) ; 0,7; mg ; 50% #
Foliumzuur (pteroylglutaminezuur) ; 100 ; µg ; 50% #
Vitamine B12 (cyanocobalamine) 1,2 ; µg ; 50% #
Biotine (d-biotine) ; 25 ; µg ; 50% #
¹Vitamine C (l-ascorbinezuur) ; 40 ; mg ; 50% #
Vitamine D (cholecalciferol) ; 10 ; µg ; 200% #
Vitamine E (dl-alfa-tocoferol-acetaat) ; 6 ; mg ; 50% #
Vitamine K (fytomenadion) ; 11 ; µg ; 15% #
Calcium (calciumcarbonaat) ; 160 ; mg ; 20% #
Chroom (chroomchloride) ; 20 µg ; 50% #
IJzer (ijzerfumeraat) ; 7 ; mg ; 50% #
Koper (kopergluconaat) ; 0,2 ; mg ; 20% #
Magnesium (magnesiumoxide) ; 75 ; mg ; 20% #
Mangaan (mangaansulfaat) ; 0,4 ; mg ; 20% #
Molybdeen (natriummolybdaat) ; 25 ; µg ; 50% #
Selenium (l-selenomethionine) ; 11 ; µg ; 20% #
Zink (zinkoxide) ; 4 ; mg ; 40% #
*RI=Referentie-inname. #

Figure 6: Kruidvat Multi A-Z Tuttifrutti Kauwtabletten voor kinderen.