Dietary Supplements for Aggressive Behavior

Studies in people with intellectual disability

David Gast

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Dietary Supplements for Aggressive Behavior: Studies in People with Intellectual Disability

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TABLE OF CONTENTS

Chapter 1	General introduction	9
Chapter 2	Diet quality among people with intellectual disabilities and borderline intellectual functioning	29
Chapter 3	Adoption of dietary supplements to reduce challenging behavior in people with intellectual disability: A qualitative study	47
Chapter 4	The effects of vitamin-mineral supplements on serious rule violations in correctional facilities for young adult male inmates: A randomized controlled trial	67
Chapter 5	Dietary supplements for aggressive behavior in people with intellectual disabilities: A randomized controlled crossover trial	89
Chapter 6	Effectiveness of multivitamin and mineral supplementation on aggressive behavior: a systematic review and meta-analysis	113
Chapter 7	Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behavior	133
Chapter 8	Summary and general discussion	151
Addendum	Nederlandstalige samenvatting	164
	List of publications	169
	Curriculum vitae	171
	Dankwoord	173

Chapter 1

GENERAL INTRODUCTION

This dissertation investigates to what extent dietary supplements can be implemented in practice as an intervention to reduce aggressive behavior in people with intellectual disability (ID). The first paragraph of this Chapter starts with general information about people with ID. The second paragraph deals with the problem of aggressive behavior in people with ID and is followed by a paragraph on treatment of this behavior. Because treatment with dietary supplements interacts with nutrition, diet quality in people with ID is discussed in paragraph four. Paragraph five explains the rationale for using dietary supplements to reduce aggressive behavior. Finally, paragraph six provides an overview of the content of the Chapters of this thesis.

People with intellectual disability

Intellectual disability is defined by both impaired intellectual functioning and a deficiency in one or more areas of adaptive behavior (APA, 2013). Adaptive behavior refers to the social, practical and conceptual skills in people's daily lives (Tassé et al., 2012). The impairments must be present before the age of 23 to differentiate ID from, for example, dementia. People with ID are characterized by a relatively high prevalence of psychological problems, health problems, and challenging behavior (Bowring, Painter, & Hastings, 2019; Matson & Cervantes, 2013). The cause of the ID can be genetically determined, as for example in the case of trisomy-21 in people with Down syndrome. However, ID can also be the result of environmental factors that disrupt an optimal development of the central nervous system (CNS), such as through a viral infection or oxygen deficiency in utero. In many cases, the cause of ID is unknown (Simpson, Mizen, & Cooper, 2016).

When diagnosing an ID, both intelligence quotient (IQ) and adaptive behavior are assessed (Tassé, Luckasson, & Schalock, 2016). Scales used for the assessment of IQ are for example Wechsler Adult Intelligence Scale (WAIS-IV; (Wechsler, 2012), Wechsler Intelligence Scale for Children V (WISC-V; (Wechsler, 2017), and the Wechsler Non-Verbal (WNV; (Wechsler & Naglieri, 2008). Also, for the assessment of adaptive behavior different scales are used, for example the Adaptive Behavior Assessment System-3 (ABAS-3; (du Preez, 2017), the Vineland-3 (Sparrow, Cicchetti, & Saulnier, 2016), and the ADaptive Ability Performance Test (ADAPT; (Jonker, Didden, Goedhard, Korzilius, & Nijman, 2021). Both the IQ tests and the adaptive behavior tests use a cut-off value of

approximately 2 standard deviations below the mean of the general population (IQ 70-75) (Boat, Wu, National Academies of Sciences, & Medicine, 2015).

Four different levels of severity of ID are distinguished within the group of people with ID (Boat et al., 2015). In the DSM-5, the severity categories are defined by a person's adaptive functioning, while in the DSM-IV IQ scores were dominant (Table 1.1). The categories are: profound ID, severe ID, moderate ID, and mild ID (MID). There are also people with an IQ between 69 and 85, a significant number of whom run into problems due to inadequate adaptive skills. In the Netherlands, they can receive comparable support from care organizations as people with MID (Nouwens, Lucas, Smulders, Embregts, & van Nieuwenhuizen, 2017). These people are not considered as having ID, but their level of functioning can be classified as borderline intellectual functioning (BIF). The prevalence of people with ID within the general population worldwide is estimated to be around 1-2%, but depends on the methods and study samples used (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011; McConkey, Craig, & Kelly, 2019). When people with BIF are also included the prevalence is much higher. In the Netherlands, the prevalence of the group of people with MID/BIF was an estimated 6.4% (4.8-8.3%) (Woittiez, Eggink, & Ras, 2019). Table 1.1 shows the distribution of severity levels of ID relative to the total number of people with an ID.

Table 1.1 Severity categories of people with ID as defined by DSM-IV

Severity Category	Distribution of Cases by Severity	DSM-IV Criteria (IQ categories)
Mild	85%	Approximate IQ range 50–69
Moderate	10%	Approximate IQ range 36–49
Severe	3.5%	Approximate IQ range 20–35
Profound	1.5%	IQ < 20

Note. Adapted from "Clinical characteristics of intellectual disabilities: In Mental disorders and disabilities among low-income children," by T. F. Boat, J. T. Wu, E. National Academies of Sciences, Engineering, and Medicine, 2015, p.171 National Academies Press (US).

Aggressive behavior in people with ID

Aggressive behavior exhibited by people with ID is a serious problem. It causes suffering in both the client and his or her environment and may contribute to the use of restrictive

measures and may affect the possibility of clients to live independently. It also contributes to the workload and burn-out of healthcare professionals. Staff members working in the care for people with ID have a high risk of being a victim of clients' aggression. The annual prevalence of staff workers encountering physical aggression at least once is 64% compared to an average of 38% across all healthcare domains (PGGM&CO, 2021).

Table 1.2 Examples of different types of aggressive behavior measured with the MOAS

Type of Aggressive Behavior	**Severity**	**Example of Behavior**
Verbal Aggression	Mild	Shouts angrily, curses mildly, or makes personal insults
	Moderate	Curses viciously, is severely insulting, has temper outbursts
	Severe	Impulsively threatens violence
	Extreme	Threatens violence repeatedly or deliberately
Aggression Against Property	Mild	Slams door, rips clothing, urinates on floor
	Moderate	Throws objects down, kicks furniture, defaces walls
	Severe	Breaks objects, smashes windows
	Extreme	Sets fires, throws objects dangerously
Physical Aggression	Mild	Makes menacing gestures, swings at people, grabs at clothing
	Moderate	Strikes, pushes, scratches, pulls hair of others (without injury
	Severe	Attacks others, causing mild injury (bruises, sprain, welts, etc.)
	Extreme	Attacks others, causing serious injury
Autoaggression	Mild	Picks or scratches skin, pulls hair out, hits self (without injury)
	Moderate	Bangs head, hits fists into walls, throws self onto floor
	Severe	Inflicts minor cuts, bruises, burns, or welts on self
	Extreme	Inflicts major injury on self or makes a suicide attempt

Aggression in people with an ID falls within the overarching concept of challenging behavior, which includes stereotypic and self-harm in addition to aggression. There is no uniform definition for aggression in people with, or without ID. Without a uniform operational definition of aggressive behavior, a wide variety of prevalence rates is to be expected. The variety is further increased by different study samples and settings in which the studies were conducted. The prevalence of aggressive behavior is estimated to lie between 9% and 50% or even higher in forensic treatment facilities (Didden et al., 2016). The prevalence rate varies with age and increases steadily from childhood until adulthood around age 45 (Davies & Oliver, 2013).

Various observer-reported instruments are used to measure aggressive behavior in people with ID. Often used examples include the Modified Overt Aggression Scale (MOAS;

(Oliver, Crawford, Rao, Reece, & Tyrer, 2007), and the Social Dysfunction and Aggression Scale (SDAS; (Wistedt et al., 1990). The MOAS, on the one hand, records the number of aggression incidents and their severity over a certain period, for example a day or a week (Table 1.2). The SDAS, on the other hand, records a score for certain forms of aggressive behavior over a certain period. There are also scales in which aggressive behavior is part of a broader spectrum of behavior, such as the Aberrant Behavior Checklist (ABC; (Aman & Singh, 1994), the Adult Behavior Checklist (ABCL; (Achenbach, Dumenci, & Rescorla, 2003), and the Behavior Problems Inventory (BPI; (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001). In the latter checklists, compared to the first, aggressive behavior is described in less detail in terms of type and severity.

Aggressive behavior usually does not have a single cause, but results from a combination of factors that together determine the risk of occurrence of the behavior. Poor emotion regulation and inefficient coping mechanisms are examples of psychological determinants. Other risk factors for aggression in people with ID can be client-specific, such as certain syndromes (Arron, Oliver, Moss, Berg, & Burbidge, 2011), a more severe level of ID, and mental health and medical problems (Crocker, Prokić, Morin, & Reyes, 2014). Some studies find that men with ID show more aggression than women, but the results are inconclusive and vary by study and by type of aggression (Crocker et al., 2006). Environmental factors can be related to aggression, such as the quality of the interaction between client and caretaker (van den Bogaard, Nijman, Palmstierna, & Embregts, 2017). There is also a negative association between the living climate and the level of aggression in the group (Neimeijer, Delforterie, Roest, Van der Helm, & Didden, 2020).

Studies have been done on the neurobiology of aggression and although neurotransmitters such as serotonin, dopamine and γ-aminobutric acid play multiple roles in the phenomenon of aggression, the causality is less clear-cut than initially thought (Willner, 2015). Because these neurotransmitters can have both activating and inhibitory functions in different brain regions involved in aggression, there is no simple causal relationship between the physiological availability of neurotransmitters and aggressive behavior (Takahashi, Quadros, de Almeida, & Miczek, 2010).

Treatment of aggressive behavior

Various approaches have been studied for the treatment of aggressive behavior in people with ID, which can be divided into four categories: 1) behavioral therapies, 2) cognitive behavioral therapies (CBT), 3) mindfulness-based techniques, and 4) psychotropic

medication. These approaches will be summarized below, with a special focus on psychotropic medication because it resembles treatment with supplements more than the other therapies.

Behavioral therapy interventions are based on Skinner's work and assume that aggressive behavior is learned and/or maintained through operant conditioning (McLeod, 2015). The intervention can consist of learning adaptive behaviors, changing the environment, changing reinforcement patterns of behavior and breaking routines. In behavioral therapies two steps are distinguished. After functional behavioral assessment (step 1) a behavioral intervention is chosen aimed at differential reinforcement or extinction of a certain target behavior (step 2) (Didden et al., 2016). A well-known shortcoming of such an approach is that generalization across settings of treatment results often does not occur and needs to be explicitly trained. Much research has been done – especially in individuals with more severe levels of ID – on behavioral interventions for aggressive behavior in people with ID and multiple systematic reviews and meta-analyses support their effectiveness (Didden et al., 2016).

Anger management Treatment (AMT) is an example of CBT that is often used in case of aggressive behavior. It is a multi-component intervention with the aim of learning to regulate anger in real life situations (Didden et al., 2016). It consists of learning to identify and control increased arousal and understand own emotions and those of others. Newly learned skills are practiced with anger-provoking stimuli in controlled environments (Didden, Nijman, Delforterie, & Keulen-De Vos, 2019). To increase effectiveness, standard CBT programs are adapted to people with ID through, among other things, simple language, using role plays, and involving significant others (Lindsay, 2009). CBT/AMT has many components and for many individuals with mild ID the approach may be too difficult. It is not yet known which parts of CBT/AMT have the most effect on aggressive behavior although it is generally assumed that role-play is more effective than cognitive elements (Didden et al., 2019).

Mindfulness-based therapies have also been used for treating aggressive behavior. Through mindful exercises, participants learn to focus their attention and reduce negative emotions and emotional reactivity (Currie, McKenzie, & Noone, 2019). An example of a mindfulness-based treatment is “Meditation on the soles of the feet”, in which a person practices with recognizing precursors to aggressive behavior and focusing his or her attention to a neutral point in the body (Singh et al., 2012). Systematic

reviews show promising results of this approach for the treatment of aggression, but both the number and quality of the studies are not yet sufficient to draw firm conclusions about its effectiveness (Patterson, Williams, & Jones, 2019).

The use of psychotropic drugs for aggression is widespread but not without controversy. Approximately 40% of people with ID who are living in a residential facility use antipsychotics, of whom only a part have an indication for these prescriptions (Koch, Dobrindt, & Schützwohl, 2021; Lunsky et al., 2017). The widespread use of antipsychotics is not without risks as there is evidence that the side effects can lower quality of life, cause serious health risks and side effects, and shorten lifespan (Espadas et al., 2020; Scheifes et al., 2016; Sheehan et al., 2017; Tyrer, Cooper, & Hassiotis, 2014). The evidence that antipsychotics are effective in treating aggressive behavior among people with ID is not strong and leans on open label trials and industry conducted RCTs with relatively small sample sizes (Cohen et al., 2013; Deb, 2016; Deb et al., 2014). The reviews and meta-analyses are not unambiguous about the direction of the effect (Brylewski & Duggan, 2001; Cohen et al., 2013; Deb et al., 2014). Good quality RCTs need to be conducted to justify its widespread use (Deutsch & Burket, 2021). Also, some studies show that tapering off antipsychotics yields health benefits and improves the quality of life of people with ID (Ramerman, Hoekstra, & de Kuijper, 2019), and does not necessarily lead to more aggression (Kuijper, Evenhuis, Minderaa, & Hoekstra, 2014; Ramerman, Kuijper, et al., 2019). The abundant use of antipsychotics among people with ID has led to the development of protocols and guidelines for a more responsible prescription. Only after psychological interventions have remained unsuccessful antipsychotics may be prescribed. In addition, there must be a clear indication, and the intervention must be regularly evaluated (Deb et al., 2009; Deutsch & Burket, 2021; Embregts et al., 2019; NICE, 2015). Despite clear protocols, the use of psychotropic drugs as an off-label medication proves difficult to control (Henderson et al., 2020). The slight decline in antipsychotic prescribing in the second decade of this century was offset by an increase in the prescribing of other psychotropic drugs, such as antidepressants, hypnotics, and anxiolytics (Henderson et al., 2020). The search for an alternative to excessive off-label prescribing of psychotropic drugs for aggressive behavior prompted this study. From the above, we can conclude that several treatment options for aggression in people with ID have been developed. But, all current treatments have their own limitations and evidence

is equivocal in people with ID. Additional therapies that are easy to implement and have few side effects remain necessary.

Nutritional status among people with ID

The nutritional status influences the composition and condition of the body and is determined by the bioavailability of nutrients on the one hand and the consumption of nutrients on the other (Kondrup, 2003). In people with ID, a good nutritional status faces multiple threats (Humphries, Traci, & Seekins, 2009; Ptomey & Wittenbrook, 2015). We will briefly discuss three of those threats here: 1) poor diet quality, 2) medication, and 3) genetic polymorphisms (Ames, Elson-Schwab, & Silver, 2002; Boullata & Armenti, 2004; Hamzaid, O'Connor, & Flood, 2019; Hoey et al., 2017). Diet quality is defined as a person's overall dietary pattern. A so-called Western dietary pattern is characterized on the one hand by too much saturated fat, animal proteins and fast carbohydrates, which increases the risk of obesity and a range of health problems. On the other hand, a Western diet is characterized by a relative deficiency of dietary fiber, vitamins, minerals and omega-3 fatty acids (Cena & Calder, 2020; Cordain et al., 2005). A healthy diet is characterized by fresh fruits and vegetables, whole grains, legumes, seeds and nuts and contains relatively little fast carbohydrates such as sugar and little animal-based foods such as processed meat (Cena & Calder, 2020). Unhealthy food is widely available and relatively cheap (Appelhans et al., 2012). The risk of a less healthy diet is related to a low socio-economic status and educational level (Giskes, Turrell, Van Lenthe, Brug, & Mackenbach, 2006; Hiza, Casavale, Guenther, & Davis, 2013). Multiple studies show that the diet quality of people with ID is lower than the standards for optimal nutrition and often lower than that of peers without ID (Ptomey & Wittenbrook, 2015).

In addition to low diet quality, there are lifestyle factors that can threaten nutritional status through a negative effect on the bioavailability of vitamins and minerals. Examples are smoking, drinking alcohol, and using certain medications, which include anticonvulsants and antipsychotics that are widely used by people with ID (van den Berg, van der Gaag, & Hendriks, 2002; Berg, 2004; Boullata & Armenti, 2004). Finally, it is assumed that a relative deficiency of micronutrients can be caused by an increased need, which can be the result of genetic polymorphisms that affect between 1% and 35% of individuals. The abnormalities in the genetic code can lead to the production of malformed enzymes that have a lower binding affinity with their cofactor (often a

vitamin), resulting in a decreased biological activity of the enzyme. A higher blood level of the cofactor involved can improve this biological activity (Ames et al., 2002).

We may conclude that there are several risks to a healthy nutritional status of people with ID. Firstly, there is a risk that the client with ID – especially clients with milder levels of ID – makes unhealthy food choices. Secondly, there may be problems swallowing and digesting healthy foods, which often occurs in people with more severe ID. Thirdly, there may be an increased need for micronutrients due to lifestyle factors, medication and genetic abnormalities.

Effect of micro-nutrients on behavior

Full-blown physical deficiency diseases due to micronutrient deficiency in the diet are rare in Western societies and are mostly seen as comorbidities of serious disease or alcohol dependence. More common is a chronic latent deficient intake of vitamins, minerals and omega-3 fatty acids, which is associated with a Western diet (Myles, 2014; Troesch, Hoeft, McBurney, Eggersdorfer, & Weber, 2012). These mild chronic deficiencies can limit optimal CNS function and are associated with a risk of disruptive behaviors (Benton, 2007; Jackson, 2016).

Vitamins, minerals and omega-3 fatty acids are important for the functioning of the CNS because of the many roles they play in the physiological processes of nerve cells. As was described in 1.2, there is no simple causality between physiological availability of neurotransmitters and aggression. Because of the complex nature of the interactions between environmental factors and the CNS and the many feedback mechanisms that characterize neurophysiological processes, the relations are less straightforward than had been expected a few decades ago. There are several hypotheses about pathways by which micronutrients affect the CNS and may influence human behavior (Huskisson, Maggini, & Ruf, 2007; Parletta, Milte, & Meyer, 2013). Here, we briefly explain three possible routes: 1) neurotransmitter function, 2) CNS energy supply, and 3) neuroprotection.

1) Neurotransmitter function

A pathway by which micronutrient bioavailability affects the CNS is that it acts as a coenzyme in the synthesis of various neurotransmitters. The B-vitamins, such as B1 (thiamine), B2 (riboflavin), B6 (pyridoxine, pyridoxal and pyridoxamine), folic acid (vitamin B11), and B12 (cobalamin) are involved as coenzymes in the metabolism of several neurotransmitters, including serotonin, dopamine, noradrenaline, and GABA.

Brain-specific symptoms of deficiency of B-vitamins include irritability, emotional disturbances, cognitive impairment, depression, psychotic symptoms and aggression (Kennedy, 2016). Vitamin D is lipophilic and has characteristics of a steroid hormone. It plays a role in the development of the CNS and the proper functioning of neurotransmitters. Low vitamin D status has been linked to a number of mental illnesses, such as schizophrenia, depression and cognitive decline (Eyles, Burne, & McGrath, 2013). Indirectly, also Omega-3 fatty acids (FA) have an effect on the functioning of neurotransmitters. The fluidity of the neuron cell membrane is increased by the presence of docosahexaenoic acid (DHA), which has a beneficial effect on the functioning of the membrane proteins such as the receptors of the monoaminergic neurotransmitters (Parletta et al., 2013).

2) CNS energy supply

The CNS needs much energy to function optimally that is about 20% of the total body requirement at rest. For special tasks, the need can increase even further. For example, self-control is linked to reduced aggressive behavior. There is evidence that self-control relies on an optimal energy management of the CNS (Gailliot et al., 2007). B vitamins are involved in the process of catabolic energy production via direct roles in the citric acid cycle and the formation of the energy carrier adenosine triphosphate (ATP) (Kennedy, 2016). Also, a number of minerals like chromium, iron, magnesium, manganese and zinc are involved in the energy metabolism of the CNS (Huskisson et al., 2007).

3) Neuroprotection

There are multiple ways in which micronutrients are involved in protecting nerve cells in the performance of their function. The below examples do not provide a comprehensive overview but illustrate the roles that the different micronutrients have in the protection of the CNS. Elevated homocysteine levels in the blood are associated with neuro damage and an increased risk of depression, schizophrenia and a decline in cognitive functions. Sufficient bioavailability of vitamin B6, folic acid and vitamin B12 as well as all other B-vitamins are indispensable for the conversion of homocysteine into methionine (Kennedy, 2016). As an end-product of the methionine cycle, glutathione is produced, which is the basis of a potent antioxidant in the CNS, a prophylaxis against oxidative damage of the CNS (Kennedy, 2016). Vitamins C, E and selenium are also antioxidants and have neuroprotective properties (Kaplan, Crawford, Field, & Simpson, 2007). Adequate bioavailability of omega-3 FA has a neuroprotective effect in another

way. Chronic low-grade inflammatory processes may contribute to neurodegeneration. Omega-3 FA have anti-inflammatory properties through the production of leukotrienes (Parletta et al., 2013). Other micronutrients such as vitamin A, B6, B11, B12, C, D, copper, iron, selenium and zinc play synergistic roles in the proper functioning of the immune system (Messina, Lampe, Birt, & Appel, 2001).

As described above, there are several ways in which vitamins, minerals, and omega-3 FA support the CNS. A reductionist view of the effect of an isolated nutrient on a single process has important limitations (Messina et al., 2001). It is not one micronutrient that facilitates a particular process, but it is a chain of reactions in which many micronutrients play a role in mutual cohesion (Kennedy, 2016). That is why we are interested in the effect of a broad spectrum of micronutrients and omega-3 FA on aggressive behavior in the present thesis.

Research among prisoners and youngsters with mental health problems shows that dietary supplements may reduce aggressive behavior. Since the 1990s, studies have shown effectiveness of dietary supplements on behavior of young male inmates (Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Schoenthaler et al., 1997; Schoenthaler, Gast, Giltay, & Amos, 2021; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak, 2010). The beneficial effects were mainly seen in the reduction of rule violations as the primary outcome measure. There was no effect on the self-report scales for aggression and anger, used as a secondary outcome measure. Furthermore, research into the effectiveness of vitamins on behavior has been conducted among other target groups such as (school) children and university students and people with mental health problems (Adams et al., 2018; Long & Benton, 2013; Raine et al., 2016; Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018; Schoenthaler & Bier, 2000). In addition to positive effects on the number of aggression incidents, there were also studies with equivocal results (e.g., Tammam, Steinsaltz, Bester, Semb-Andenaes, & Stein, 2016), and a study showing no effect (De Bles, 2022).

Aim and outline of this thesis

Aggressive behavior of people with ID is a major and – in many cases – persistent problem. Several psychological therapies are currently being used such as behavioral therapy, anger management, and mindfulness-based therapy. Also, off-label antipsychotics are widely used with potentially serious side effects and limited evidence of effectiveness. Despite these therapies, there remains a need for affordable, effective,

and low-impact therapies for aggression in individuals with ID. Research into the effect of dietary supplements on aggressive behavior among prison inmates shows promising results. Due to the low diet quality in people with ID, we expect that dietary supplements may be effective. The primary aim of this thesis is to investigate whether an intervention with dietary supplements can be used in clinical practice to reduce aggressive behavior in people with ID.

In Chapter 2, we conduct a cross-sectional study on the quality of nutrition in people with ID. We use the "Eetscore" food frequency questionnaire to measure nutritional quality and use participants from the "Eet, weet en meet studie" as control group. We hypothesize that people without ID have a higher diet quality than people with ID.

Next, in Chapter 3, we conduct a qualitative study into the acceptability of an intervention with dietary supplements among clients with ID, client representatives and professionals of a facility for ID-care. Using focus groups, we collect data and use constant comparison analysis based on grounded theory.

In Chapter 4, with access to data from a study conducted in the 1990s, we investigate the effect of multivitamin and mineral supplementation on serious rule-breaking behavior of inmates in correctional facilities in California in a three arm RCT. The placebo arm is compared with a dose of approximately 100% and 300% ADH. The primary outcome measure is serious rule-breaking behavior, and the duration of the intervention is 15 weeks.

In Chapter 5, we study the effect of multivitamin-mineral, and omega-3 FA supplementation on aggressive behavior in people with ID. The age of the participants is 12 to 40 years old; they live in a care facility for people with ID or receive day care. It is a triple-blind randomized placebo-controlled pragmatic study, and the aggression incidents are measured daily with the MOAS (see 1.2). The intervention period is 16 weeks, followed by a cross-over of the same duration. We hypothesize that dietary supplements are effective to reduce aggressive behavior.

In Chapter 6, we conduct a systematic review of studies on the effect of vitamins and minerals on aggressive behavior. In addition, we perform a meta-analysis to determine the pooled effect size of these different studies.

In Chapter 7, we focus on the challenges encountered when conducting an intervention study with dietary supplements in vulnerable target groups. We will thereby focus on five main themes: 1) multiple sites study, 2) inclusion of vulnerable participants, 3)

intervention with dietary supplements, 4) behavioral outcomes, and 5) collecting bio samples.

In Chapter 8, finally, we start with a summary of the main findings and continue with a general discussion of the methods and outcomes of the studies included in this thesis and provide recommendations for clinical practice and further research.

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Chapter 2

DIET QUALITY AMONG PEOPLE WITH INTELLECTUAL DISABILITIES AND BORDERLINE INTELLECTUAL FUNCTIONING

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ABSTRACT

Background: We sought to assess diet quality among people with intellectual disabilities or borderline intellectual functioning, living in residential facilities or receiving day care.

Methods: We measured diet quality using the Dutch Healthy Diet Food Frequency Questionnaire (DHD) and compared this between participants with (n = 151) and controls without intellectual disabilities (n = 169). Potential correlates of diet quality were explored.

Results: We found lower mean diet quality among people with intellectual disabilities (M = 80.9) compared to controls (M = 111.2; mean adjusted difference -28.4; 95% CI [-32.3, -24.5]; p< .001). Participants with borderline intellectual functioning and mild intellectual disabilities had lower diet quality and higher body mass index than individuals with severe to profound intellectual disabilities. Being female was a predictor of better diet quality.

Conclusion: Overall, we found that diet quality was low in the sample of people with intellectual disabilities or borderline intellectual functioning.

INTRODUCTION

Individuals with intellectual disabilities are at an increased risk of poor diet, but there is insufficient information to understand how nutritional problems are expressed in this population (Humphries et al., 2009). Obesity, diabetes and stunted growth are examples of chronic diet-related health problems that are relatively prevalent in individuals with intellectual disabilities (Cushing et al., 2012; Ptomey & Wittenbrook, 2015). These health problems are not evenly distributed across the different severity levels among intellectual disabilities. A high prevalence of obesity (34.4%–43.9%) is found in people with mild intellectual disabilities and moderate intellectual disabilities (Hsieh et al., 2014). There is a relatively high prevalence of being underweight (10.1%) in people with severe to profound intellectual disabilities (Hsieh et al., 2014). Nutritional status among the different severity levels of intellectual disabilities needs to be systematically assessed to support effective nutritional interventions. In this study, we focused on the dietary intake of people with intellectual disabilities or borderline intellectual functioning, which is usually assessed using food frequency questionnaires (FFQs) and food diaries (Koritsas & Iacono, 2016). Compared to the recommended daily intake, people with intellectual disabilities scored low on the dietary intake of fibres (Adolfsson et al., 2008; Bertoli et al., 2006), vegetables and fruits (Draheim et al., 2007; Hamzaid et al., 2020; Humphries et al., 2004) and poly-unsaturated fatty acids (PUFAs; Molteno et al., 2000; Soler Marín & Graupera, 2011). In several studies, the relative proportion of saturated fats or simple carbohydrates to the total energy intake was high (Cunningham et al., 1990; McGuire et al., 2007; Robertson et al., 2000). However, the concept of diet quality goes beyond looking at the individual micro- or macronutrients; it aims to evaluate the entire food intake (van Lee et al., 2016; Wirt & Collins, 2009). The relationship between diet quality and the severity of an intellectual disability has not yet been explored. Furthermore, people with borderline intellectual functioning are not often included in studies, even though they may adaptively function at the same level as people with mild intellectual disabilities (Arvidsson & Granlund, 2018). To date, no quality diet studies have been conducted among people with intellectual disabilities or borderline intellectual functioning that differentiate between the levels of intellectual disabilities. Diet studies in which diet quality was compared to a control group from the general population are

also scarce. Being overweight is linked in complex bidirectional ways to caloric intake and food choices. Sundararajan et al. (2014) found that body mass index (BMI) was inversely associated with diet quality in the general population, but there is a gap in the literature regarding the potential association between BMI and diet quality among people with intellectual disabilities. The first aim of our study was to assess diet quality among people with intellectual disabilities or borderline intellectual functioning and to compare this assessment to the general population. The second aim of our study was to compare diet quality and BMI distribution between the people with different levels of intellectual disabilities.

METHOD

The current study was part of an overarching research project investigating the effectiveness of nutritional supplementation on aggressive behaviour among people with intellectual disabilities (clinicalTrials. gov, NCT03212092). There were two steps in the inclusion procedure. First, the inclusion criteria to participate in the informed consent procedure included having an IQ < 85 and living in a residential facility or receiving day care for at least 5 days a week. During this first step, we collected dietary and all other data used for the current analyses. Second, participants who met specific exclusion criteria regarding age, behavior, breastfeeding, medication, morbidity or pregnancy could not proceed with the randomised controlled trial (RCT).

Ethical statement

The research was conducted in full accordance with the ethical principles of the World Medical Association Declaration of Helsinki. The ethical review board of the Leiden University Medical Centre (LUMC) approved the study (NL60839.058.17). All study participants or their legal representatives gave their written informed consent before the start of the data collection. Certain participants had sufficient cognitive functions to judge what participation in the study would entail, but they nevertheless had a legal representative because of their minor age or because a legal representative had been appointed by the court. In these cases, both the client and the legal representative gave written informed consent. Special versions of informed consent forms were designed to be comprehensible for people with moderate to mild intellectual disabilities.

Participants

Table 2.1 Descriptive Characteristics of Participants and Control Subjects

	Participants with Intellectual Disabilities			Controls			
	n	Mean (*SD*) or %	Range	*n*	Mean (*SD*) or %	Range	*p**
Male	98	64.9%		142	84.0%		
Female	53	35.1%		27	16.0%		
Age (years)	151	23.2 (7.9)	12–57	169	26.4 (7.5)	14–40	<.001
Body Mass Index (BMI)	149	24.9 (6.1)	14–52	168	22.7 (3.8)	16–44	<.001
IQ	142	52.6 (20.6)	10–85				
Receiving Day Care Only	9	6.0%					
Staying in a Residential Facility	142	94.0%					

Note. * Difference between groups

All persons who gave informed consent (or for whom informed consent was given) were included in this study. We also included participants who were not included in the subsequent RCT. Participants were recruited between March 2018 and April 2020 from six intellectual disabilities service provider organisations located throughout the Netherlands. For the sake of readability, we will refer to this entire group as 'people with intellectual disabilities' and will only refer to 'borderline intellectual functioning' when it is necessary to distinguish between these groups. Two of the organisations were forensic care facilities for people with mild intellectual disabilities.

Table 2.2 BMI, Mean Age, and Proportion of Females Among Participants

Severity of ID	*n*	BMI (*SD*)	*n*	Age in Years (*SD*)	% female
Borderline	42	26.1 (5.9)	42	20.2 (7.4)	52.4%
Mild	41	27.1 (7.8)	42	23.6 (7.9)	38.1%
Moderate	22	23.4 (4.8)	22	25.3 (6.6)	27.3%
Severe to Profound	44	22.4 (3.9)	45	24.5 (8.5)	20.0%
Total	149	24.9 (6.1)	151	23.2 (7.9)	35.1%

Note. Borderline = borderline intellectual functioning, BMI = Body Mass Index

The control group was drawn from of the 'EetMeetWeet' (EatMeasureKnow) study (www.eetmeetweet.nl). This longitudinal online study on the relationship between food and health is open to all adults who want to commit themselves to a long-term study on

this topic. For the control group, we included all participants between the ages of 12 and 40 years who applied to the 'EetMeetWeet' study between February 2017 and July 2017. The control group consisted of 169 participants who had a mean age of 26.4 (SD = 7.5) years.

Data collection

We assessed diet quality using the Dutch Healthy Diet Food Frequency Questionnaire (DHD) (www.eetscore.nl), a questionnaire based on the 2015 Dutch food-based guidelines for a healthy diet (Gezondheidsraad, 2015; Kromhout et al., 2016). The DHD is a short self-report screener with 40 items and is derived from the more extensive Dutch Healthy Diet Index (Looman et al., 2017; van Lee et al., 2016). The DHD evaluates to what extent someone adheres to the Dutch Dietary Guidelines as suggested by the Health Council of the Netherlands (Gezondheidsraad, 2015). The total score ranges from 0 to 160, with higher scores indicating a better diet quality. Sixteen food groups, with a score between 0 and 10, include vegetables, fruits, whole-wheat products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meats, processed meats, sweetened beverages, alcohol, salt and unhealthy food products. The last group is based on the guidelines set by the Netherlands Nutrition Centre (Brink et al., 2019). For the healthy food groups, such as 'fruits' and 'vegetables', a higher intake resulted in a higher score (between 0 and 10). For unhealthy food groups, such as 'processed meats' or 'sweetened beverages and fruit juices', a higher intake resulted in a lower score. Whole grain products were based on the ratio of whole grain to refined grain, and 'fats and oils' were based on the ratio of saturated to unsaturated fats. For dairy, we used an optimum score of 300–450 g per day (Looman et al., 2017; see Appendix 2.1). In the paper questionnaires, participants provided details regarding their daily diet from the preceding month. A caregiver assisted the participants with mild intellectual disabilities when the detailed nutritional questions were too complex for them to complete independently. The caregiver completed the questionnaire as a proxy for participants with severe to profound intellectual disabilities (Table 2.3). We included three additional questions that determined who decided what the participants ate, how well informed the proxy was about the food habits of a participant, and who completed the DHD. The control group completed the DHD questionnaire online using an e-form (http://www.eetscore.nl/). Caregivers obtained the following demographic characteristics from participants: age, gender, weight (kilogramme) and height (metre). We used the case-file data provided by the healthcare

organisations to obtain participants' IQ scores. The IQ and developmental age tests were conducted by psychologists at various time points, who used the following validated tests: Bayley, Snijders-Oomen non-verbal intelligence test (Son-R), Vineland Adaptive Behavior Scale (VABS), Wechsler Adult Intelligence Scale (WAIS), Wechsler Intelligence Scale for Children (WISC), Wechsler Non-Verbal (WNV) and the Universal Non-verbal Intelligence Test (UNIT). When a participant with severe to profound intellectual disabilities did not have a measured IQ, we estimated that participants' IQ from his or her developmental age using the WHO developmental age range as a reference (World Health Organization, 2010). The IQ cut-off values used for the intellectual-disabilities severity groups are shown in figure 2.2 (Boat & Wu, 2015). The BMI (in kg/m2) was calculated and used as a potential predictor for diet quality, in addition to age and gender (Hiza et al., 2013; Temple et al., 2010).

Table 2.3. Additional Questions in the Group of People With Intellectual Disabilities About the Food Choice and the Use of Proxy Informants for Completing the DHD (n = 150)

		n	%
Who Decides What the Participant Eats?			
	Not the caregiver nor the participant	20	13.3
	Caregiver	50	33.3
	Caregiver together with the participant	71	47.3
	Participant only	1	0.7
	Parents	8	5.3
Who Completed the DHD?			
	Proxy	64	42.7
	Proxy together with participant	85	56.7
	Participant alone	1	0.7
Does the Proxy Know Everything the Participant Is Eating?			
	Yes, every meal including snacks	89	59.3
	All meals except snacks	32	21.3
	Two meals a day	20	13.3
	One meal a day	8	5.3
	No	1	0.7

Note. DHD = Dutch Healthy Diet Food Frequency Questionnaire

Data analysis

Multivariate linear regression analysis was used to compare the DHD total and subscores between people with intellectual disabilities and controls, adjusting for age, gender and

BMI. Furthermore, as potential correlates of the DHD total score, we entered the categories age, gender, BMI and IQ into a linear regression model. Using an ANCOVA, we assessed the difference in BMI between the severity groups of people with intellectual disabilities, adjusting for age and gender. Significance levels were adjusted for multiple testing based on the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995). Data were analysed using SPSS statistical software 25.0 (version 25, IBM Corp.) and the R statistical software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria 2016, https://www.R-project.org/)

RESULTS

Demographic characteristics of participants and controls are presented in Table 2.1. We included 320 participants (of whom 21.9% were women): 151 people with intellectual disabilities and 169 controls. The mean age of the group of people with intellectual disabilities was significantly higher than that of the controls. Men were overrepresented in both groups: 64.9% (people with intellectual disabilities) and 84.0% (controls). The group of people with intellectual disabilities showed a higher mean BMI than controls. Table 2.2 shows the mean BMI according to intellectual disability severity group. It is noteworthy that the BMI is significantly higher in participants with mild intellectual disabilities than participants with severe and profound intellectual disabilities, $F(3, 143) = 5.3$, $p = .002$.

At most locations, the food choices were made by the caregiver together with the participant (Table 2.3). Figure 2.1, the mean DHD total score of the participants with intellectual disabilities was 80.9 (SE ± 1.4; range: 26–18). The poorest adherence to the Dutch Dietary Guidelines was seen in the subcategories unhealthy choices (mean score 1.1), nuts (score 1.9), tea (score 2.3), processed meats (score 2.7), sweetened beverages (score 3.2) and fish (score 3.6). The best adherence was seen in the subcategories coffee (score 7.3), red meat (score 8.9) and alcohol (score 9.4). The total DHD score of participants with intellectual disabilities was on average 30 points lower compared to that of controls (80.9 vs. 111.2; $p < .001$). Furthermore, significant mean differences were observed for all subcategories except for red meat, fats and oils and dairy. All subcategory scores that differed significantly from the control group showed a lower score in the

group of people with intellectual disabilities compared to the control group, except for alcohol. The largest mean differences in subcategory scores were observed for the following categories: processed meats (3.2 points lower), nuts (3.4 points lower), tea (3.8 points lower) and sweetened beverages (4.7 points lower). Significant associations persisted after adjusting for multiple testing.

Food groups	Crude difference (95% CI)	P-value	Adjusted difference (95% CI)	Statistic	P-value
DHD total score	30.27 (26.48; 34.07)	< 0.001	28.39 (24.46; 32.32)	14.150	< 0.001
Sweetened beverages	4.79 (4.08; 5.49)	< 0.001	4.69 (3.94; 5.43)	12.360	< 0.001
Nuts	3.33 (2.57; 4.09)	< 0.001	3.39 (2.58; 4.19)	8.253	< 0.001
Tea	4.11 (3.27; 4.95)	< 0.001	3.82 (2.93; 4.70)	8.462	< 0.001
Processed meat	3.23 (2.49; 3.98)	< 0.001	3.19 (2.41; 3.97)	8.030	< 0.001
Salt	2.06 (1.43; 2.69)	< 0.001	2.19 (1.53; 2.85)	6.475	< 0.001
Unhealthy choices	2.09 (1.35; 2.83)	< 0.001	2.24 (1.45; 3.02)	5.604	< 0.001
Vegetables	2.12 (1.48; 2.76)	< 0.001	1.84 (1.17; 2.51)	5.360	< 0.001
Fish	1.99 (1.32; 2.67)	< 0.001	1.77 (1.06; 2.49)	4.859	< 0.001
Wholegrain products	1.57 (1.02; 2.12)	< 0.001	1.31 (0.74; 1.89)	4.462	< 0.001
Legumes	2.05 (1.21; 2.90)	< 0.001	1.81 (0.92; 2.70)	3.984	< 0.001
Fruit	1.63 (0.90; 2.36)	< 0.001	1.40 (0.64; 2.17)	3.601	< 0.001
Coffee	0.83 (0.26; 1.40)	0.005	0.80 (0.20; 1.40)	2.613	0.009
Red meat	0.68 (0.24; 1.12)	0.003	0.44 (-0.02; 0.90)	1.894	0.06
Fats and oils	0.82 (-0.24; 1.88)	0.13	0.54 (-0.58; 1.66)	0.944	0.35
Dairy	-0.81 (-1.55; -0.07)	0.03	-0.61 (-1.39; 0.16)	-1.551	0.12
Alcohol	-0.55 (-1.08; -0.02)	0.04	-0.82 (-1.37; -0.26)	-2.876	0.004

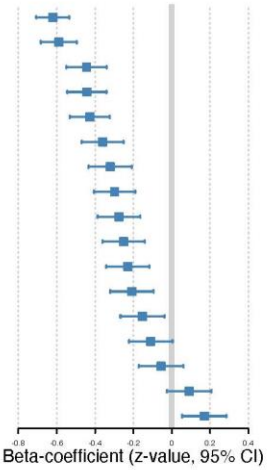

Figure 2.1 Frequency questionnaire (DHD) score of participants with intellectual disabilities and controls and their adjusted differences. DHD = Dutch Healthy Diet Food Frequency Questionnaire

Predictors of diet quality

Figure 2.2 presents the analyses of the potential correlates of overall diet quality for the 151 participants with intellectual disabilities. In the multivariate analysis, women had on average a better diet quality compared to men (p = .01). Participants with mild intellectual disabilities and borderline intellectual functioning had a lower diet quality compared to participants with severe to profound intellectual disabilities (p = .007). Age and BMI groups were not significant predictors in the multivariable model.

Predictor	n	Crude mean (SE)	Crude beta (95% CI)	p-value	Adjusted mean (SE)	Adjusted beta (95% CI)	t-stat	p-value
Gender:								
Male (ref)	98	79.6 ± 1.7	0 (Ref.)		80.5 ± 2.1	0 (Ref.)		
Female	51	83.3 ± 2.4	3.72 (-1.97; 9.40)	0.20	88.0 ± 2.8	7.50 (1.83; 13.2)	2.592	0.01
Age:								
<20 years	61	78.5 ± 2.2	0 (Ref.)		82.2 ± 2.4	0 (Ref.)		
20-29 years	58	83.2 ± 2.2	4.74 (-1.31; 10.8)	0.13	85.7 ± 2.6	3.49 (-2.93; 9.92)	1.066	0.29
>=30 years	30	81.3 ± 3.1	2.80 (-4.55; 10.1)	0.46	84.9 ± 3.4	2.77 (-4.65; 10.2)	0.732	0.47
BMI:								
18.5-25: Normal weight	77	81.0 ± 1.9	0 (Ref.)		81.8 ± 2.0	0 (Ref.)		
<18.5: Underweight	13	88.6 ± 4.6	7.62 (-2.22; 17.5)	0.13	89.5 ± 4.7	7.66 (-1.86; 17.2)	1.577	0.12
>25: Overweight/obese	59	79.0 ± 2.2	-1.94 (-7.62; 3.74)	0.50	81.4 ± 2.2	-0.44 (-6.12; 5.24)	-0.151	0.88
IQ, intellectual disability:								
70-85: Borderline (BIF)	42	76.3 ± 2.5	0 (Ref.)		79.6 ± 3.1	0 (Ref.)		
50-69: Mild	41	76.8 ± 2.5	0.42 (-6.55; 7.38)	0.91	79.8 ± 2.9	0.15 (-7.14; 7.44)	0.040	0.97
35-49: Moderate	22	82.9 ± 3.5	6.53 (-1.83; 14.9)	0.13	86.0 ± 3.7	6.33 (-2.62; 15.3)	1.386	0.17
<35: Severe to profound	44	88.1 ± 2.4	11.7 (4.88; 18.6)	0.001	91.6 ± 2.8	12.0 (4.36; 19.7)	3.077	0.003

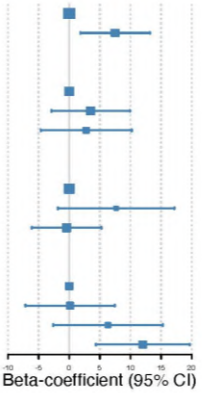

Figure 2.2 Predictors of diet quality in people with intellectual disabilities, crude and adjusted means and crude and adjusted betas with Forest plots. BIF, borderline intellectual functioning; BMI, body mass index; IQ, intelligence quotient

DISCUSSION

Overall, our results showed that diet quality in participants with intellectual disabilities was lower than that of the control group. This applied to almost all food groups, with the exception of dairy products and alcohol. The general pattern was that participants with intellectual disabilities tended to over-consume sugar, processed meats and other unhealthy food products and under-consume omega-3 FAs (i.e., fish and nuts). Male participants and those with mild intellectual disability and borderline intellectual functioning were at the highest risk of consuming a low-quality diet. It is likely that a change in eating habits in these individuals will reduce the burden of disease. The finding of an overall low-diet quality in people with intellectual disabilities compared to the controls is consistent with previous research (Bertoli et al., 2006; Braunschweig et al., 2004; Draheim et al., 2007; Hoey et al., 2017; McGuire et al., 2007). Likewise, many studies found similar consumption patterns in the 'unhealthy choices' and 'sweetened beverages' categories (Cartwright et al., 2015; Chia-Feng & Jin-Ding, 2010). In our study, alcohol consumption was low in all severity categories among people with intellectual disabilities. Among people with mild intellectual disabilities; however, alcohol consumption can be similar or even higher than that found in peers of average intelligence (Didden et al., 2020). The difference in our study can be explained by the fact that many of our participants with mild intellectual disabilities had zero or restricted

access to alcoholic beverages. Although our research was not designed to study potential causes of the relatively low-diet quality in people with intellectual disabilities, some speculations can be made. First, it is often easier and cheaper to make unhealthy food choices (Appelhans et al., 2012; Jetter & Cassady, 2006). Without proper support, people with intellectual disabilities lack the insight and money to go for the healthier choices. In previous studies among people with moderate and mild intellectual disabilities, researchers have suggested that unsupported autonomy in food choice may lead to less healthy food choices (Adolfsson et al., 2012; Bryan et al., 2000; Grammatikopoulou et al., 2008). Second, the support staff may also lack sufficient training in foods and nutrition (Humphries et al., 2004). The low-diet quality in people with mild intellectual disabilities is of concern. We found different intake levels of diverse food groups, which may increase the risk of weight gain and abdominal obesity (Barnes et al., 2015; Ruanpeng et al., 2017; Schlesinger et al., 2019). It is also known that the prevalence of obesity and nutrition-related diseases in people with moderate intellectual disabilities to mild intellectual disabilities is high (Bryan et al., 2000; Hsieh et al., 2014; Ptomey & Wittenbrook, 2015; Ranjan et al., 2018). It is likely that a change in eating habits in these individuals will reduce the burden of disease.

Limitations

The DHD is a 40-item screener providing a rough estimate of the diet quality. This retrospective questionnaire may be susceptible to recall bias. The method of administration of the DHD differed among the cases and controls. Participants with intellectual disabilities often needed assistance from the support staff (observer) to complete a paper questionnaire; the control group used an online version of the questionnaire as a self-report scale. Both methods have their own risks of measurement error and bias. When filling in a self-report scale, there may be an increased risk of participants giving socially desirable answers. When support staff helps to complete the questionnaire, some errors may be introduced because the observer is not always observing what the client is eating. Although our sample size is larger than that of previous diet quality studies in this study population, it is still small for our purposes. Moreover, participants and controls were not matched by age or gender, but we adjusted for these potential confounders in the multivariate analyses. The IQ data of the care organisations were measured using various instruments and collected at various time points, which makes a comparison of the scores less accurate. In addition, the

classification of the severity level of intellectual disabilities based solely on IQ scores is outdated (Tassé et al., 2016). Since the DSM-5, it is advised to include the level of adaptive functioning in a patient's assessment (American Psychiatric Association [APA], 2013, p. 33). Furthermore, our participants may not be representative of the whole population of people with intellectual disabilities, as they were recruited for a study on aggression and displayed higher levels of aggressive behavior. Therefore, our findings need to be replicated in other groups of people with intellectual disabilities. Additionally, the control group may have had some self-selection for a relatively healthy lifestyle (given the lower than average BMI) compared to the general population (RIVM, 2012).

Strengths

The same FFQ was used in people with intellectual disabilities and controls. Moreover, we adjusted our analysis for potential confounders, and we analysed the potential effects of different severity levels among intellectual disabilities. Additionally, the data were collected in 76 locations from four intellectual disabilities care organisations and two forensic intellectual disabilities care organisations in the Netherlands, which increased the external validity.

Conclusion

Even if people with moderate to mild intellectual disabilities can identify healthy food, they still need support to translate this knowledge into making healthy choices (Adolfsson et al., 2012; Kuijken et al., 2016). To sustainably increase the diet quality, more is needed apart from simply training the support staff. In a study regarding the facilitating factors for health promotion, Kuijken et al. (2019) concluded that a healthy lifestyle should be embedded in the mission of the care organisation and in the individual support plans of the clients with intellectual disabilities and should also be part of the employees' job descriptions. Diet quality among people with intellectual disabilities might be improved through a deeper integration into the entire care system.

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APPENDIX

Appendix 2.1 Components of the Dutch dietary guidelines with the maximum and minimum score based on the DHD15-index (Looman *et al.* 2017).

Component	Recommendations Dutch dietary guideline	Minimum score (=0)	Maximum score (=10)
Vegetable	Eat at least 200 gram vegetables / day	0 g	≥ 200 g
Fruit	Eat at least 200 gram fruit / day	0 g	≥ 200 g
Wholegrains	1. Eat at least 90 grams of brown, whole grain bread or other whole grain products per day (50%). 2. Replace refined grain products with whole grain products (50%)	0 g No consumption of whole grain products OR ratio of whole grain to refined grain products ≤ 0.7	≥ 90 g No consumption of refined grain products OR ratio of wholegrain / refined grain products ≥ 11
Legumes	Eat legumes weekly	0 g	≥ 10 g
Nuts	Eat at least 15 grams unsalted nuts / day	0 g	≥ 15 g
Dairy	Take a few servings of dairy a day, including milk and yogurt	0 g OR ≥ 750 g	300-450 g
Fish	Eat fish, preferably fatty fish, once a week	No fish consumption	Consumption of fish at least 4 times a month, of which at least 3 times fatty fish.
Tea	Drink three cups of tea a day	0 ml	≥ 450 ml
Fats and oils	Replace butter, hard margarine and cooking and frying fat with soft margarine, liquid baking and frying fat and vegetable oils.	No consumption of soft margarines, liquid shortening and vegetable oils OR ratio of liquid shortening / hard cooking fat ≤ 0.6	No consumption of butter, hard margarines and hard cooking fats OR ratio of shortening / hard cooking fat ≥ 13
Coffee	Replace unfiltered with filtered coffee	Consumption of unfiltered coffee	Consumption of only filtered coffee or no coffee consumption
Red meat	Limit the consumption of red meat	100 g	≤ 45 g
Processed meat	Limit consumption of processed meat	≥ 50 g	0 g
Sugar containing beverages	Drink as few sugar containing beverages as possible	≥ 250 g	0 g
Alcohol	Do not drink alcohol, or at least no more than 1 glass a day	2 glasses or more a day OR binge drinking (4 glasses or more per day) 3 glasses or more a day OR binge drinking (6 glasses or more per day)	No alcohol, or no more than 1 glass a day
Salt	Eat no more than 6 grams of table salt per day	≥ 3.8 g (sodium)	< 1.9 g (sodium)
Unhealthy choices*	Energy dense and nutrient poor food items not included in one of the 15 DHD components	Less than 3 unhealthy choices	7 or more unhealthy choices

Note. * "Unhealthy choices" are added to the DHD-15 components and consist of food products that contribute significantly to the total energy intake

Chapter 3

ADOPTION OF DIETARY SUPPLEMENTS TO REDUCE CHALLENGING BEHAVIOR IN PEOPLE WITH INTELLECTUAL DISABILITY: A QUALITATIVE STUDY

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D.A.A. Gast, E.J. Giltay, A.J.C. van der Slot, J.K. de Wit, J. Heijstek-van Grootheest, A.M. van Hemert , R. Didden. Adoption of Dietary Supplements to Reduce Challenging Behavior in People with Intellectual Disability: A qualitative study

ABSTRACT

Introduction: Dietary supplements may improve challenging behavior in people with intellectual disability, but it is unclear to what extent these people and their caregivers, are open to this intervention. In this focus group study, we aimed to explored which factors influence the adoption of a dietary supplement intervention.

Methods: We conducted seven focus group sessions with people with intellectual disabilities, professionals and client representatives. The focus groups were analysed following the steps of 'constant comparison analysis.'

Results: Five topics emerged from the data: (1) relationship with other interventions, (2) professional roles, (3) characteristics of the intervention, (4) being informed (5) supplements and healthy diet.

Conclusion: Adoption of an intervention with dietary supplements can be facilitated by clarifying the professional roles, a prerequisite is evidence about the effectiveness and safety of the intervention. Adoption by people with intellectual disabilities can be facilitated by involving them in assessing the attractiveness of the intervention.

INTRODUCTION

Implementation of a new intervention for challenging behavior in people with intellectual disability can be challenging, even if there is evidence of effectiveness (Lloyd and Kennedy, 2014). This is known as the research-to-practice gap (Proctor et al., 2009), often caused by a mismatch between the intervention and the potential users' needs and capacities (Dingfelder and Mandell, 2011). Involving users in the implementation and assessing their perspectives on the intervention's acceptability may help facilitate successful adoption of the intervention (Greenhalgh et al., 2004).

Challenging behavior is common among people with intellectual disabilities. The most common types of such behaviors are aggressive and self-injurious behavior (Emerson et al., 2001), with a prevalence of up to 50%-80% within specific subpopulations (Bowring et al., 2019). A range of interventions is used to treat challenging behavior, such as anger management, applied behavior analysis, mindfulness-based therapy, and psychotropic medication among others (Didden et al., 2016). Despite these efforts, challenging behavior often persists and there remains a need for additional effective, minimally invasive, safe, and cost-effective ways to reduce challenging behavior (Campbell et al., 2014; Sheehan and Hassiotis, 2017). Dietary supplements may complement the repertoire of approaches.

The effect of multivitamin, mineral, and omega-3 fatty acid supplements on behavior has been studied among prisoners and children with problem behaviors (Benton, 2007; Frensham et al., 2012; Rucklidge and Kaplan, 2013). Studies have shown that daily doses of supplements may have a small to moderate effect on aggression and antisocial behavior (Adams, 2015; Gesch et al., 2002; Raine et al., 2016; Rucklidge et al., 2018; Schoenthaler et al., 1997; Zaalberg et al., 2010). Besides, an intervention with dietary supplements could well fit the needs of people with intellectual disabilities since their nutritional status on average has been found to be suboptimal (Humphries et al., 2009) and their ability to implement a healthier food intake has been found to be relatively unsuccessful (Heller et al., 2011).

According to the "diffusion of innovations" model, transferring an effective intervention into daily clinical practice is a complex process in which four phases can be distinguished (Rogers, 2002; Durlak and DuPre, 2008). The first "dissemination phase" comprises the

information supply to the users. In the second "adoption phase," users decide whether they agree with using the intervention. The third "implementation phase" is the start of practical use. The final "sustainability phase" is the maintenance of the use of the intervention. The present study seeks to facilitate the adoption phase. Qualitative research can be used to support the process of adoption (Palinkas, 2014). We are not aware of other studies on the adoption of interventions for challenging behavior in people with intellectual disabilities.

The use of dietary supplements to reduce challenging behavior is a new type of intervention that is currently tested in a pragmatic randomized controlled trial (clinicalTrials.gov, NCT03212092). It is unclear to what extent people with intellectual disabilities, as well as their representatives and caregivers, are open to using supplements as an intervention for challenging behavior. Therefore, in this focus group study, we aimed to explore which factors influence the adoption of a dietary supplement intervention.

METHODS

The group process may help participants form and express their ideas and opinions. That is why focus groups are suitable for dealing with topics, even if not all participants have prior opinions on the matter (Morgan and Krueger, 1993). Since no studies have been conducted on the adoption of dietary supplements for challenging behavior, we chose to set up the study according to the "Grounded Theory Approach", in which concepts from the data emerge in an interactive process of data collection and theory formation (Strauss and Corbin, 1994).

All participants provided written informed consent, which included permission to make a video recording of the session. Anonymity was achieved by giving each participant a random code used in the transcription of the recordings. Participants with intellectual disabilities received a gift voucher worth €5 for attending the focus group meetings. Professional caregivers and client representatives could claim their travel allowance.

Recruitment and Participants

We recruited participants with and without intellectual disabilities from an organization for the care of people with intellectual disabilities located in the western part of the

Netherlands. The participants with mild intellectual disabilities / borderline intellectual functioning came from three pre-selected locations. Inclusion criteria were: living in a care facility for people with intellectual disabilities, legally competent to give informed consent and the ability to participate in a focus group discussion. To create a safe environment, we invited people with intellectual disabilities who knew each other beforehand, and the focus groups took place in their living/working environment (Barr et al., 2003). The recruitment of professionals started with an in-company email with an open invitation. The theoretical sampling method was used for the groups that followed (Breckenridge and Jones, 2009). This meant that after coding and analysing the initial data, we looked for professionals and representatives who could provide an extra perspective on the topic and emailed them an invitation. The final sample size resulted from the data saturation principle, which was achieved when new data entries no longer yielded new information or insights (Khan, 2014).

Procedure

We developed separate moderator guides for moderating the groups with participants with intellectual disabilities and for the professionals and client representatives. Each moderator guide included a questioning route based on guidelines (Krueger and Casey, 2002), with questions about the adoption of the intervention (Appendix 3.1). We adapted the questions to the cognitive abilities of the participants. In focus group sessions with individuals with intellectual disabilities, illustrations and objects were used to support comprehension. Each of the seven focus groups lasted 45-90 minutes and was led by a trained focus group moderator (fourth author), who has extensive experience working as a psychologist with people with intellectual disabilities.

Data analysis

The sessions were transcribed from the video recordings. Due to a technical problem, focus group session number two (see Table 3.1) has not been recorded, but the reporting has been done using notes. Analyses were conducted after each focus group and were done by the first five authors who discussed their findings in regular meetings. If concepts remained unclear, we introduced these themes as questions in the next focus group. Meaningful units were distinguished in the text and were given an open code, using the constant comparative method (Corbin and Strauss, 1990). The open codes were combined in more general categories by axial coding. Finally, concluding themes that emerged from the categories were defined (Appendix 3.2). We used the software

program Atlas.ti (version 8, Scientific software development GmbH, Berlin, Germany) for the analysis.

RESULTS

Participants

Seven focus groups were held between February 2019 and May 2019, ranging from three to nine participants (total *n* = 35) (see Table 3.1). The participants with intellectual disabilities had an average age of 26.7 years (*SD* = 12.0), and 69% were female. The average age of the other participants was 46.4 years (*SD* = 14.3), and 91% was female.

Table 3.1. Distribution of the participants across the seven focus groups

Session Number	Participants	Representatives	Support staff	Psychologists	Medical staff	Managers	Total
1	3						3
2	6						6
3			4				4
4	4						4
5		1	3	3		2	9
6		1			4	1	6
7					1	2	3
Total	13	2	7	3	5	5	35

Note. Participants = participants with mild intellectual disabilities, or borderline intellectual functioning

The results will be discussed per topic and themes. The supporting quotes are listed in Appendix 3.3. We have identified the following five topics related to the adoption of the nutritional supplement intervention: (1) relationship with other interventions, (2) professional roles, (3) characteristics of the intervention, (4) being informed, and (5) supplements and healthy diet.

Topic 1: Relationship with other interventions

There was consensus among professionals that the approach to challenging behavior requires a wide range of interventions such as care methodologies, psychotropic medication, emotion regulation, and other behavioral therapies, not only dietary supplements.

Topic 2: Professional roles

Because the intervention with nutritional supplements is new, it is not yet embedded in the facilities' usual care for people with intellectual disabilities. Two themes were distinguished within this topic: the physician's role and the role of other professionals.

The physician's role

In several groups, the issue was brought up that it was not clear who would be in charge of this new intervention. Various options were discussed, such as a potential leading role for a dietitian because it concerns an intervention with dietary supplements or a psychologist because it concerns challenging behavior. Ultimately, most participants agreed that the physician should be responsible for prescribing and evaluating the intervention with supplements. Many professionals and people with intellectual disabilities considered an intervention with dietary supplements as a medical intervention, which should therefore take place under a physician's responsibility.

The role of other professionals

The intervention was not seen as solely a matter for the physician. Psychologists mentioned that preferably the start and evaluation of the intervention is discussed in a multidisciplinary team consisting of the client/representative, a support staff member, a dietician, and a psychologist, and a physician. Support staff discussed that their role is to motivate the client and facilitate daily supplement intake.

Topic 3: Characteristics of the intervention

The participants with intellectual disabilities were the largest contributors to this topic on the characteristics of the intervention. Two themes emerged from the data: the swallowability and the costs of the supplements.

Swallowability

Most people with intellectual disabilities had some experience with the use of nutritional supplements. They agreed that many of the supplements were difficult to swallow due to their large size and that this was made worse by an unpleasant smell and taste. They discussed how taking the supplements could be made easier and suggested making the supplements smaller, with a better taste. They also wondered if frequency of intake over the day could be reduced.

Costs

Both professionals and people with intellectual disabilities debated the question of who should pay for the supplements. Several support staff members suggested that the

supplements should be paid from the client's budget. However, the people with intellectual disabilities in the focus groups suggested that health insurance should cover these costs.

Topic 4: Being informed

On the one hand, this topic was about the information and opinions on the use of supplements that people already had, and on the other hand, about the information they lacked. The following themes were discussed: opinions about the intervention's efficacy and safety and the need for reliable information.

Opinions about the efficacy and safety

In all seven groups, the benefits of supplements were thought to comprise general health and resistance against the flu, while a minority believed it could positively affect challenging behavior. The low risk of side effects, relative to for example psychoactive medication, was often mentioned as a positive aspect of supplements. Still, many also expressed concerns about the intervention, including possible drug interactions, potential side effects, and the risk of excessive levels of micronutrients.

Lack of unambiguous, understandable, and evidence-based information

The support staff pointed out that they came across different and conflicting information about dietary supplements' efficacy and safety and were no longer sure what to believe. Several professionals agreed that the use of supplements had not been part of their formal education and that further training would be necessary. The medical staff and psychologists stressed the importance of scientific evidence of the intervention. For the physicians, the information about effectiveness and safety had to be endorsed by the guidelines of their professional associations. People with intellectual disabilities said they wanted to be informed about the intervention and indicated that the information should be understandable.

Topic 5: Supplements and a healthy diet

Although it was explained that the intervention aimed at reducing challenging behavior and not replace a healthy diet, animated discussions arose in all focus groups about the relationship between supplementation and a healthy diet.

Several professionals expressed concern that support staff's motivation to improve diet quality would decrease if they began prescribing nutritional supplements within the organization. For them, dietary supplements would only be an option if other attempts to improve diet quality had failed. Other professionals argued that providing healthy food

did not necessarily guarantee healthier diet for people with intellectual disabilities. Some people with intellectual disabilities preferred a healthy diet over supplements. Others made clear that they did not care at all about a healthy diet. Opinions differed about the extent to which professionals should try to control the client's eating habits. Some professionals emphasized that a healthy diet should always be a goal, while others said they consider freedom of choice as an equally important principle.

DISCUSSION

This qualitative study aimed to identify factors influencing the adoption of an intervention with nutritional supplements to reduce challenging behavior in people with intellectual disabilities. The analysis of the input of people with intellectual disabilities, their representatives, and professionals revealed five relevant topics. First, there was a broad consensus that treatment for challenging behavior should consist of combining different approaches and not a monotherapy with nutritional supplements. Second, professionals agreed that there must be clarity about their roles in the intervention. Third, concerning the intervention's characteristics, people with intellectual disabilities stressed the importance of easy-to-swallow supplements of limited size and with no unpleasant odour and taste, or high costs. Fourth, there was a need for more reliable information about the intervention's effectiveness and safety for all groups, and the different groups had different information needs. Finally, it was discussed whether it would be better or not to provide the micronutrients by improving the diet than taking supplements.

We will further discuss the results in order of the five topics that had emerged (1-5). (1) The intervention with supplements can be combined with other interventions and therefore fits into the multi-component approach often used in the treatment of challenging behavior (Embregts et al., 2019; Gore et al., 2013; Tanwar et al., 2017). (2) Physicians could play a key role in the adoption by the multidisciplinary teams, because the other professionals expect them to be in charge of the intervention. Awareness of the therapeutic potential and risks of dietary supplements has grown over the past decades in various medical fields (DiMaria-Ghalili et al., 2014; Eussen et al., 2011; Rittenhouse et al., 2020). Incorporation in evidence-based guideline is required to enable large-scale

adoption of the intervention by physicians, which should be endorsed by their professional association. (3) People with intellectual disabilities find it important to be involved in choosing an intervention for challenging behavior (Wolkorte et al., 2019). In order to increase the acceptance of the supplements by people with intellectual disabilities, details such as how they experience the taste and swallowability of the supplements should be assessed. Pill properties such as smell, taste and size are important to the acceptance of drug therapy in general (Liu et al., 2014). A wide range of nutritional supplements are available with approximately the same content but different dosage forms. People with intellectual disabilities should be involved assessing the characteristics of specific supplements on properties such as taste and swallowability. (4) Support from the caregiver is needed to integrate the information about the intervention into the daily lives of people with intellectual disabilities (Codling and McDonald, 2010). Thereby, positive wording of the indication is a concern so that the implementation of the intervention does not contribute to a negative label in a population already suffering from stigmatization (Ali et al., 2012). (5) The attitude towards the intervention could affect opinions about the relationship between supplement use and a healthy diet. A positive attitude of the caregiver could motivate the client to adopt the intervention (Sundblom et al., 2015), this is a point to consider for communication to the support staff.

Beyond adoption

Adoption by individuals is a necessary step in the diffusion of an innovation, but more is needed for a sustainable use of the intervention in an organization (Greenhalgh et al., 2004). Further research is needed in the political, economic, regulatory, professional, and sociocultural context of the intervention and the embedding and adaptation over time (Greenhalgh et al., 2017).

Strengths and limitations

We can note several strengths of our study. The focus groups were joined by all different professionals who had to deal with challenging behavior. The moderator was trained in leading focus groups and had extensive experience working with people with intellectual disabilities, which facilitated a pleasant and open atmosphere during the focus groups, and participants could speak up freely. A balanced interpretation of the data was promoted as five researchers analysed the data and discussed their findings in regular meetings until they reached consensus.

There are also several potential limitations that need to be discussed. Firstly, participants with profound to severe intellectual disabilities could not participate in the focus group for obvious reasons, although two client representatives participated to represent them. Secondly, when analysing focus group session 2, the notes taken during the session had to be used because the video recordings had failed, causing information to be lost. Thirdly, the participants were not a random sample, as most of the professionals who responded to our initial invitation had special interest in the subject, which was likely greater than the people who did not respond. This is a desirable characteristic to ensure richer content, but it remains unclear to what extent this selection may have resulted in missing topics that may be of concern to less interested parties.

Conclusion

This focus group study showed that adopting an intervention as part of a multicomponent treatment for challenging behaviors can be facilitated by clarifying the professional roles. If the intervention is perceived as a medical intervention, the doctor is expected to be in charge and has an important role in the adoption by the other parties involved. A prerequisite is sufficient scientific evidence about the effectiveness and safety of the intervention. The adoption by people with intellectual disabilities can be facilitated by informing them and involving them in assessing the attractiveness of the intervention. Information dissemination should consider the values and sensitivities of both caregivers and people with intellectual disabilities.

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APPENDIX

Appendix 3.1. The questions used in the focus groups

Question topics	People with Intellectual disabilities	Professionals and representatives
About expectations of the intervention	What are the benefits of taking vitamin pills?	What are the benefits of intervention with dietary supplements?
	What are the disadvantages of vitamin pills?	What are the disadvantages of intervention with dietary supplements?
	What do you think about taking vitamins to become less angry/busy/restless?	To what extent do you expect this intervention to work, and why?
Concerning the acceptance of the intervention	Would you take vitamins yourself and why (not)?	What can influence (positive, negative) the effectiveness of the intervention?
	What do your friends/colleagues/parents think of vitamin pills?	What risks do you expect from an intervention with dietary supplements?
	What are the dangers of taking vitamin pills?	What can make this intervention unsuitable or suitable for use in care for the intellectual disabled?
Implementation of the intervention	How can we best tell other people with intellectual disabilities about vitamin pills to reduce aggression?	What special points of interest can you think of that could be important if this intervention is used in healthcare?
	How can we best tell carers about vitamin pills to reduce aggression?	If the intervention is effective, how could we ensure that it will be implemented?
Completion	Did any of you have a question in mind they expected during the interview, but which has not (yet) been asked?	Did any of you expect a question during this focus group that has not (yet) been asked?

Appendix 3.2. The Themes, Sub-themes, and Topics that emerged from the data

Topic	**Theme**	**Sub-theme**
The relationship with other interventions	Other interventions	Methodologies
	Other interventions	Medications
		Not only supplements
The professional roles	Who is in charge	Physician
		Other staff
	Role of other professionals	Role other professionals

		Support staff
		Multidisciplinary consultation
Characteristics of supplements	Swallowability	Frequency
		Dosage
		Swallowing supplements
		Vitamin drink
		Odour
		Taste
		Fish oil
		Vitamins
	Costs	Supplement costs
		Who pays?
Being informed	Opinion about efficacy	Health booster
		Does (not) work on behaviour
	Opinion about safety	Side effects
		Interaction
		Too many vitamins
	Lack of information	Contradictory information
		Too little information
	Understandable information	Explanation for people with intellectual disabilities
	Evidence	Scientific evidence on safety
		Scientific evidence on the effect
	Stigmatizing	Stigma
Supplements and a healthy diet	Healthy diet	Benefits healthy diet
		Determination of deficiencies
		Supplements vs. nutrition
	Freedom of choice	Free choice of what to eat

Appendix 3.3. Quotes from the focus groups

Topic	Theme	Participant	Quote
The relationship with other interventions	Other interventions	Sup Fb	It (treatment of challenging behaviorur) must remain in balance, and not everything has to be dependent on eh eh, for example, a vitamin deficiency ... no ... it must be embedded .. it must not be the only entrance
		Sup Fd	(agrees) it should be complementary and not the only treatment
		Psy Vc	I think there are many more things underlying behavior; ... And that this (nutritional supplements) could be one of those things, with which you could intervene.
The professional roles	Who is in charge	Part Rc	"I think you should discuss the intervention with the doctor. Because what if he says you don't need it?... I think you should consult him."
		Sup Vh	we just said we want it (supplements) on a (medical) prescription anyway, so then you have that extra (motivation) because the doctor says they need to take them

		Ma/Po Kb	if you would like to get this intervention accepted in the care organizations, then you should at least have the doctors with you; otherwise, it will not happen…
	Role of other professionals	Ma/Po Vf	I do not think you can leave this (the decision for an intervention) to one person. A multidisciplinary consultation should be planned, with at least a doctor, dietician, and psychologist.
		Sup Fd	... I see clients who take such bad care of themselves ... if they understand that they can get those problems due to vitamin deficiency ... we could motivate them to take those vitamins.
Characteristics of the intervention	Swallowability	Part Oa	if you have to swallow such large pills, you may choke yourself
		Part Rb	I don't like the taste of vitamin pills. I am sensitive to certain types of flavors. And I thought they tasted very sour. I got sick of that.
		Part Od	if you really have to take it every day, you don't want that anymore ... they are not so good ... my home mate had to gag
		Part Oc	I would prefer chewable tablets with strawberry flavor.
		Part Oa	It would be better if you only had to take them once a week
	Costs	Part Ra	I stopped taking supplements ... because they were expensive.
		Part Rc	if your doctor says: this must be paid through the insurance. Wouldn't that just have to be possible?
		Medic Kc	I think it (the supplements) should be (funded) in the same way as now with clients who receive certain vitamins … on a prescription from their GP
		Ma/Po Kb	And in terms of costs, we like to spend our money on things where we see results
Being informed	Opinion about efficacy	Part Hd	Vitamins keep up your resistance!
		Repre Vd	(supplements are for) the prevention of diseases because people may not get all nutrients, but that may also be different for everyone; I imagine
		Ma/Po Nc	You used to learn that when you are sick, you had to take a multivitamin
	Opinion about safety	Part Hf	They should also write on the package insert what the side effects are
		Psy Vb	I do not see the risks (of supplement use). Well, I have to say that I have not read too much about it, so that is purely my first impression.
		Sup Vk	Well, you may think it is not harmful because it is just a vitamin pill, but maybe the client can get too

			much ... we do not know enough about supplements ...
	Lack of information	Sup Fb	(we need more) information, good information that everyone understands, and knows what needs to be done
		Ma/Po Vf	I find it very confusing because one says uh ... you need (supplements) because not everything is in food, and the other says ... um ... you do not need it. I do not know…
	Understandable information	Part Hc	An understandable explanation is important if you want someone to take vitamins...
		Part Ra	you can make a digital guideline with an email address so that people with intellectual disabilities and representatives can ask their questions.
	Evidence	Ma/Po Kb	I think (within the organization) the resistance of the medics (for the introduction of the intervention) is greatest… because they do not know how it works … or if it works at all ...
		Medic Ne	If there is enough evidence of efficacy, the intervention will also be included in the guideline ... yes if there is enough hard evidence, it will get through to the doctor … doctor's prescriptions are based on guidelines and advice from the Health Council.
	Stigmatizing	Part Rb	I hated to hear why I had to take those (vitamin) pills. I said, what are you talking about. I am relaxed.
		Moderator	So, you found it especially annoying because they labelled you?
		Part Rb	Yes, absolutely.
Supplements and a healthy diet	Healthy diet	Repre Nb	Basically, I would first look at how we can offer healthy nutrition ... and if more is needed to use nutritional supplements only then ... but administering supplements without proper nutrition, I am not in favor of that.
		Psy Va	With a healthy diet, you also have other benefits. Many of my clients suffer from constipation, for them eating a little fiber would also be nice ... because of constipation, they can be in pain and behave problematically
		Sup Vk	It is also possible that support staff will think that (healthy) food is no longer necessary, we will give them pills instead … that is a risk.
		Ma/Po Vg	Yes, that is a pitfall!
	Freedom of choice	Ma/Po Ng	we keep talking about how our clients should do it ... how we should do it for the clients... If they do have a choice, they can say ... give me that pill, then I feel better, but then I can eat what I want. You know, I find it problematic to control a lot of things, and I find that with nutrition too. Of course, you offer it (healthy food), and you stimulate it, but to what extent are we going to control (their lives)?

	Medic Kc	of course, it would be really nice if you offer a perfectly balanced diet on the house, but if a client thinks that is not necessary and walks up to their room, and there are four bags of chips ... they are going to eat that instead of the healthy meal

Note. Ma/Po = Manager/ policy maker, Medic = medical staff, Part = participant with mild intellectual disabilities, or borderline intellectual functioning, Psy = psychologist, Repre = client representatives, Sup = support staff

Chapter 4

THE EFFECTS OF VITAMIN-MINERAL SUPPLEMENTS ON SERIOUS RULE VIOLATIONS IN CORRECTIONAL FACILITIES FOR YOUNG ADULT MALE INMATES: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: We investigated whether vitamin-mineral supplementation could reduce serious rule violations.

Methods: In this randomized, controlled, double-blind trial, young adult male inmates were included. For 15 weeks, they received a daily dose with vitamin-mineral supplements of approximately 100% Recommended Dietary Allowance (RDA) (n = 149), or a higher-dose formula (n = 150), or placebo (n = 150). Serious rule violations were the primary outcome.

Results: In the lower-dose group there were 39% fewer rule violations than in the placebo group (relative risk = .61; 95% confidence interval [*CI*]:.41–.90, p = .01). In the higher-dose group the difference did not reach statistical significance.

Conclusion: 100% RDA, but not higher doses supplements, resulted in less serious rule violations than placebo.

INTRODUCTION

Rule violation is a major problem in correctional facilities in the U.S., with about 946 incidents per 1,000 inmates per year (Steiner & Cain, 2016, p.166). About half of the prison inmates violate at least one prison rule each year (Steiner & Cain, 2016, p. 167). The consequences of institutional misconduct are costly, and research has been done to determine what works to reduce this misconduct. Variables concerning both prisoner and prison characteristics predict inmate misconduct and include age <25, crowding, and prison security level (Steiner et al., 2014). Cognitive-behavioral therapy and social learning approaches are among the most studied interventions and have shown mixed results (Auty et al., 2017). In a meta-analysis on the effectiveness of correctional treatment for reducing institutional misconducts, a well-designed randomized controlled trial (RCT) with dietary supplements received attention (French & Gendreau, 2006). This RCT showed tentative evidence of a beneficial effect compared to placebo, as vitamin-mineral supplements reduced institutional misconduct. Three RCTs on the effect of vitamin-mineral supplements on institutional misconduct have been published so far. The first study was a randomized, placebo-controlled trial among 62 delinquents in a maximum-security psychiatric center in Oklahoma (Schoenthaler et al., 1997). The delinquents who took vitamin-mineral supplements for 3 months showed 28% fewer rule infractions than those randomized to placebo (95% *CI*: 15%–41%, $p = .005$). This study was adjusted and replicated in 231 young adult male prisoners in the United Kingdom. Those on active supplements showed 26% fewer offenses than those randomized to placebo (95% *CI*: 8.3%–44.3%, $p = .03$) (Gesch et al., 2002). Similarly, in 221 young adult male prisoners, there was a reduction of 48% offenses in the active versus placebo group ($p = .017$, onetailed) (Zaalberg et al., 2010). An association between healthier nutrition and lower misconduct was also found in open-label studies with a change of prison diet as the intervention (Schoenthaler, 1985), and in observational studies (Schoenthaler et al., 1991). All RCTs showed small to medium effect sizes in favor of the vitamin-mineral supplements, without any excess of adverse effects.

There is no monocausal relation between micronutrients and behavior, but results from numerous studies have shown that an adequate supply of vitamins and minerals is essential for the functioning of the central nervous system (CNS) (Parletta et al., 2013). A sub-optimally

functioning CNS can play an important role in the complex interplay of bio-psycho-social and environmental factors that predispose social problem behavior (Jackson & Beaver, 2013; Lee, 2015). For example, imbalances in the monoaminergic neurotransmitter systems can adversely affect executive functions, including self-control (Logue & Gould, 2014). There are multiple mechanisms of action by which vitamins and minerals can influence the CNS, including neurotransmitter synthesis, energy provision, neuroprotection, neuroplasticity, and neurogenesis (Calderon-Ospina & Nava-Mesa, 2020; Kennedy, 2016; Parletta et al., 2013). Vitamins and minerals have complex synergetic actions; therefore, it is not rational to focus on the effect of one isolated micronutrient (Messina et al., 2001), but rather on the combined effect of micronutrients. For practical reasons, vitamin-mineral supplements are used as a proxy for meals with a healthy combination of micronutrients to study the effect of nutrition on behavior.

This study aimed to assess the effect of two different formulas and doses of multi-vitamin and mineral supplements versus placebo on serious rule violating behavior in two California Youth Authority (CYA) institutions. The study was designed as a three-arm randomized, double-blind placebo-controlled trial. One active arm contained approximately 100% of the RDA for vitamins and minerals (i.e., the lower-dose group), and the other (i.e., higher dose group) received higher doses of vitamins B and C and some additional minerals. We hypothesized that the number of serious rule violations would be lower in the lower-dose group versus the placebo group and that this effect would be more substantial in the higher-dose group versus the placebo group.

METHODS

An Oversight Committee appointed by the Chancellor of the University of California Berkeley supervised the procedures. Recruitment and informed consent took place from September 1990 to June 1991 after approval by the California State University, Stanislaus Institutional Review Board (IRB).

Sample

Within the two participating institutions of the CYA, all prisoners were eligible and were approached for participation by the researcher assistants. Four hundred forty-nine male inmates, mean age 19.4 years (SD 1.4), entered the trial after giving informed consent. The participants were housed in 21 residential units. Details of the recruitment and allocation are shown in the flowchart in Figure 4.1. To compare 3 group means, with a 5% type I error rate and an effect size of d = .20, 120 subjects per group would be required to have 90% statistical power (Faul, Erdfelder, Lang, & Buchner, 2007). Since we expected that approximately 15% of subjects would be lost 'due to release,' efforts were made to recruit 150 subjects per group.

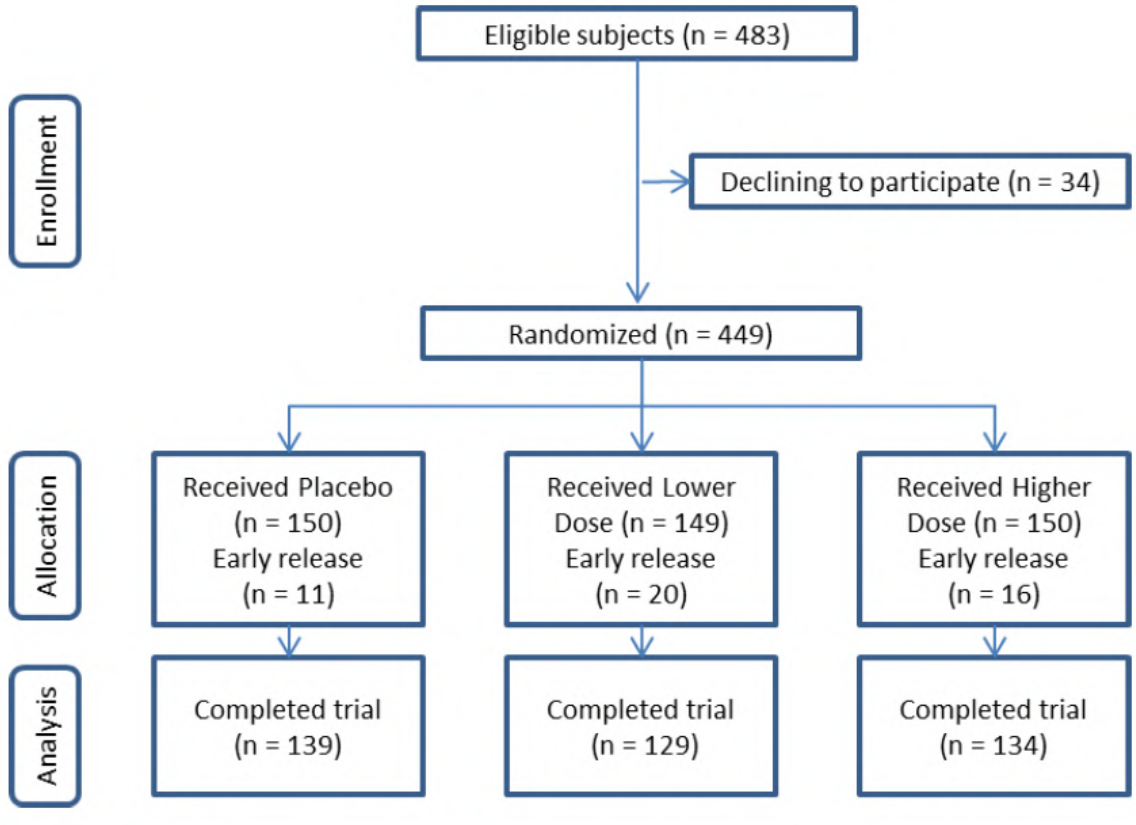

Figure 4.1. Flow diagram.

Intervention

The effect of two different dose vitamin-mineral supplements and placebos on rule violating behavior was investigated. Booker Nutritional Products Ltd. made the supplements and placebos, of which one active supplement contained approximately 100% of the US RDA for most of the vitamins and minerals, we call this the "lower-dose supplement". The "higher-dose supplement" had the same amount of vitamin A, D, E, K, Folic acid, Biotin, Copper, Iodine, Iron

and Zinc, but had a higher dose of the water-soluble B and C vitamins and addition of Selenium, Chromium, Manganese, and Molybdenum. In contrary to the other minerals, the dose of Magnesium and Calcium was higher in the lower-dose supplement. The dosages are listed in Appendix 4.1. We added the most recent US RDAs to the table, because the RDA of some micronutrients changed since 1990. The supplements were delivered in coded boxes of which the key was held by the oversight committee. The randomization table was generated from a list of randomized numbers published in Social Statistics (Blalock 1972). Using this table, the research assistants sequentially assigned each participant to a code. During the 15-week intervention period, the participants received their daily supplement from the research assistants who registered compliance. Baseline intervention incident rates were measured from 15 weeks before the start of the intervention. The post-testing measurements took place during the last week of the intervention.

Table 4.1 Baseline Demographics and Characteristics of the Randomized Groups

	n	Placebo	*n*	Lower-dose	*n*	Higher-dose	*n*	All participants
Age	139	19.4 (1.4)	129	19.5 (1.4)	134	19.3 (1.5)	402	19.4 (1.4)
IQ (non-verbal WAIS-R)	125	92 (13)	119	92 (11)	118	91 (14)	362	91.4 (12.9)
African American	36	25.9%	29	22.5%	37	27.6%	102	25.4%
Asian	9	6.5%	9	7.0%	7	5.2%	25	6.2%
Caucasian	48	34.5%	58	45.0%	55	41.0%	161	40.0%
Hispanic	46	33.1%	33	25.5%	35	26.1%	114	28.4%
Cigarettes per day	139	24 (26)	129	27 (27)	134	24 (29)	402	25 (27)
Soft drinks per week	139	9.1 (15)	129	9.8 (15.3)	134	9.8 (16.1)	402	9.6 (15.5)
Coffee cups per week	139	2.7 (6.1)	129	1.8 (3.1)	134	2.0 (3.3)	402	2.2 (4.4)
Tension (POMS)	114	51 (11)	107	48 (10)	114	48 (9)	335	49 (10)
Depression (POMS)	114	55 (12)	107	53 (11)	114	52 (10)	335	53 (11)
Anger (POMS)	114	63 (13)	107	62 (12)	114	62 (12)	335	62 (12)
Fatigue (POMS)	114	51 (11)	107	54 (10)	114	52 (10)	335	52 (10)
Confusion (POMS)	114	48 (10)	107	48 (10)	114	47 (10)	335	48 (10)
Vigor (POMS)	114	49 (10)	107	46 (10)	114	47 (9)	335	48 (10)
Psychosis (EPQ)	108	7.7 (3.4)	104	7.5 (4.1)	112	6.8 (3.1)	324	7.3 (3.6)
Extraversion (EPQ)	109	12.1 (5.5)	104	12.3 (4.2)	112	11.3 (4.5)	325	11.9 (4.8)
Neuroticism (EPQ)	109	12.9 (4.1)	104	14.4 (3.5)	112	14.5 (3.8)	325	13.9 (3.9)
Lie (EPQ)	107	7.1 (3.8)	104	7.0 (3.9)	112	7.7 (3.6)	323	7.3 (3.8)
Pre-intervention incidents	139	102	129	117	134	130	402	349

Note. No statistical significant differences between the groups were found in the demographic variables at baseline. EPQ = Eysenck personality profile; POMS = profile of moods states; WAIS-R = Wechsler Adult Intelligence Scale-revised.

Outcome

Correctional facilities distinguish between serious and less serious rule violations. Serious violations include for example: use of violence against another person, hazard to facility

security, and serious disruption of facility operations (15 CCR 3315). Less serious misconduct includes: misuse of food, use of vulgar or obscene language and, failure to meet work or program expectations (15 CCR 3314). The primary outcome was the difference between the assignment groups in the sum of all registered serious rule violations committed by the prisoners during the 15-week intervention period. Participants who were paroled, released, or transferred within six weeks from the start of the intervention, were excluded. Subsequently, we made a distinction between violent and non-violent offenses.

Questionnaires

The secondary outcome was the change of mood during the intervention period measured with the Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1971). The POMS is a self-report questionnaire with 65 questions on a 5-point Likert scale ranging from “not at all” to "extremely." It measures six dimensions of mood states: Tension, Anger, Vigor, Fatigue, Depression, and Confusion. The psychometric qualities of the POMS are reasonable, with Cronbach's alphas on the subscales; .90 (Tension), .92 (Anger), 95 (Depression), 93 (Vigor), .93 (Fatigue), .81 (Confusion), and .92 (total), the reliability of the scale is good (Curran, Andrykowski, & Studts, 1995).

To measure personality traits, we used the Eysenck Personality Questionnaire revised version (EPQ-r) (Eysenck, Eysenck, & Barrett, 1985). It is a self-report scale with 94 items that measure four dimensions of personality: Extraversion, Neuroticism, Psychoticism, and Lie. The reliability of the scale varies with the dimensions measured with lower reliability for the dimensions Psychoticism (.66) and Lie (.77) than Extraversion (.82) and Neuroticism (.83) (Caruso, Witkiewitz, Belcourt-Dittloff, & Gottlieb, 2001).

We measured the Intelligence quotient (IQ) with the non-verbal subset of the revised Wechsler Adult Intelligence Scale (WAIS-R) consisting of "picture completion," "picture arrangement," "block design," "object assembly," and "coding." Among a prison population, the non-verbal subset of the WAIS-R is preferable because verbal items could cause bias (Jensen & Faulstich, 1988).

Blood analysis

Blood samples were analyzed at baseline and in the last week of the trial. Blood values were measured for vitamins A, B1, B2, B3, B5, B6, and E, folic acid, iron, chromium, calcium, manganese, copper, selenium, zinc, and magnesium. Vitamins were assayed using micro-

protozoan growth techniques (Voigt & Eitenmiller, 1978) and minerals with atomic absorption spectrometry.

Adverse effects

The intervention consisted of an over the counter supplement of which no severe side effects were expected. In order not to worry the participants there was no active assessment of side effects.

Statistical analyses

The primary hypothesis was that the count of serious rule violations in the intervention period was lower in the two treatment groups than in the placebo group. Because the primary outcome measure was count data, and there was evidence of overdispersion, we used a negative binomial distribution for the primary analysis (Hilbe, 2014). We incorporated as an offset variable into the analysis the logarithm of the subject's number of days at-risk during the intervention. The dependent variable was the sum of the incidents during the experimental period, and treatment assignment was the grouping variable. A zero-inflated model was fitted to compare the effects on rule violations among the randomized groups. This model was compared to the negative binomial model using the Vuong test (Desmarais & Harden, 2013). A post hoc analysis was used to explore whether the effect would be more robust in a violent and non-violent fraction.

The secondary outcome was the effect of the intervention on the mood states. The difference on Total Mood Disturbance score was used as dependent variables, and treatment as the grouping variable. These variables were analyzed using a analyses of variance (ANOVA) model. In addition, change from baseline to endpoint on total non-verbal IQ, and the four dimensions of EPQ-r were explored using ANOVA. Differences in the micro-nutrient blood values were explored using ANOVA, with post hoc Tukey tests. Finally, the Chi-square test was used to assess whether participants guessed their group assignment.

The statistical packages 'pscl' and 'MASS' for the R statistical software (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org) and IBM SPSS statistical software (version 23, IBM Corp) were used for the analyses.

RESULTS

Table 4.2. Compliance (n = 402)

Group assignment	Placebo	Lower dose	Higher dose	Total
Mean days enrolled in the study	96.1 (16.9)	97.4 (15.9)	96.9 (16.1)	96.8 (16.2)
Mean days the supplements were taken	83.8 (19.1)	84.7 (19.7)	85.6 (19.1)	84.7 (19.2)
Percentage of days during the trial the tablets were taken	87.2%	87.0%	88.3%	87.5%

Of the 449 inmates who gave informed consent, 47 were released or transferred within six weeks of the start of the intervention and four participants were underaged. These subjects were left out of the analysis, reducing the sample to 398 adult males, with a mean age of 19.4 years (SD 1.4). Days at-risk of offending ranged from 42 to 104, with a mean of 96.8 days (SD 16.1). Group characteristics are listed in table 4.1. These included the non-verbal part of the WAIS-R, EPQ-r, POMS, race, age, and the use of coffee, cigarettes, and soft drinks. At the start of the trial, the group means were not significantly different for any of these variables, and neither was there a significant difference in the mean pre-intervention rule violations per person per day.

Blinding and compliance

We operationalized compliance as the total number of supplements the participants took during the research period of 105 days, registered by the research assistants. The mean number of days the participants took the supplements was 84.7 (87.5%, see Table 4.2), in all 402 participants, and there were no statistically significant differences among the three randomized groups ($F(2, 399) = .284$, $p = .753$).

The micronutrient blood values were measured at baseline in 259 participants and at the endpoint in 194 participants ($n = 153$ for both time points). Appendix 4.2 shows the post hoc analysis (Tukey's test) of blood values in the active groups compared to the placebo group. These results showed increases compared to the placebo group in the 16 micronutrients, of which six were statistically significant. The increase in blood micro-nutrient levels was mainly caused by the higher dose group, confirming that compliance was considerable.

Table 4.3 Group assignment x guess of group assignment (n = 209)

		Group assignment			
		placebo	low	high	total
Guess	Placebo	37	32	29	98
	Low	16	17	25	58
	High	16	19	18	53
	Total	69	68	72	209

After the study, each participant was asked to guess whether he had received placebos or supplements, and 209 of the 402 participants responded (Table 4.3). While most participants guessed that they had been using placebo supplements, there were no statistically significant differences among the groups ($\chi 2(4) = 3.61$, $p = .46$).

Main finding

The overall negative binomial test showed that the mean number of serious rule violations per day differed between the groups ($p = .039$). The difference between the placebo and lower-dose group was statistically significant with a rate ratio (i.e., Exp(B)) of .61 (95% *CI*: .41–.90; $p = .013$). This can be interpreted as 39% fewer rule violations in the lower dose group relative to the placebo group. There was a small and statistically nonsignificant difference between the placebo and the higher-dose group with a rate ratio of .90 (95% *CI*: .63–1.30; $p = .58$). Moreover, the difference in the count of total rule offenses for the higher-dose versus lower-dose group almost reached statistical significance (with a rate ratio of 1.48; 95% *CI*: .99–2.23; $p = .06$). The effect estimates of the post hoc analyses to explore whether the effect would be more robust in a violent and non-violent fraction were not importantly different from those with the total rule offenses, although the confidence intervals were slightly wider (Figure 4.3).

Because of the large number of participants with zero incidents, an additional zero-inflated model was used. The Vuong test comparing the zero inflated model with a negative-binomial regression model was statistically significant, indicating that the zero-inflated model better fitted the count data (AIC-corrected, z-statistic = −2.41, $p = .016$, BIC-corrected z-statistic = 2.99; $p = .001$). The odds ratio for structural zero incidents did not differ significantly, neither for the lower-dose group (lower-dose vs. placebo; *OR* = 0.80; 95% *CI*: .27–2.34), nor for the higher-dose group (higher-dose; vs. placebo; *OR* = 1.04; 95% *CI*: .75–1.44).

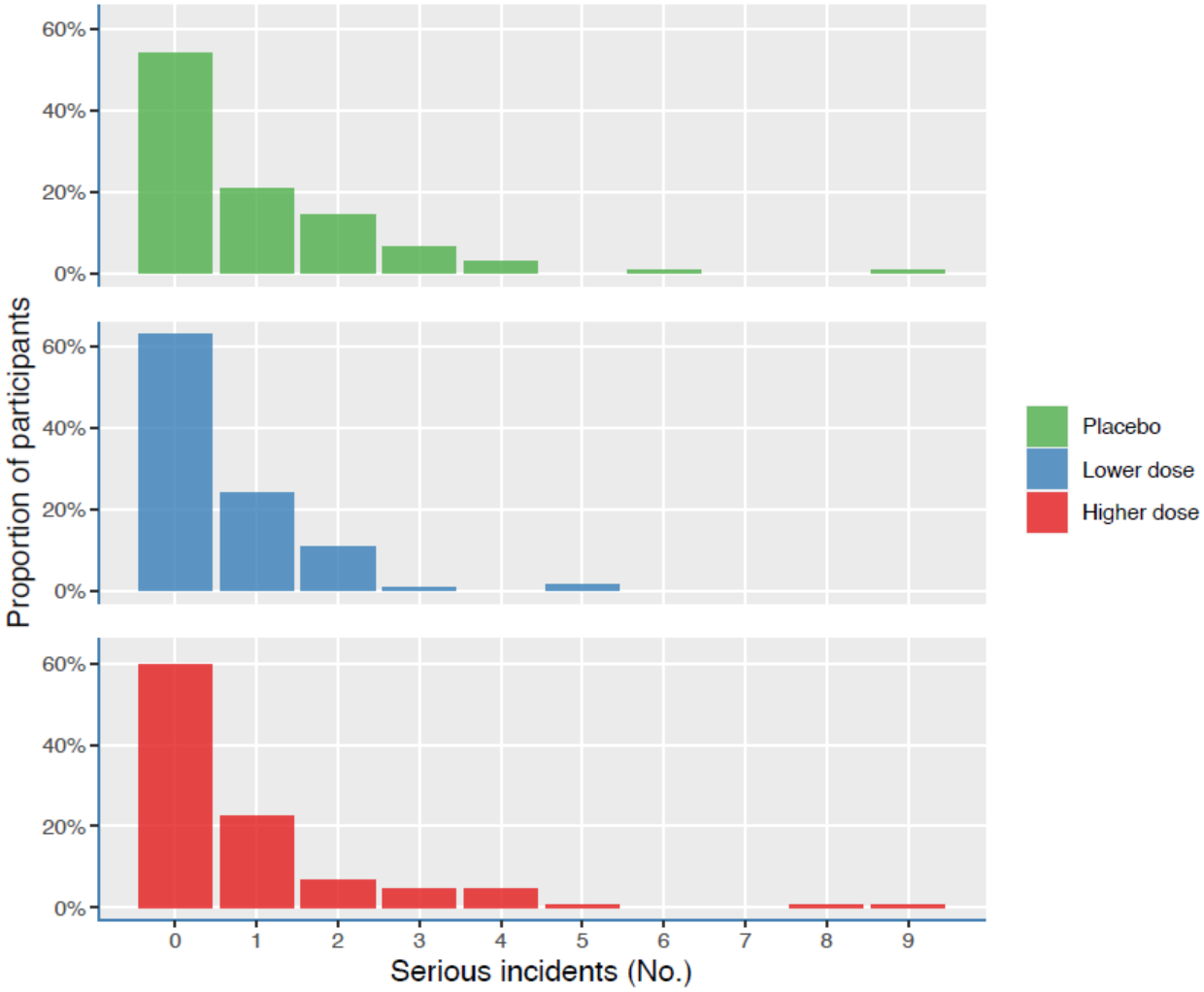

Figure 4.2. Number and percentages of rule violations during the intervention period according to the randomized groups.

Secondary findings

We found no statistically significant difference between baseline and endpoint on the Total Mood Disturbance ($F(2, 215) = 1.30$, $p = .275$). Likewise, we found no significant changes in non-verbal IQ ($F(2, 273) = 2.05$, $p = .131$), nor was there a significant difference on, Extraversion (F (2, 213) = 1.07, p = .344), Lie (F (2, 210) = .11, p = .892), Neuroticism (F (2, 213) = 1.61, p = .203), and Psychosis (F (2, 209) = 2.53, p = .082).

Adverse effects

No adverse effects were reported.

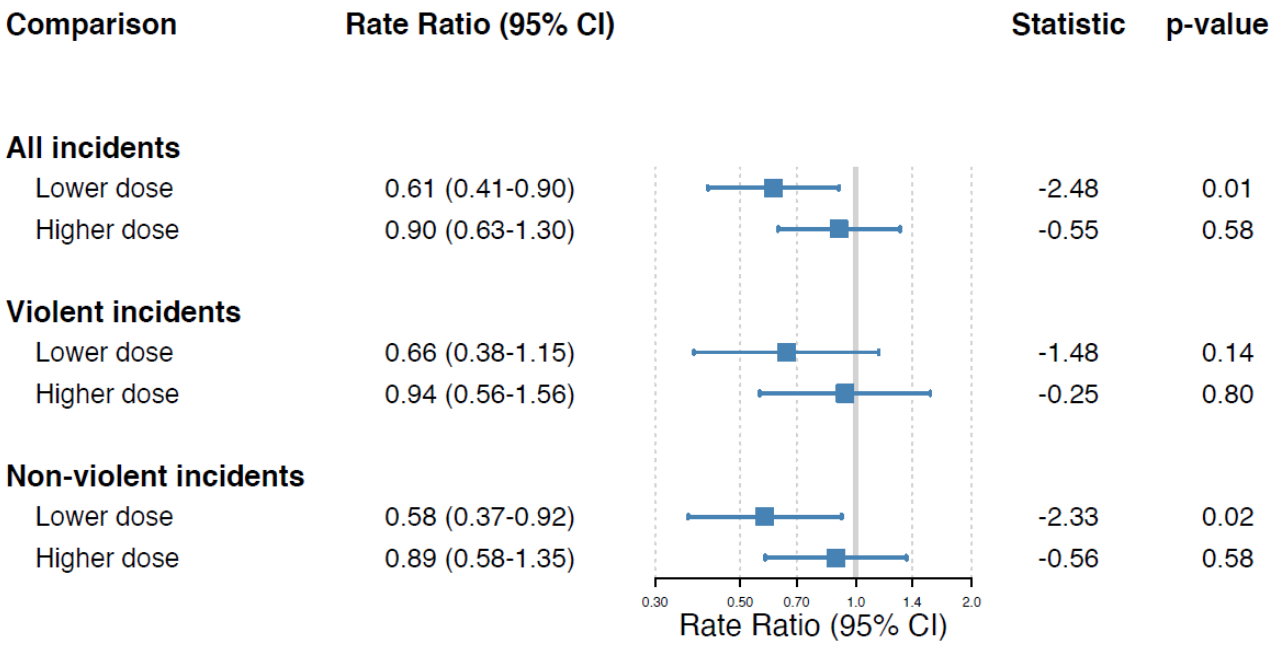

Figure 4.3 Forest plot of the rate ratios with 95% confidence intervals (CI) of all rule offenses, and those partitioned into violent and non-violent fractions

DISCUSSION

There were 39% and 10% fewer serious offenses in the lower-dose and higher dose groups, respectively, compared to the placebo group. Only the effect in the lower-dose group was statistically significant. The null finding in the higher-dose group was unexpected and did not support a dose-response relationship. Our findings suggest that physiologic rather than supraphysiologic doses of minerals and vitamins benefit this outcome. The difference in the lower and higher dose effects is difficult to explain and can only be speculated. The dosages of vitamins and minerals used in other studies vary. In the other studies among young adult male inmates, doses of approximately 100% RDA were used and obtained similar results as in our lower-dose group (Gesch et al., 2002; Zaalberg et al., 2010). On the other hand, studies among children with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) found a positive effect of higher doses of multi-vitamin and mineral supplementation on behavior (Adams et al., 2011; Rucklidge et al., 2018). Whether age, gender, and psychiatric comorbidity may explain the discrepancies should be further investigated, as these are of critical importance for determining the most effective dosage of supplements.

Institutional misconduct generates higher costs for prisons in more than one way. First, there is direct damage caused by the misconduct, such as the replacement of destroyed property or hospitalization. Secondly, the misconduct can raise the expenses on personal and safety precautions, for instance, the necessity for the employment of more staff or the investment in security systems. It also contributes to additional costs due to increased work stress and burnout of the prison staff (Keinan & Malach-Pines, 2016). Finally, institutional misconduct can affect the parole decision-making process and cause longer periods of incarceration (Mooney & Daffern, 2011). The serious misconducts in the California Youth Authority are "B-level" incidents that must statutorily delay parole from 3 to 6 months with an average of 4 months. According to the California Legislative Analyst's Office, the costs of confinement for each inmate per year was $21,582 for health care, $2,437 for rehabilitation, and $3,484 for food and activities, equaling $9,168 for four months of added confinement per infraction (LOA, 2018). The inmates receiving the lower-dose formula produced 49 fewer incidents than baseline at $9,168 per incident totaling $449,232. Apart from these problems in the prison environment, there is limited support that misconduct in prison can predict post-release recidivism (Mooney & Daffern, 2015; Trulson et al., 2011). These findings are supported by the meta-analysis of (French & Gendreau, 2006), showing that interventions causing a reduction in institutional misconduct are associated with a reduction in recidivism.

Some limitations need to be discussed. First, the trial was conducted in the years 1990 and 1991; as the prison population and nutritional insights have changed since then, the interpretation and implementation of these older data need to be done with care. For example, in more recent times, the number of inmates with criminogenic needs has increased, while participation in institutional programs has decreased (Chamberlain, 2011). In addition, there is little detailed information on trends in the food supply for inmates, but research indicates that there is much room for improvement in the current prison diet (Collins & Thompson, 2012; Cook et al., 2015; Smoyer, 2019). As mentioned before, there were shifts in the RDA of micronutrients since 1990, causing the lower-dose formula to deviate from what is nowadays regarded as 100% RDA; see Appendix 4.1 for details (Food and Nutrition Board Institute of Medicine National Academies, 2011). The finalization for publication of the data was delayed for many years by someone with a critical stance against research on improving the welfare of prisoners and filed a protracted federal lawsuit against the state for authorizing this study. Eventually, the federal courts dismissed the court case. Second, adverse effects may have been

underreported as these were not proactively monitored. A third limitation concerns the interpretation of the blood values. The blood analyses results should be interpreted with caution because of the high number of subjects who rejected giving blood samples and the use of currently outdated measurement techniques with a high relative measurement uncertainty (± 20%) (Zhang et al., 2018). A fourth limitation was that the data of 402 (89.5%) of the 449 randomized participants were analyzed, and therefore no intention-to-treat (ITT) analysis was conducted. The oversight committee determined the exclusion of inmates who participated in the trial for less than 6 weeks because they believed it would take several weeks for the micronutrients to affect behavior. As shown in Figure 4.1, the percentage of early releasers is much higher in the active than in the placebo groups, making it unlikely that omitting the early releasers would have inflated the intervention's effect size. Likewise, parole due to good behavior was likely to attenuate the effect size, as a weight (i.e., offset) factor based on days present was included in the analysis. Finally, there was a substantial heterogeneity in the number of incidents per participant (ranging from 0 to 9 incidents during the intervention), which was partly take into account by the dispersion parameter in the negative binomial regression analysis, but also led to larger confidence intervals of the effect estimates.

This trial's strengths are the large sample size, the relative homogenous group, which guarantees internal validity, and relatively good compliance. However, findings are not straightforwardly generalizable to other groups and settings. A recommendation for further research would be to investigate the effect of dietary supplementation in other settings with high problem behavior, such as special education schools, chronically admitted psychiatric inpatients, and residential care for people with intellectual disability. As the proportion of older inmates with typical misconduct has increased in recent times (Blowers & Blevins, 2014), it may also be interesting to include middle-age inmates in future studies on this topic.

It is important to emphasize that serving sufficient meals in an institution does not ensure that all recipients will eat it. Many inmates still make unhealthy food choices (Eves & Gesch, 2003; Schoenthaler et al., 1991). Sarris et al. (2015) published a position paper in the Lancet where they wrote that: "there is a need to move toward a new integrated framework in Psychiatry, whereby consideration of nutritional factors should be standard practice." This paper and several systematic reviews show that their position has empirical support in criminology (Benton, 2007; Rucklidge & Kaplan, 2013). Sufficient nutrition is a precondition for classical

deterrence theory to deter crime generally or rehabilitation theory to deter crime among specific offenders.

Conclusion

In this study, we found that supplementation of multi-vitamins and minerals in doses of approximately 100% RDA, but not of a higher dose, can help to reduce the number of serious rule violations in prisons. Although achievement through a high-quality diet is to be preferred, controlled trials are essential to help to support the hypothesis that there is a causal relationship between nutritional supplements and rule violations.

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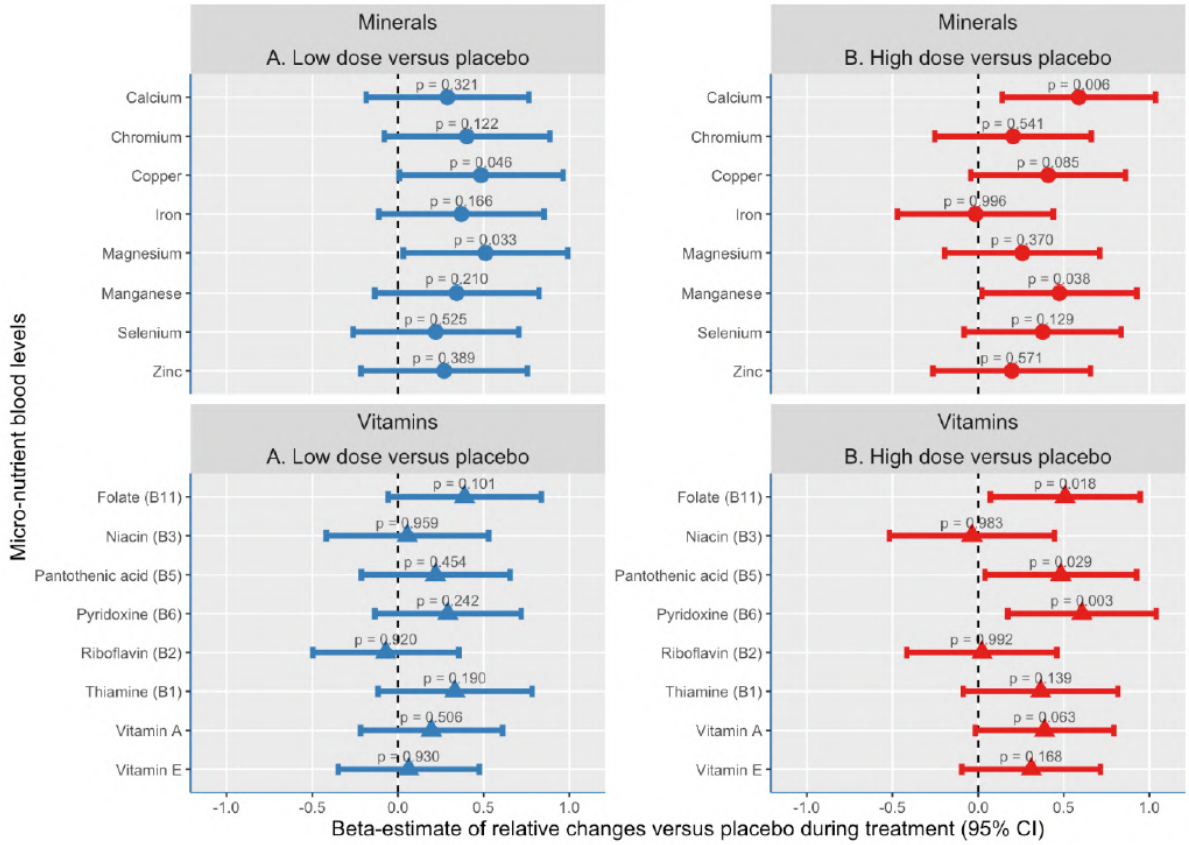
APPENDIX

Appendix 4.1. Dosage of Vitamins and Minerals in the Two Groups

Vitamins / Minerals	Higher dose Formula	Lower dose Formula	US RDA or AI[a)] (Food and Nutrition Board, 2011)
Vitamin A	5,000 I.U.	5,000 I.U.	3000 I.U.
Vitamin D	200 I.U.	200 I.U.	600 I.U.
Vitamin E	30 I.U.	30 I.U.	23 I.U.
Vitamin C	120 mg.	60 mg.	90 mg.
Thiamin (B1)	4.5 mg.	1.5 mg.	1.2 mg.
Riboflavin (B2)	5.1 mg.	1.7 mg.	1.3 mg.
Niacin (B3)	60 mg.	20 mg.	16 mg.
Pantothenic Acid (B5)	30 mg.	10 mg.	5 mg.[a)]
Pyridoxine (B6)	6 mg.	2 mg.	1.3 mg.
Folate	400 mμ.	400 mμ.	400 mμ.
Vitamin B12	18 mμ.	6 mμ.	2.4 mμ.
Biotin	300 mμ.	300 mμ.	30 mμ.[a)]
Vitamin K	50 mμ.	50 mμ.	120 mμ.[a)]
Calcium	122 mg.	200 mg.	1000 mg.
Magnesium	59 mg.	80 mg.	400 mg.
Iron	18 mg.	18 mg.	8 mg.
Zinc	15 mg.	15 mg.	11 mg.
Iodine	150 mμ.	150 mμ.	150 mμ.
Copper	2 mg.	2 mg.	0.9 mg.
Manganese	2.5 mg.		2.3 mg.[a)]
Chromium	100 mμ.		35 mμ.[a)]
Selenium	100 mμ.		55 mμ.
Molybdenum	120 mμ.		45 mμ.

Note. AI = adequate intake; IU = international unit; mg = milligram; mμ = microgram; RDA = recommended dietary allowance

Appendix 4.2 Forrest plots of the standardized mean differences (using the posthoc Tukey tests) patterns or comparisons between low dose and higher dose groups versus the placebo group.



Note: Error bars represent 95% confidence intervals of the difference between the two groups.

Chapter 5

DIETARY SUPPLEMENTS FOR AGGRESSIVE BEHAVIOR IN PEOPLE WITH INTELLECTUAL DISABILITIES: A RANDOMIZED CONTROLLED CROSSOVER TRIAL

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ABSTRACT

Background: Aggressive incidents are common in people with intellectual disabilities. Therefore, we aimed to assess whether supplementation of multivitamins, minerals, and omega-3 fatty acids (FA) reduces aggressive incidents.

Methods: We conducted a randomized, triple blind, placebo controlled, single crossover intervention trial. People with intellectual disabilities or borderline intellectual functioning, between 12-40 years of age, and showing aggressive behavior were included. Participants received either a daily dose of dietary supplements, or placebo. Primary outcome was the number of aggressive incidents, measured using the Modified Overt Aggression Scale (MOAS).

Results: there were 113 participants (placebo, n= 56), of whom 24 (placebo, n = 10) participated in the crossover phase of the trial. All 137 trajectories were included in the analyses. There was no significant difference in mean number of aggressive incidents per day between those assigned to supplements and those who received placebo (Rate Ratio = 0.93: 95% Confidence Interval (CI) = 0.59 - 1.45).

Conclusion: In this pragmatic trial, we did not find significant differences in the outcomes between the supplement and placebo arms. The COVID-19 pandemic started midway through our trial, this may have affected the results.

INTRODUCTION

Aggressive behavior is common in people with intellectual disabilities. Prevalence rates range from 10% to more than 45% depending on the definitions of aggressive behavior, the sub-population studied and the measurement methods used (Bowring, Painter, & Hastings, 2019; Didden et al., 2016; Drieschner, Marrozos, & Regenboog, 2013). Much can be done to reduce aggression, for example through the use of anger management interventions, behavioral therapies, contextual approaches, sedatives, and off-label antipsychotics (Didden, Nijman, Delforterie, & Keulen-De Vos, 2019; Lloyd & Kennedy, 2014). However, other evidence-based and safe treatment options remain necessary (Didden et al., 2016; Scheifes, 2015).

In vivo and in vitro research has revealed multiple mechanisms of action by which micronutrients may influence the central nervous system (CNS), including neurotransmitter synthesis, energy production and neuroprotective properties (Calderon-Ospina & Nava-Mesa, 2020; Kennedy, 2016; Khanna, Roy, Parinandi, Maurer, & Sen, 2006; Parletta, Milte, & Meyer, 2013). A sub-optimal functioning CNS is associated with reduced self-control and aggressive behavior (Jackson, 2016). There also is accumulating evidence for the hypothesis that dietary supplements may reduce aggressive behavior (Benton, 2007; Frensham, Bryan, & Parletta, 2012; Rucklidge & Kaplan, 2013). A decrease in antisocial behavior was found in four randomized trials for multivitamins and minerals on inmates' behavior (Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Schoenthaler et al., 1997; Schoenthaler, Gast, Giltay, & Amos, 2021; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak, 2010). Positive effects of dietary supplements on externalizing behavior in children with and without mental health problems were found in another four randomized trials (Adams et al., 2011; Raine et al., 2016; Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018; Schoenthaler & Bier, 2000). Although there are also two randomized trials in students that showed inconclusive results (Long & Benton, 2013; Tammam, Steinsaltz, Bester, Semb-Andenaes, & Stein, 2016), the overall effect of the supplements versus placebo on antisocial behavior was statistically significant and in favor of the active supplements (Benton, 2007; Rucklidge & Kaplan, 2013).

Given the effectiveness in randomized controlled trails (RCTs) among other study populations, we conducted a randomized trial on the effectiveness of dietary supplements to reduce aggressive incidents in people with intellectual disabilities. Other studies on aggressive

behavior in people with intellectual disabilities have shown that recruiting enough participants can be a problem (Oliver-Africano et al., 2010). In order to achieve sufficient statistical power with a relative small number of participants (Richens, 2001), we added a crossover arm after the second year of recruitment. We found little information about the carry over effect of the combination of dietary supplements used, so we chose to use the same wash out time for participating in the crossover part as for the initial inclusion. Our hypothesis was that the supplementation of vitamins, minerals, and omega-3 FA would lead to a reduction in aggressive behavior in people with intellectual disabilities and borderline intellectual functioning. Our second hypothesis was that this intervention would also improve their quality of life.

METHODS

Design and Procedure

This study was a pragmatic, randomised, triple-blind, placebo controlled, multicentre, crossover intervention study to investigate the effect of dietary supplements on aggressive behavior among people with intellectual disabilities and borderline intellectual functioning. The data was collected at locations of six care organizations between April 11, 2018 and February 1, 2021. Participants first entered a run-in phase and received placebo supplements for 2 weeks. Thereafter, they were randomized and included in the 16-week study. After completion, they were asked to participate in the crossover trial, and after a new informed consent procedure and a washout period of at least two weeks, they would repeat the study in a different treatment arm, while the study pharmacist maintained the blind to treatment allocation. Support staff offered the supplements and reported incidents daily. Trained research assistants collected baseline and endpoint data from the support staff, and if possible, from the participants. On a weekly basis, they monitored incident reports and adverse events collected by support staff. The participants received a gift voucher of 5 euros twice for their contribution to providing baseline and endpoint data.

Participants

Participants were recruited from six care organizations for people with intellectual disabilities in different regions in the Netherlands (i.e., Amarant, Amerpoort, Gemiva-SVG-groep, Schakenbosch, ‘s Heeren Loo, and Trajectum). People with borderline intellectual functioning

may need similar support as people with mild intellectual disability due to psychological co-morbidity and deficits in adaptive abilities (Jonker et al., 2021). In the Netherlands they can receive support through the care system for people with intellectual disabilities. Therefore, these people were also recruited to participate in our study. To explain the study to potential participants an animation film and folders in simple language were developed. People who were willing to participate were asked to provide informed consent. For legally incapacitated people with intellectual disabilities, as monitored by the organizations' psychologist, and children under the age of 16, informed consent was (also) requested from the legal representative.

The following inclusion and exclusion criteria were used: Successfully completing the run-in phase; Age between 12-40 years; Receiving care from an intellectual disabilities-organisation; IQ < 85; Score ≥ 5 on the Social Dysfunction and Aggression Scale (see Measurements); Not pregnant or breast feeding; Does not have one of the following conditions: Williams syndrome, Wilson's diseases, hemochromatosis, or hyperparathyroidism; Not using levothyroxine, methyldopa or levodopa; No fish allergy; Not using dietary supplements with vitamins or minerals for the past 14 days (only vitamin D supplements up to 50 µg per day were allowed). Participants received 4 capsules daily with one meal, consisting of 2x multivitamin minerals and 2x omega-3 FA. The multivitamin minerals contained 12 vitamins and 9 minerals and consisted of a powdered multivitamin tablet (Bonusan Multi Vital Actief) divided into two opaque, size "0" capsules. The omega-3 supplements (Bonusan Omega-3 Forte) contained 200 mg DHA and 300 mg EPA and were bovine gelatin soft gel capsules with an opaque coating. As can be seen in appendix 5.1, 5.2, 5.3 and 5.4, the daily dose of the micronutrients used in our study is in the range of doses used in other studies on the effect of dietary supplements on behavior. The placebos were visually indistinguishable from the active supplements according to a test panel of staff workers and people with mild intellectual disabilities and borderline intellectual functioning. A vanilla scented silica gel sachet was added to each jar of supplements and placebos to give them a similar scent. For the placebo capsule contained a small amount (0.8 mg) of riboflavin. The supplements/placebos were administered by the LUMC research pharmacy and was ordered by the researcher using a unique randomly assigned participant code.

Table 5.1 Socio-demographic and baseline characteristics according to randomized groups

	Active (*n*=57)	**Placebo** (*n*=56)
Demographics:		
Age (year)	22.9 (7.1)	22.8 (7.3)
Female gender	22 (38.6%)	17 (30.4%)
Living with parents	4 (7.0%)	5 (8.9%)
BMI	24.2 (4.9)	25.5 (7.0)
Diet Quality	79.7 (16.2)	82.0 (17.2)
Smoking	12 (21.1%)	18 (32.1%)
IQ and severity of ID:		
IQ	47.2 (19.9)	50.0 (21.6)
Severe to profound ID	21 (36.8%)	19 (33.9%)
Moderate ID	9 (15.8%)	9 16.1%)
Mild ID	16 (28.1%)	12 (21.4%)
Borderline IF	11 (19.3%)	16 (28.6%)
Clinical data:		
SDAS-11 (baseline)	17.1 (6.3)	17.3 (7.7)
IDQOL-16 (baseline)	58.6 (9.8)	57.4 (9.2)
Medication and therapy:		
Any medication	48 (84.2%)	47 (83.9%)
Antipsychotics	26 (45.6%)	29 (51.8%)
Antiepileptics	4 (7.0%)	6 (10.7%)
Behavior therapy	4 (7.0%)	10 (17.9%)
Psychiatric co-morbidity:		
Autism	26 (45.6%)	22 (39.3%)
ADHD	5 (8.8%)	6 (10.7%)

Note. ADHD = attention-deficit/hyperactivity disorder, BMI = body mass index, ID = intellectual disability, IDQOL-16 = intellectual disability quality of life-16, IF = intellectual functioning, IQ = intelligence quotient, SDAS-11 = social dysfunction and aggression scale-11, In brackets is the percentage of the group (%), or the standard deviation (SD) if the value is an outcome score.

Randomization

Block randomization was used with a block size of 8 participants at a 1: 1 ratio through a computerized random number generator. Four strata were made according to age (i.e., younger than 18 or 18 and older) and aggression score in the preceding week (low aggression [SDAS < 18] or high aggression [SDAS ≥ 18]). The allocation was managed by an independent LUMC research pharmacist and only released upon completion of the statistical analysis on the primary outcome.

Measurements

The primary outcome was the sum of the aggressive incidents at either the residential or the daycare facility, as reported daily with the Modified Overt Aggression Scale (MOAS) by the support staff (Kay, Wolkenfeld, & Murrill, 1988; Silver & Yudofsky, 1991; Sorgi, Ratey, Knoedler, Markert, & Reichman, 1991). The MOAS is a reliable tool to measure aggressive behavior in

people with intellectual disabilities (Cohen et al., 2010), and has an intraclass correlation coefficient (ICC) of 0.93 (Oliver, Crawford, Rao, Reece, & Tyrer, 2007). Four types of aggression are reported using this scale: verbal, against objects, physical, and self-harm. The severity of the incidents were scored on a scale from 0 (i.e., mild) to 4 (i.e., extreme) for each type of aggressive behavior. On the MOAS we added a daily record of whether the supplements had been taken. The MOAS was completed daily by the support staff and monitored weekly for clarity and completeness by the research assistants. If the data was incorrect or missing, the assistant would call the support staff for clarification. The support staff of all participating sites were trained on site to report the aggressive incidents using the MOAS.

As a secondary outcome, quality of life was measured with the Intellectual Disability Quality of Life Scale (IDQOL-16). This self-report scale consists of 16 statements, which were visualized with pictograms and were scored on a 5-point Likert scale in the shape of faces (smiley´s), with the leftmost face smiling and the rightmost face looking angry (Hoekman, Douma, Kersten, Schuurman, & Koopman, 2001). The score ranges from 16 to 80, with higher scores indicating a better QoL. The Cronbach's alpha in our sample was 0.87. The IDQOL-16 was completed at baseline and in the last week of the trial. If the participant was unable to complete the scale, the support staff was asked to help complete it as a proxy.

The Social Dysfunction and Aggression Scale (SDAS-11) is an 11-item observer-rated questionnaire used to measure social dysfunction and aggressive behavior during the previous week. Support staff scored each item on a 5-point Likert scale, ranging from 0 (not present) to 4 (extremely severe). The total score ranges from 0 to 44, with higher scores indicating more social dysfunctional and aggressive behavior (Wistedt et al., 1990). Psychometric qualities of the SDAS were found to be acceptable to good (Kobes, Nijman, & Bulten, 2012). Cronbach's alpha in our sample was 0.88. The SDAS-11 was completed by a support staff of the participant at baseline and in the last week of the trial.

The Dutch Healthy Diet Food Frequency Questionnaire (DHD) can be used to estimate the extent to which the eating pattern is in accordance with the Dutch guidelines for a healthy diet from 2015 (Looman et al., 2017). It has 40 items and yields a DHD index score ranging from 0 to 160, with higher scores indicating a better diet quality. The scale is made up of 16 components, namely: vegetables, fruits, whole wheat products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meats, processed meats, sugar containing beverages, alcohol, salt, and unhealthy food products. The scale has acceptable concurrent validity and can be used for

epidemiological studies (van Lee et al., 2016). The DHD was completed at baseline by the support staff and participant (if possible).

We used case file data provided by the healthcare organizations to obtain IQ scores, medication, autism spectrum diagnosis, and demographic characteristics of participants. This information was collected at baseline by the research assistant.

Sample size

The primary outcome measure was the number of aggressive incidents measured with the MOAS. The power calculation was based on an effect size of incidence rate ratio (IRR) = 0.75 with an α of .05 in order to achieve a power of at least .80. This is a low estimate derived from the effect sizes found in previous RCTs (Gesch et al., 2002; Zaalberg et al., 2010). This yielded a sample size of at least 126, with at least 18 crossover participants.

Statistical analyses

Characteristics and outcomes were summarized as means with standard deviations (*SD*) for continuous variables, and as numbers and proportions for categorical variables. Adherence proportion was calculated by dividing the number of days the supplements were offered by the number of days the supplements were taken. The MOAS data was calculated in two ways. First, we summed all counts (number of marks). In addition, the sum of the counts per any of the four types of aggression was calculated (i.e., verbal, against objects, physical, and self-harm). Because of the crossover design, we used a generalized linear mixed model (GLMM). The GLMM was preferred over a generalized linear model (GLM) to allow statistical testing based both on both between-group and within-subject variance. Those that crossed-over were added as repeated measurements in the model. The negative binomial distribution was used for the analyses, since the dispersion statistic of the count data was expected to be higher than one (De Bles et al., 2022; Gesch et al., 2002; Zaalberg et al., 2010). The frequency of aggressive incidents was presented as the estimated mean number of incidents per day. The log number of days in the trial was used as offset variable. As a dependent variable, the total number of incidents and four types of incidents were entered consecutively. In order to investigate the trend of the incidence rate ratio (IRR) over time according to the intervention, a negative binomial regression was performed for each period of 10 days separately, of which the estimated means were plotted over time.

For the secondary outcomes, the endpoint minus baseline was calculated and the difference between the active and placebo group was analyzed with a linear mixed model analysis. The

difference in the number of reported adverse events among the randomized groups was tested with chi-squared test.

The governmental measures on COVID-19, such as closing down the daycare centers, social distancing, and restricted visiting of family has had an impact on the incidence rate and types of aggression incidents in people with intellectual disabilities (Gleason et al., 2021; Schuengel, Tummers, Embregts, & Leusink, 2020). Because COVID-19 may have affected the outcome of our study, the main analyses were also performed with "COVID-19" as dichotomous covariate. We used March 17th, 2021 as cut-off point to distinguish trajectories pre and during the pandemic (being the date of the closing down of most daycare centers in the Netherlands). We made three additional analyses to explore the effects of COVID-19 on our study. First, we entered "COVID-19" as covariate in the GLMM model, and also calculated the interaction between the intervention and COVID-19 using a generalized linear model (GLM). Second, we explored the effect of COVID-19 on aggressive behavior in our sample, by entering "COVID-19" as predictor and "treatment condition" as covariate in the GLMM model. Third, we used an independent *t*-test to test for selective differences in the pre and during COVID-19 samples for Age, Body Mass Index (BMI), Diet Quality, and IQ.

Blinding was tested by asking participants and support staff at the final assessment in the trial whether they thought participants had been taking the active supplements or the placebo. With chi-squared test we checked whether participants and staff gave the correct answer more often than expected by chance.

Analyses were performed using IBM SPSS statistical software (version 27, IBM Corp Released 2020, IBM SPSS Statistics for Windows), and forest plots and figures using R with RStudio (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/).

RESULTS

The flowchart of the recruitment is presented in Figure 5.1. We approached 539 people to participate, 426 were excluded mainly because they did not want to participate or their legal representative did not give consent. Of the 113 participants (57 active, 56 placebo), 24 (14 active, 10 placebo) progressed to the crossover trial, yielding in total 137 treatment

trajectories. Socio-demographic and baseline characteristics of participants are presented in Table 5.1. Mean age was 22.8 years (*SD* 7.2), and 34.5% were female. The level of intellectual disabilities varied from profound and severe (*n* = 40), moderate (*n* = 18), to mild ID (*n* = 28) and borderline intellectual functioning (*n* = 27). There were some differences between the initial and the crossover trial, with the participants in the crossover having a higher mean age of 26.3 y (SD = 6.6) vs 22.8 y (SD = 7.2), a higher mean diet quality of 87.9 (SD = 13.0) vs 80.9 (SD = 16.7), and a lower mean IQ of 31.9 (SD = 11.1) vs 48.6 (SD = 20.7). In the participants with a crossover the average time interval between both interventions was 36.1 weeks (*SD* 26.5).

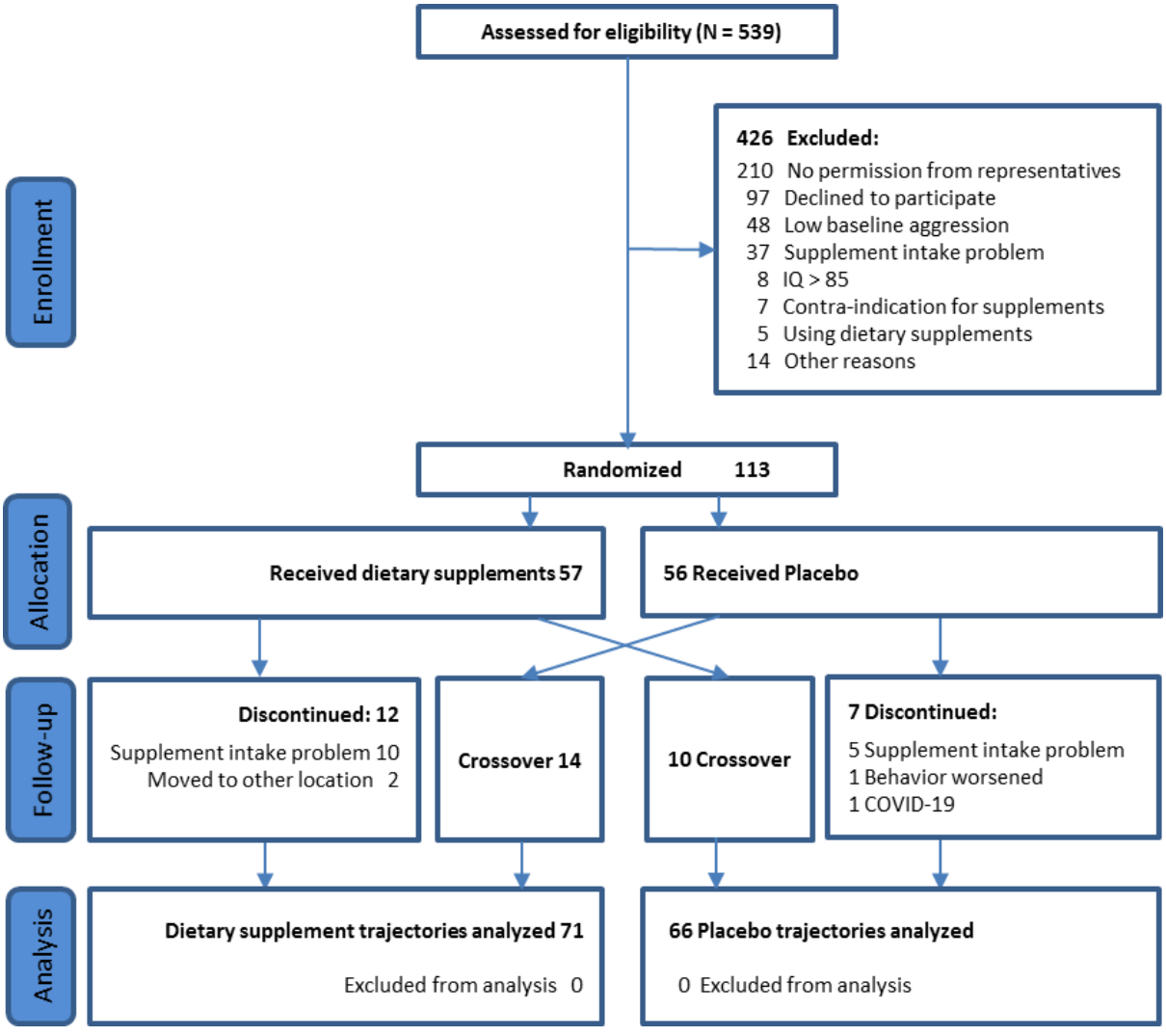

Figure 5.1. flowchart of inclusion of participants in the trial

Primary outcome

An overview of the effects of supplements on the primary outcome, based on the negative binomial regression analysis, is shown in Figure 5.2. During the trial period, a total of

13,432 aggressive incidents were registered with the MOAS. There was no significant difference in mean number of incidents per day between those assigned to supplements (0.94; 95% confidence interval [CI]: 0.69-1.29) and those who received placebo (1.02; 95% CI: 0.73-1.41), with a rate ratio of 0.93 (95% CI: 0.59-1.46; p = 0.74). The breakdown by types of aggression (verbal, against objects, physical and self-harm) did not yield significant differences either.

Variable	Supplement Inc/day	Placebo Inc/day	Rate Ratio (95% CI)	t-stat	p-value
Sum of all	0.94 (0.69-1.29)	1.02 (0.73-1.41)	0.93 (0.59; 1.45)	-0.335	0.74
Categories:					
- Verbal aggression	0.26 (0.17-0.38)	0.36 (0.24-0.53)	0.72 (0.41; 1.26)	-1.151	0.25
- Aggression against objects	0.12 (0.07-0.19)	0.17 (0.10-0.28)	0.70 (0.33; 1.45)	-0.975	0.33
- Physical aggression	0.21 (0.13-0.34)	0.21 (0.13-0.34)	1.01 (0.52; 1.95)	0.018	0.99
- Self-harm	0.30 (0.18-0.50)	0.22 (0.13-0.37)	1.38 (0.68; 2.83)	0.897	0.37
Adjusted for COVID-19					
Sum of all	0.82(0.62-1.09)	1.05 (0.78-1.41)	0.78 (0.51; 1.19)	1.283	0.26
Categories:					
- Verbal aggression	0.25 (0.18-0.34)	0.36 (0.26-0.51)	0.68 (0.42; 1.10)	2.503	0.11
- Aggression against objects	0.12 (0.08-0.19)	0.16 (0.10-0.26)	0.75 (0.38; 1.46)	0.733	0.39
- Physical aggression	0.21 (0.14-0.33)	0.24 (0.15-0.38)	0.89 (0.47; 1.66)	0.145	0.70
- Self-harm	0.23 (0.13-0.39)	0.25 (0.14-0.45)	0.89 (0.39; 1.99)	0.084	0.77

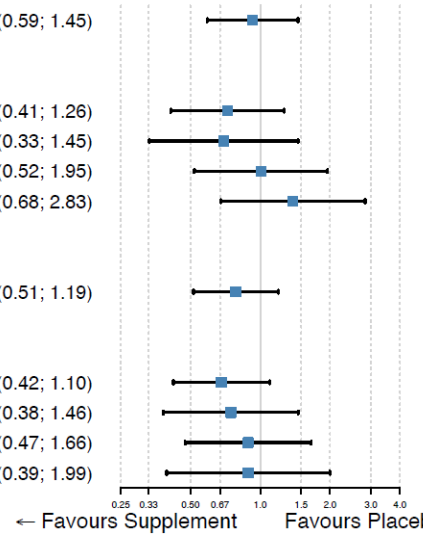

Figure 5.2 Effects of dietary supplements on aggressive incidents assessed with the MOAS, according to subtype and severity of aggression. The incidents/day are the estimate of the mean in the negative binomial regression analysis

There was no unambiguous difference in effect between active and placebo group over time, as can be seen in the timeline in Figure 5.3, which shows the mean number of incidents (with 95% CI's) per 10 days.

Secondary outcomes

The change in QoL over time did not differ significantly between the randomized groups, active arm (mean change = 0.61; 95% CI: -10.48; 11.71) and placebo arm (mean change = 3.0; 95% CI: -8.09; 14.13). For the secondary outcome of changes in aggressive behavior from baseline till endpoint there was no statistically significant difference between active arm (mean change = -3.58; 95% CI: -14.17; 7.00) and placebo arm (mean change = -2.98; 95% CI: -13.58; 7.62) either.

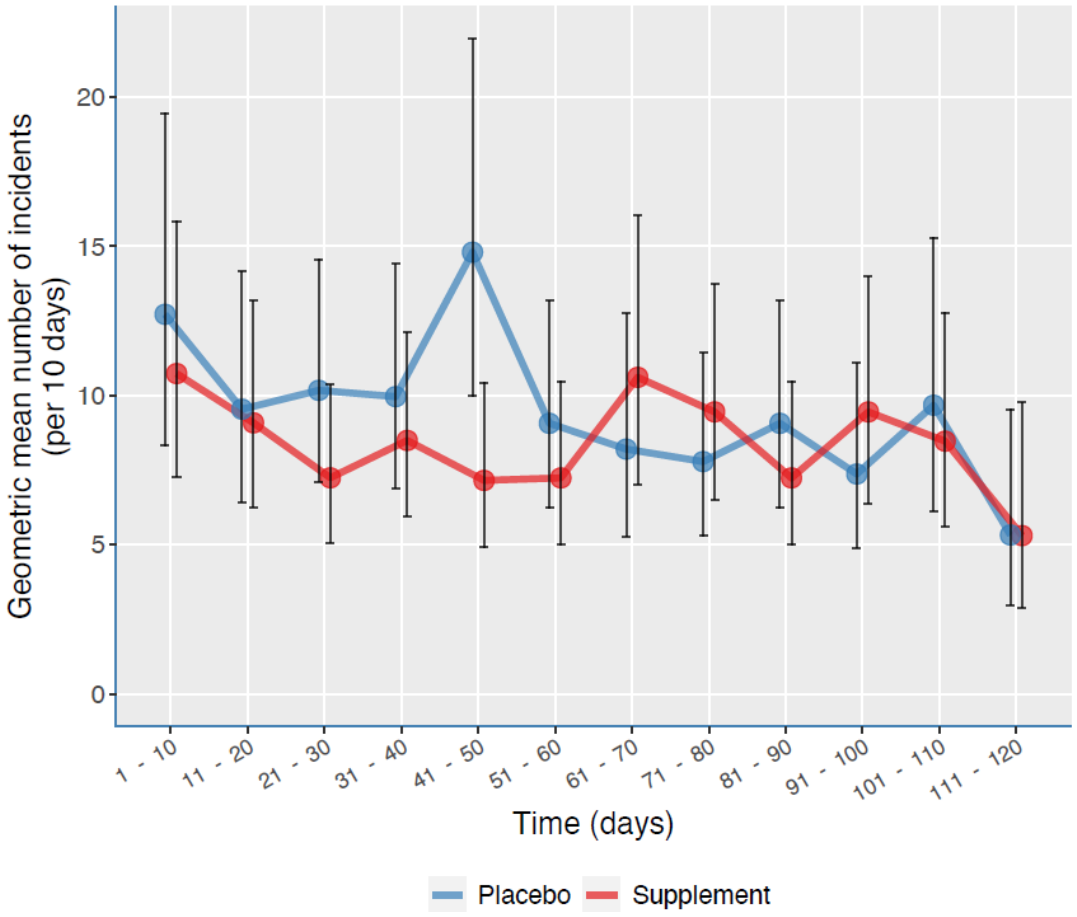

Figure 5.3 Effects of dietary supplements on aggressive incidents per 10 days

COVID-19 outcomes

In total 40 (29.2%) participants were in our trial during COVID-19 time (57.5% active vs 42.5% placebo), of which all 24 crossover participants. Adding the COVID-19 covariate to the models did not change the results significantly IRR 0.78 (95% *CI*: 0.51-1.19; $p = 0.28$) although there seemed to be a difference in the directions of the effect before and during the pandemic. Pre COVID-19, the effect was in favor of the active supplements IRR 0.62 (95% CI: .34 - 1.15), and during the COVID-19 the effect was in favor of the placebo IRR 1.44 (95% CI: .77 - 2.70), the interaction 'treatment' x 'COVID-19' did not reach statistical significance $B = -0.84$ (95% *CI*: -1.73; 0.06; $p = 0.067$). Finally, during COVID-19 there were more aggressive incidents registered then before COVID-19; IRR 1.99 (95% CI: 1.30; 3.01), especially for physical aggression IRR 2.51 (95% CI: 1.34; 4.70) and self-harm IRR 3.10 (95% CI: 1.67: 5.76). The samples pre- and during COVID-19 differed significantly on IQ (pre $M = 50.6$ [19.9], during $M = 33.7$ [16.4]; $t = 4.75$, $p < 0.01$), Age (pre $M = 22.6$ [7.3], during 25.3 [6.6]; $t = -2.11$, $p = 0.04$), and

Diet Quality (pre *M* = 79.8 [16.9], during *M* = 87.6[13.2]; *t* = -2.88, p = 0.01. The difference on baseline BMI did not reach significance.

Adherence

The adherence to the daily intake of the supplements in the total sample was (83.8%), and did not differ significantly between active group (84.4%) and placebo (83.2%).

Blinding

Table 5.2. Group assignment x guess of group assignment by participants and support staff

	Participant guess				Support staff guess			
	No Idea	**Placebo**	**Active**	**Total**	**No Idea**	**Placebo**	**Active**	**Total**
Active	54(78.3%)	8(11.6%)	7(10.1%)	69	42(60.9%)	18(26.1%)	9(13.0%)	69
Placebo	54(84.4%)	6 (9.4%)	4 (6.3%)	64	40(62.5%)	19(29.7%)	5(7.8%)	64
total	108(81.2%)	14(10.5%)	11(8.3%)	133	82(61.7%)	37(27.8%)	14(10.5%)	133

Table 5.2 shows success of blinding. The vast majority of participants during the 137 treatment trajectories (*n* = 108, 81.2%) and their support staff (*n* = 82, 61.6%) did not guess correctly whether either supplements or placebo had been provided. Among the participants who thought they knew which group they were in, there was no significant difference between the proportion of wrong and correct guesses (*p* = .60). A similar result was found for the support staff (*p* = 0.74).

Adverse events

Table 5.3. Number of adverse effects reported at the end upon inquiry

	Active	%	Placebo	%
Gastrointestinal problems	7	10.1	11	17.2
Low energy	7	10.1	4	6.3
Skin-related problems	3	4.3	2	3.1
Nosebleeds	1	1.4	1	1.6
Headache	3	4.3	1	1.6
Sleeping problems	10	14.5	6	9.4
Participants with any adverse event	21	29.6	21	31.8

Table 5.3 shows the number of adverse events reported at the end of the study. The most common symptoms were gastrointestinal problems and lack of energy. The absolute number of participants with at least 1 adverse event in the active group (*n* = 21, 29.6%) did not significantly differ from that in the placebo group (*n* = 21, 31.8%). There were no significant differences in number of adverse events between the two groups.

Chapter five

DISCUSSION

In this pragmatic RCT involving people with intellectual disabilities and borderline intellectual functioning, we found no significant difference in the number of aggressive incidents between those assigned to dietary supplements and those assigned to placebo: neither in the total score, nor in the scores broken down by type of aggression. We neither found a significant difference in effectiveness on secondary or safety outcomes. Finally, we found no difference in the total number of adverse reactions reported between the two groups. It should be noted, however, that the number of registered incidents had doubled during the COVID-19, and we found a trend that the direction of the effect changed during the pandemic, which may have affected our effect estimates.

In the past decades, eleven RCTs have been performed with multivitamin-mineral supplements as an intervention and aggressive behavior as an outcome (De Bles et al., 2022; Gesch, 2011; Long & Benton, 2013; Raine et al., 2016; Rucklidge et al., 2018; Schoenthaler et al., 1997; Schoenthaler & Bier, 2000; Schoenthaler et al., 2021; Tammam et al., 2016; Zaalberg et al., 2010). Many different outcome measures have been used to map behavior, ranging from self-report (Long & Benton, 2013), and observer report questionnaires (Raine et al., 2016; Rucklidge et al., 2018), to the count of incidents (Schoenthaler et al., 1997; Schoenthaler & Bier, 2000; Schoenthaler et al., 2021), or both (De Bles et al., 2022; Gesch et al., 2002; Tammam et al., 2016; Zaalberg et al., 2010). All but one study (De Bles et al., 2022) had an effect in favor of the supplements on at least one of the outcome measures. The effect may be modified by age. The only study that also included older participants had a null finding (De Bles et al., 2022). The age of the participants in the other studies ranged from 6 to 25 years. A large proportion of the participants in our RCT used psychotropic medication (58.4%). In most previous RCTs people who used psychotropic medication were only a small minority of the sample or were excluded (Raine et al., 2016; Rucklidge et al., 2018; Schoenthaler et al., 1997). An exception was the study by De Bles et al. (2022) in which patients with mental disorders were included. In a post-hoc subgroup analysis supplements seemed to be less effective in those using antipsychotics (De Bles et al., 2022). We may conclude that all trials differed in multiple ways from each other and from our trial. But trials that excluded the use of psychotropic medication tended to show a larger beneficial effect than the trials that did not.

Strengths and limitations

A strong point of the study was the sample-wide large number of registered incidents, which protected against floor effects. This was the result of a threshold of a minimum level of aggressive behavior as an inclusion criterion, and also by weekly monitoring of the daily registrations of incidents. Another strength was the successful blinding, which has been less successful in some previous supplement studies (Long & Benton, 2013; Tammam et al., 2016; Zaalberg et al., 2010).

Some limitations must also be acknowledged. First, a significant portion of our research trajectories (40, 29.2%), including all crossover trials, took place during the COVID pandemic. COVID-19 and associated restrictions caused major changes in the lives of people with intellectual disabilities, for example, social distancing, closing of the day care centers, and an entry ban for visiting family members (Embregts et al., 2020; Gleason et al., 2021). Behavioral changes as a result of COVID-19 affected many studies, and may have affected their outcomes (Aman & Pearson, 2020; Stiles-Shields, Plevinsky, Psihogios, & Holmbeck, 2020). In our sample, the number of reported aggression incidents per person during COVID-19 had doubled and the direction of the effect during COVID-19 changed direction from in favor of supplement to in favor of the placebo, which was a statistical trend (p = 0.067). The change in effect size was mainly driven by a rise in self-harm and physical aggression in a subgroup of people with a lower IQ, higher age, and higher diet quality. Explanations for this change of effect direction remains speculative. A second limitation was that only a small and selected sample of participants progressed to the crossover study, with more participants in the active then in the placebo condition. A third limitation is that we do not know much about the washout time of the effect of micronutrients on behavior, so the participants who took placebo during the crossover may still have benefited from the supplements in the first trial. Finally, we received feedback from the support staff of people with severe to profound intellectual disabilities that they thought the MOAS did not always match with the behavior of their participants. For example, what is the validity of rating verbal aggression if the participant is not able to speak? Despite the good psychometric properties of the MOAS from previous research, it appears to be difficult to find an instrument that is well suited for measuring aggression of people with severe and those with mild levels of intellectual disabilities.

Conclusions

In this pragmatic trial, we did not find significant differences in the primary and secondary effectiveness between the supplement and placebo arms among people with intellectual disabilities. Since the COVID-19 pandemic coincided with our trial, we recommend a replication of our study.

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Ethics approval: Approval for conducting the study was granted by the Medical Ethics Committee of the Leiden University Medical Center (LUMC) (NL60839.058.17).

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Appendix 5.1 Daily dosages of minerals in supplement studies

	Schoenthaler et al. 1997	Schoenthaler et al. 2000	Gesch et al. 2002	Zaalberg et al. 2010	Adams et al. 2011	Long et al. 2013	Tammam et al. 2016	Rucklidge et al. 2018	de Bles et al. 2022	Gast et al. 2022
Potassium (mg)	-	-	4	4	50	40	-	192	-	-
Calcium (mg)	122	200	100	100	100	162	-	1056	-	-
Manganese (mg)	3	1	3	3	3	2	2	7.7	5	0.5
Iron (mg)	18	9	12	12	-	5	12	10.8	8	4
Zinc (mg)	15	8	15	15	12	5	15	38.4	7.5	10
Copper (mg)	2	1	2	2	-	0.5	1	5.8	0.5	0.5
Magnesium (mg)	59	80	30	100	100	100	94	480	-	70
Molybdenum (µg)	250	120	250	250	150	50	-	120	13	13
Borium (mg)	-	-	-	-	-	-	-	-	-	1
Selenium (µg)	100	50	50	50	22	30	55	168	75	75
Chromium (µg)	100	50	200	200	70	40	50	504	13	100
Iodine (µg)	150	75	140	140	100	100	130	163	150	80
Lithium (µg)	-	-	-	-	500	-	-	-	-	
Sulfur (mg)	-	-	-	-	500	-	-	-	-	
Phosphorus (mg)	-	-	-	-	-	125	-	672	-	
Chloride (mg)	-	-	-	-	-	36.3	-	-	-	

Appendix 5.2 Daily dosages of vitamins in supplement studies

	Schoenthaler et al. 1997	Schoenthaler et al. 2000	Gesch et al. 2002	Zaalberg et al. 2010	Adams et al. 2011	Long et al. 2013	Tammam et al. 2016	Rucklidge et al. 2018	de Bles et al. 2022	Gast et al. 2022
A (mg)	1.5	0.75	0.75	0.75	0.6	0.8	0.4	1.4	-	
Beta carotene mg	-	–	–	0.13	-	-	-	-	6	2.9
B1 (mg)	4.5	0.75	1.2	1.2	20	1.4	6	48	15	12
B2 (mg)	5.1	0.9	1.6	1.6	20	1.75	3	14.4	15	16
B3 (mg)	60	10	18	18	25	20	18	72	20	35
B5 (mg)	30	5	4	4	15	7.5	6	24	15	25
B6 (mg)	30	1	2	2	40	2	8	56	5	5
B11 Folic acid (µg)	400	200	400	400	100	200	400	640	400	200
B12 (µg)	18	3	3	3	500	2.5	15	720	25	70
Biotin (µg)	-	150	100	100	150	62.5	75	864	25	25
C (mg)	120	40	60	60	600	100	80	480	100	80
D3 (µg)	5	5	10	5	7.5	5	20	60	25	15
E (mg)	10	10	10	270	15	-	8	200	53	8
K (mg)	50	-	-	-	-	-	-	-	-	50

Appendix 5.3 Daily dosages of omega-3 fatty acids in supplement studies

	Schoenthaler et al. 1997	Schoenthaler et al. 2000	Gesch et al. 2002	Zaalberg et al. 2010	Adams et al. 2011	Long et al. 2013	Tammam et al. 2016	Rucklidge et al. 2018	de Bles et al. 2022	Gast et al. 2022
LA	-	-	1260	-	-	10	-	-	-	-
γ-LA (mg)	-	-	160	100	-	-	-	-	-	-
EPA (mg)	-	-	80	400	-	-	165	-	307	300
DHA (mg)	-	-	44	400	-	673	116	-	175	200

Appendix 5.4 Ingredients of the placebo supplements used in the Gast et al. (2022) trial:

The multivitamin-mineral placebo:

- 13 mg rice bran extract
- 440 mg microcrystalline cellulose
- 0.8 mg riboflavin (to secure the blind)

The omega-3 placebo:

- 500 mg high oleic sunflower oil
- 0.75 mg mixed tocopherol

Chapter 6

EFFECTIVENESS OF MULTIVITAMIN AND MINERAL SUPPLEMENTATION ON AGGRESSIVE BEHAVIOR: A SYSTEMATIC REVIEW AND META-ANALYSIS

Submitted for publication as:

D.A.A. Gast, T.A. Wissink, A.M. van Hemert, R. Didden, E.J. Giltay; Effectiveness of Multivitamin and Mineral Supplementation on Aggressive Behavior: A Systematic Review and Meta-Analysis

ABSTRACT

Background: Randomized controlled trials (RCTs) reported beneficial effects of multivitamin and mineral supplements on aggressive behavior. However, the strength of the association differed across populations, and it is unknown whether the effects on observed incidents or more subjective (continuous) outcome measures are consistent. We aimed to investigate the overall effectiveness of multivitamin and mineral supplements on aggressive behavior in a systematic review with meta-analysis.

Methods: Systematic searches were performed in the databases Cochrane Library, Embase, PsycINFO, and PubMed for all RCTs that used multivitamins/minerals (with or without n-3 PUFA) versus a control group with at least one measure of aggressive behavior. Two meta-analyses were conducted using a random-effects model, one with the pooled Hedges' *g* effect sizes for continuous outcome data and one with the incidence rate ratios for count outcome data (IRR).

Results: Eleven RCTs met the inclusion criteria, yielding 18 effect sizes. There were 948 subjects in the multivitamins/mineral group and 811 in the control group. The supplements showed substantial variation in micronutrient doses and composition across trials. The target groups of the studies consisted of young adult prisoners, school-aged youth and students, psychiatric patients, and people with an intellectual disability. Multivitamin/mineral intervention versus placebo reduced aggressive behavior, with an IRR of 0.72, 95% confidence interval (CI) [0.56, 0.93], for the count data, and a Hedges' *g* of -0.23, 95% CI [-0.38, -0.07], for the continuous data.

Conclusion: Multivitamin mineral supplements versus placebo showed a small but significant pooled beneficial effect size on aggressive behavior.

INTRODUCTION

Aggressive behavior is a serious problem among various institutional groups, such as psychiatric patients, adolescent prisoners, and people with intellectual disabilities (Bader, Evans, & Welsh, 2014; Bowring, Painter, & Hastings, 2019; Emerson et al., 2001; Steiner & Cain, 2016). For victims it can be harmful or traumatizing (Needham, Abderhalden, Halfens, Fischer, & Dassen, 2005), and for the aggressor it is associated with institutionalization and medicalization (Didden et al., 2016). Aggressive behavior may also cause chronic stress, increased workload, and burnout for professionals who care for aggressive clients or patients (Hensel, Lunsky, & Dewa, 2012). There is a range of interventions to prevent aggressive behavior (Lee & DiGiuseppe, 2018; Lloyd & Kennedy, 2014), but they all have their inherent limitations and side effects. Vitamin/mineral supplementation may provide a cost-effective, accessible, and well-tolerated adjunct to the standard treatments for aggressive behavior.

Positive effects of micronutrients on behavior have been found in an open-label trial (Hambly et al., 2017) and in several randomized controlled trials (RCTs; (Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018; Schoenthaler et al., 1997; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak, 2010). There are several hypotheses about underlying mechanisms. Micronutrients are involved in the synthesis of neurotransmitters (Calderon-Ospina & Nava-Mesa, 2020), and B-vitamins and minerals play an important role in the energy production of the central nervous system (Kennedy, 2016). Also, micronutrients contribute to healthy functioning and longevity of neurons and their connectivity (Parletta, Milte, & Meyer, 2013). Furthermore, micronutrients may help to maintain a healthy microbiome, which may affect behavior through the gut–brain axis (Choi et al., 2020; Liu et al., 2017; Luthold, Fernandes, Franco-de-Moraes, Folchetti, & Ferreira, 2017). Over all, the effect of vitamins and minerals is best understood as a complex interplay between multiple micronutrients, which is also found in a healthy and balanced diet, and less as the effect of a single micronutrient on a single process (Messina, Lampe, Birt, & Appel, 2001; Parletta et al., 2013).

Several systematic reviews on the effect of dietary supplements on behavior have been published so far. However, many reviews focused on omega-3 fatty acids (FAs) rather than multivitamins and minerals (Bent, Bertoglio, & Hendren, 2009; Bozzatello, Brignolo, De Grandi,

& Bellino, 2016; Choy & Raine, 2018; Cooper, Tye, Kuntsi, Vassos, & Asherson, 2016; Gajos & Beaver, 2016; Gould, Roberts, & Makrides, 2021). Two systematic reviews performed a meta-analysis of RCTs on the effect of only omega-3 FA supplementation on aggression, with pooled effect sizes ranging from small to medium (Cooper et al., 2016; Gajos & Beaver, 2016). Five systematic reviews were published on the effect of multivitamin and mineral supplements on behavioral outcomes. The outcome measures of the reviews differed between trials and included behavior and cognition in general (Frensham, Bryan, & Parletta, 2012), behavior within psychiatric disorders (Johnstone, Hughes, Goldenberg, Romijn, & Rucklidge, 2020; Rucklidge & Kaplan, 2013), and anti-social and criminal behavior (Benton, 2007). Another review had aggressive behavior as outcome, but did not distinguish between single micronutrient interventions and multivitamin and mineral supplements (Qureshi, Kunaratnam, Kolla, & Konkoly Thege, 2021).

To the best of our knowledge, no meta-analysis on the effect of multivitamin and mineral supplements on aggressive behavior has been conducted to date. Therefore, the aim of this meta-analysis was to investigate whether multivitamin and mineral supplementation is effective and safe in reducing aggressive behavior and to explore potential sources of heterogeneity.

METHODS

Search strategy

We searched through the following databases: Cochrane Library, Embase, PubMed, and PsycINFO. We took into account all literature up to December 12, 2020. In addition, we checked all reference lists of the main articles and contacted the expert authors. The Boolean search string consisted of three parts: aggressive behaviors, AND dietary supplements, AND RCT (Appendix 1). Furthermore, in the reference list of the relevant articles, we searched for additional literature, and finally we contacted five experts and asked them to provide additional data. We exported the results of the search strategy to EndNote (Clarivate, 2019).

Eligibility criteria and study selection

In our meta-analysis, we included randomized placebo controlled trials (RCT) that used oral multivitamin/mineral supplements as an intervention alongside diet as usual and aggressive

behavior as an outcome. No selection was made regarding the setting of the study or the age and background of the participants. The dietary supplement had to contain a combination of at least five vitamins and four minerals but could also contain other micronutrients. We used a broad inclusive definition of aggressive behavior: harmful behavior that violates social norms (Bandura, 1973). All trials with at least one outcome meeting that definition were included in our meta-analysis. To operationalize aggression, we used the counts of incidents as well as measures like self-report and observer-rated questionnaires. This included measurements of conduct problems, rule offending behavior, anti-social behavior, disruptive behavior, and other externalizing behaviors.

After removing duplicates, we selected articles via titles. The next selection we made via abstracts, after which we assessed the full-text article.

Data extraction

The following data were extracted: study design, sample size, timeline, intervention details, outcome measures, and overall results. We also extracted characteristics of the participants, including age, gender, setting, medical diagnosis, and psychotropic medication. The internal validity of the trials was assessed using the Cochrane Risk of Bias Tool that features seven criteria: random sequence generation, allocation concealment, participant blinding, outcome data blinding, incomplete outcome data, selective reporting, and other biases (Higgins et al., 2011).

Two separate pooled effect sizes were calculated: an incidents rate ratio (IRR) for the count-data outcome and a Hedges' *g* for the continuous data (Hedges, 1986). The interpretation of an IRR can be compared to that of an odds ratio, whereby a value of 1 represents no effect. The magnitude of Hedges' *g* can be interpreted as small (0.20), moderate (0.50), or large (0.80; (Fritz, Morris, & Richler, 2012).

To be able to import them into the Comprehensive Meta-Analysis (CMA), we (re)calculated the IRR of four trials (Gesch et al., 2002; Schoenthaler et al., 1997; Schoenthaler & Bier, 2000; Tammam, Steinsaltz, Bester, Semb-Andenaes, & Stein, 2016) using the OpenEpi calculator (Sullivan, Dean, & Soe, 2009). From the study of Gesch et al. (2002), we extracted additional information on the data from Gesch's PhD thesis (Gesch, 2011). From Tamman et al. (2016), additional information was gleaned from the supplementary material (S1). Finally, we corresponded directly with Schoenthaler et al. (1997, 2000 & 2021) to gain further information for our dataset. To avoid selection bias, we made a correction for one study outcome of

Schoenthaler et al. (2000). This study excluded 308 of 388 participants who had no incidents during the intervention. We reanalyzed the effect size by including these 308 participants in the analysis. In a three-arm study (Schoenthaler, Gast, Giltay, & Amos, 2021), the two active arms were combined to avoid a unit-of-analysis error (Rucker, Cates, & Schwarzer, 2017). Random and fixed effects were calculated and the difference between these outcomes was assessed as an indication for risk of heterogeneity (Higgins & Green, 2011). We further investigated the risk of heterogeneity using the Q value, the I-squared (I^2), and Tau-squared (T^2) statistics. A difference between the Q value and the df(Q) indicates heterogeneity. Furthermore I^2 indicates which proportion of the variance can be attributed to a difference in effect sizes and not to the SE. Publication bias was assessed using the Egger test and by visual examination of the funnel plot (Jin, Zhou, & He, 2015). All steps including the search, selection, extraction, and analysis were performed independently by two researchers (first and second authors). Inconsistencies regarding the results were discussed with a third researcher (last author) until consensus was reached. The data were analyzed using CMA (Clarivate, 2019).

RESULTS

Study selection

As depicted in the flow chart (Figure 6.1), the search strategy identified 1003 records, from which we removed 164 duplicates. We screened the remaining 839 articles, yielding 11 trials that we included in the meta-analysis.

Study characteristics

The study characteristics are summarized in Table 6.1. The trials were published between 1997 and 2018; two trials were still under submission (De Bles et al., 2022; Gast et al., 2022).The number of participants per study ranged from 71 to 468, for a total of 2466. We included 1759 participants (71.3%) in our analyses, whereof 948 (53.9%) received the active supplements. Seven of the 11 trials included women; the total number of women in the statistical analysis was 285 (16.2%). Participants included people with psychiatric symptoms and people with intellectual disabilities (Adams et al., 2011; De Bles et al., 2022; Gast et al., 2022; Rucklidge et al., 2018) prisoners (Gesch et al., 2002; Schoenthaler et al., 1997; Schoenthaler et al., 2021; Zaalberg et al., 2010), and school-aged children and university students (Long & Benton, 2013;

Schoenthaler & Bier, 2000; Tammam et al., 2016). In five out of 11 trials, the intervention with vitamins and minerals was supplemented with omega-3 FAs (De Bles et al., 2022; Gast et al., 2022; Gesch et al., 2002; Tammam et al., 2016; Zaalberg et al., 2010). The intervention periods ranged from 2 weeks to 9 months.

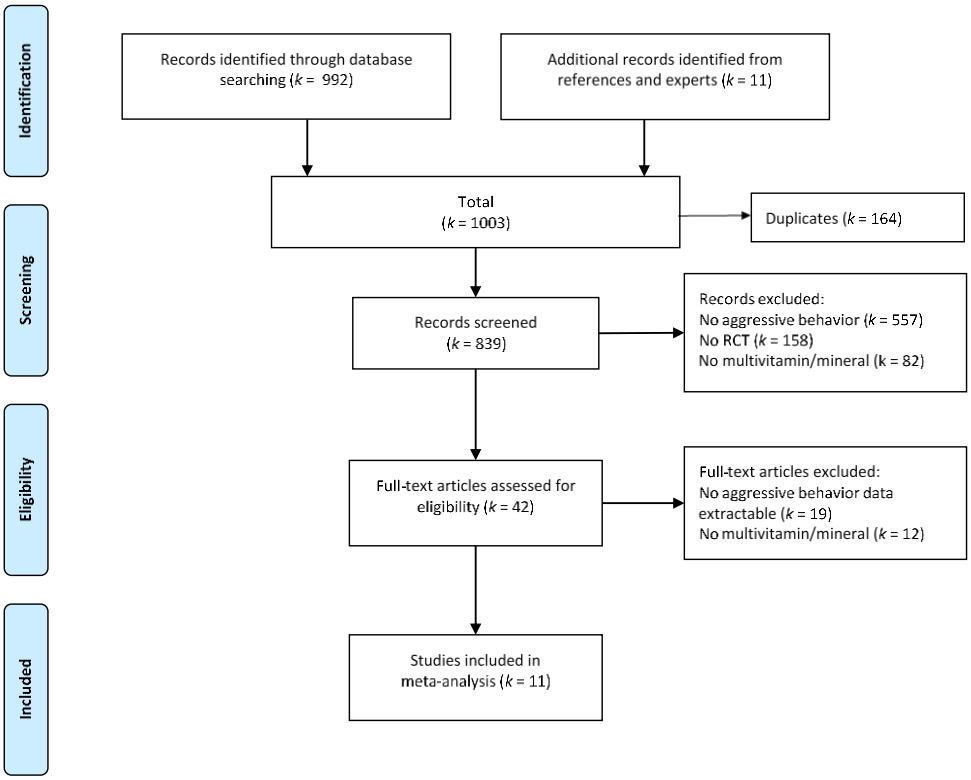

Figure 6.1 Flow chart

Measurements

Various methods have been used to measure aggressive behaviors, which we categorized into two groups: (a) the count of observed aggression-related incidents and (b) the use of data from continuous scales. Three trials used incident counts as a single outcome (Schoenthaler et al., 1997; Schoenthaler & Bier, 2000; Schoenthaler et al., 2021). Three trials used continuous scales as a single outcome (Adams et al., 2011; Long & Benton, 2013; Rucklidge et al., 2018), and five trials used both (De Bles et al., 2022; Gast et al., 2022; Gesch et al., 2002; Tammam et al., 2016; Zaalberg et al., 2010). In the prison and school trials, we used the institutional reported rule violations (Gesch, 2011; Schoenthaler et al., 1997; Schoenthaler et al., 2021; Zaalberg et al., 2010) to count the incidents. De Bles et al. (2022) used the Staff Observation

Aggression Scale-Revised (Nijman et al., 1999), and Gast et al. (2022) used the Modified Overt Aggression Scale (Oliver, Crawford, Rao, Reece, & Tyrer, 2007).

Table 6.1 provides an overview of the measuring instruments used in the various studies. For the continuous data, 8 questionnaires or scales were used to measure aggressive behaviors. Of these, four were self-report scales; namely, three different versions of the Aggression Questionnaire (Bryant & Smith, 2001; Buss & Perry, 1992) were used (De Bles et al., 2022; Long & Benton, 2013; Zaalberg et al., 2010) and Gesch et al. (2002) used the Survey Anger Scales (O'Rourke, 1994). Furthermore, five proxy reported scales were used. The Social Dysfunction and Aggression Scale (SDAS; (Wistedt et al., 1990) was used in three trials (De Bles et al., 2022; Gast et al., 2022; Zaalberg et al., 2010). Different versions of the Conners Behaviors Scales (Conners, Sitarenios, Parker, & Epstein, 1998) were used in two trials (Rucklidge et al., 2018; Tammam et al., 2016). Furthermore, Rucklidge et al. (2018) used the Parent/Teacher Strengths and Difficulties Questionnaires (SDQ; (Goodman, 2001), and Adams et al. (2011) used the Parent Global Impressions-Revised (PGI-r; Adams & Holloway, 2004).

Main effect

From eleven trials, we extracted 18 effect sizes that were included in our meta-analysis—eight trials and eight effect sizes came from count data, and seven trials and 10 effect sizes from continuous data. This yielded two pooled random effect sizes. We found an IRR of 0.72, 95% confidence interval (CI) [0.56, 0.93], p = .011, for the count data and a Hedges' g of -0.23, 95% CI [-0.38, -0.07], p = .001, for the continuous data (Figure 6.2 and 6.3).

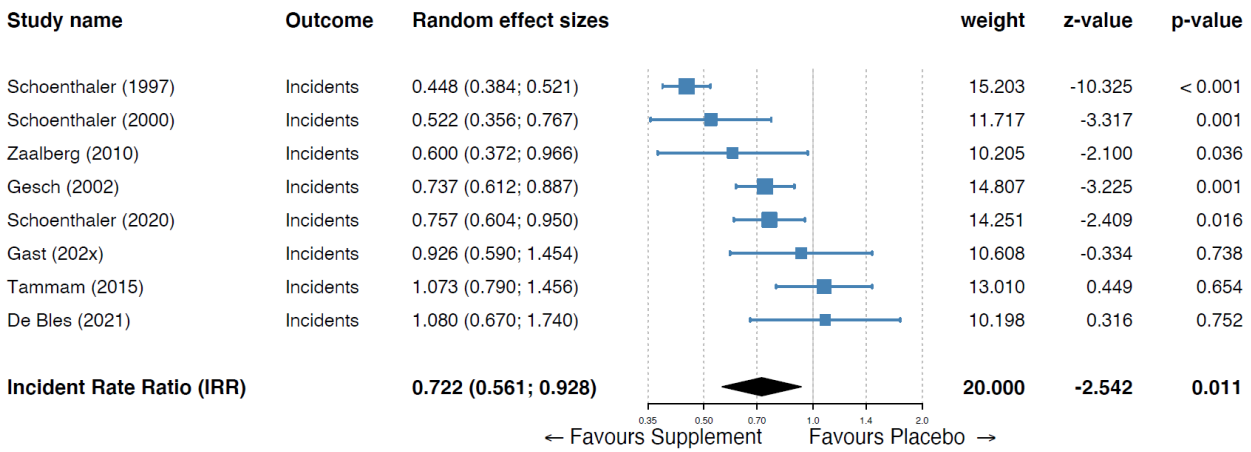

Figure 6.2. Effect sizes (rate ratio) of the externalizing behavior incidents counts.

Table 6.1. Characteristics of included studies (*k* = 11)

Study	*N* (analyzed)	Fem. %	Age (years)	population	Intervention (*n*)	Duration	Outcome measures aggressive behavior	Results
Adams et al. (2011)	141 (104)	11.3%	3–60, *M* = 10.8	Children and adults with ASD	(13)Vi & (13)Mi (*n*=**53**) vs. Pla (*n*=**5**1)	3 m	CS: Parental Global Impressions Revised, subscale tantrumming	Decrease of tantrumming score in active vs. placebo group; *d* = .51, *p* = .009. More withdrawals due to adverse effects in placebo group
De Bles et al. (2022)	176 (176)	35.8%	*M* = 49.3 (14.5)	Psychiatric patients	(12)Vi & (8)Mi & (2)EFA (*n*=87) vs. Pla (*n*=89)	6 m	CD: Incidents reported with the staff observation aggression scale–revised (SOAS-r) CS: Social Dysfunction and Aggression Scale (SDAS-11) and AVL-AV	No significant difference on any outcome measure. More burping in active group (adverse event)
Gast et al. (2022)	113 (113)	34.5%	*M* = 22.8 (7.2)	People with intellectual disabilities	(12)Vi & (9)Mi & (2)EFA (*n*=57) vs. Pla (*n*=56)	16 w	CD: Incidents reported with Modified Overt Aggression Scale (MOAS) CS: SDAS-11	No significant difference on any outcome measure, nor on reported adverse events
Gesch et al. (2002)	231 (231)	0%	18–21	Young adult prisoners	(12)Vi & (12)Mi & (4)EFA (*n*=116) vs. Pla (*n*=115)	2 w–9 m	CD: Number of reported prison rule offences	Decrease of offences in active vs. placebo group 26.3% (95% CI [8.3, 44.3%]); *p* = .03. No adverse effects have been reported.
Long et al. (2013)	202 (85)	0%	*M* = 20.9	Young adult men	(13)Vi & (13)Mi & (2)EFA (*n*=43) vs. Placebo (*n*=42)	3 m	CS: Aggression Questionnaire (AQ)	No significant difference in score on AQ active vs. placebo; *d* = −.24, *p* > .05, nor on the reported side effects
Rucklidge et al. (2018)	93 (93)	23.7%	7–12	Children with ADHD	(13)Vi & (17)Mi (*n*=47) vs. Placebo (*n*=46)	10 w	CS: Parental strengths and difficulties questionnaire (SDQ): conduct problems score; Teacher SDQ: conduct problems score	Decrease of parent SDQ score in active group: *d* = 0.52, *p* = .015. No significant difference on teacher SDQ score in active group *d* = 0.47, *p* = .055, nor on reported adverse events
Schoenthaler et al. (1997)	71 (62)	33.9%	13–17	Adolescent prisoners	(12)Vi & (11)Mi (*n*=32) vs. Pla (*n*=30)	3 m	CD: Number of reported prison rule offences	Decrease of offences in active vs. placebo group; RR = .45, (95% CI [.38, .52]). No adverse events have been reported
Schoenthaler et al. (2000)	468 (80)	31.3%	6–12	Children	(13)Vi & (10)Mi (*n*=40) vs. Placebo (*n*=40)	4 m	CD: Number of reported school offences	Decrease of offences in active vs. placebo group; RR = .52, (95% CI [.36, .77]). No adverse events have been reported.
Schoenthaler et al. (2021)	449 (398)	0%	18–24	Young adult prisoners	(13)Vi & (6–10)Mi (*n*=260) vs. Pla (*n*=138)	15 w	CD: Number of reported prison rule offences	Decrease of offences in active group; RR = .76 (95% CI [.61, .95]). No adverse events have been reported.
Tammam et al. (2016)	196 (196)	50%	13–16	Adolescents	(12)Vi & (8)Mi & (2)EFA (*n*=98) vs. Pla (*n*=98)	12 w	CD: number of school rule offences CS: Conners teacher rating assessment Subscale: Disruptive behavior	No significant difference number of offences in active vs. placebo group; *d* = .039, *SE* =.154. Decrease of disruptive behavior in active group vs. placebo group; *d* = 0.35, *p* = .02. No reported adverse events
Zaalberg et al. (2010)	326 (221)	(0%)	18–25	Young adult prisoners	(12)Vi & (12)Mi & (3)EFA (*n*=115) vs. Pla (*n*=106)	1–3 m	CD: Number of reported prison rule offences. CS: SDAS; Aggression Questionnaire (AQ)	SDAS: no significant difference, *p* = .23 (one-tailed); AQ: no significant difference, *p* = .091; Incident rate 40% decrease (95% CI [4, 63]) (one-tailed) intervention vs. placebo. No reported adverse events

ADHD = attention deficit/hyperactivity disorder; **ASD** = autism spectrum disorder; **AVL-AV** = a Dutch aggression questionnaire; **CBT** = cognitive behavioral therapy; **CD** = count data; **CS** = continuous scale; ***d*** = Cohen's *d*; (X)**EFA** = (number of) essential fatty acids; ***k*** = number of studies; **m** = months; *M* = mean; (X)**Mi** = (number of) minerals; **NS** = No supplements; **Pla** = Placebo; (X)**Vi**= (number of) vitamins; **w** = weeks

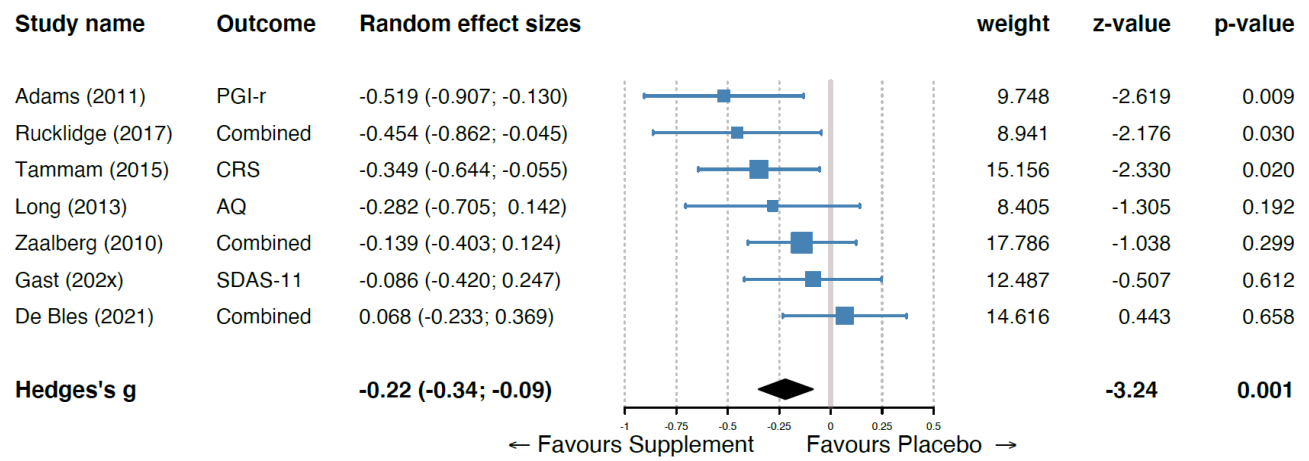

Figure 6.3. Effect sizes (Hedges' *g*) of studies with continuous outcome measures.

Heterogeneity

To explore sources of heterogeneity, we performed a sensitivity analysis by calculating both the random and the fixed effect. For the count data, the degree of statistical heterogeneity was substantial: fixed IRR, 0.64, 95% CI [0.59, 0.70]; and random IRR, 0.72, 95% CI [0.56, 0.93]. The high risk of heterogeneity was confirmed by $I^2 = 84.35$, $Q(7) = 44.72$, $p < .001$. In the case of the continuous data, there was only a small difference between the fixed Hedges' *g*, -0.22, 95% CI [-0.34, -0.09], and random Hedges' *g*, -0.23, 95% CI [-0.38, -0.07], indicating acceptable statistical heterogeneity. The lower risk of heterogeneity was also confirmed by $I^2 = 32.13$, $Q(6) = 8.84$, $p = .18$.

Risk of bias

	Random sequence generation	Allocation Concealment	Blinding of participants	Blinding of outcome data	Incomplete outcome data	Selective reporting	Other bias	Over all bias
Adams (2011)	2	2	1	1	2	2	2	2
De Bles (2021)	1	1	1	2	1	1	1	1
Gast (2021)	1	1	1	1	1	2	2	2
Gesch (2002)	1	1	1	1	2	2	1	2
Long (2013)	1	1	3	2	2	2	2	3
Rucklidge (2018)	1	1	1	1	1	2	2	2
Schoenth. (1997)	2	2	1	2	2	2	2	2
Schoenth. (2000)	2	2	1	2	3	2	3	3
Schoenth. (2021)	1	1	1	1	2	2	2	2
Tammam (2016)	1	1	3	1	1	2	2	3
Zaalberg (2010)	2	1	3	1	2	2	2	3

Figure 6.4. Risk of bias

Figure 6.4 shows the results of the risk of bias assessment. Overall, the risk of bias was substantial: Four trials showed a high level of bias, seven trials showed inconclusive levels, and one trial had a low risk of bias. The greatest risks of bias were insufficient blinding, incomplete outcome data, and selective reporting. Other risks of bias were the COVID-19 pandemic during the cross-over phase of the research (Gast et al., 2022) and using an experimental statistical analysis (Schoenthaler & Bier, 2000). Selective reporting was present in all but one of the trials (De Bles et al., 2022).

Publication bias

The funnel plot of the SE by IRR in Figure 6.5 was not symmetrical, and three studies fell outside the 95% CI. However, the Egger test did not indicate a substantially increased risk of publication bias, 3.14, 95% CI [-1.78, 8.10], p = .17. Given the distribution of the trials over the funnel plot, the asymmetry does not appear to be caused by small trials with large effect sizes but by the variation in trial outcomes with relatively many participants. The funnel plot of the SE by Hedges' g (Figure 6.5) was fairly symmetrical and did not indicate publication bias. This is supported by the results of the Egger test, which showed no significance, -3.68, 95% CI [-10.16, 2.79], p = .20. The various test results have shown that the risk of publication bias was small.

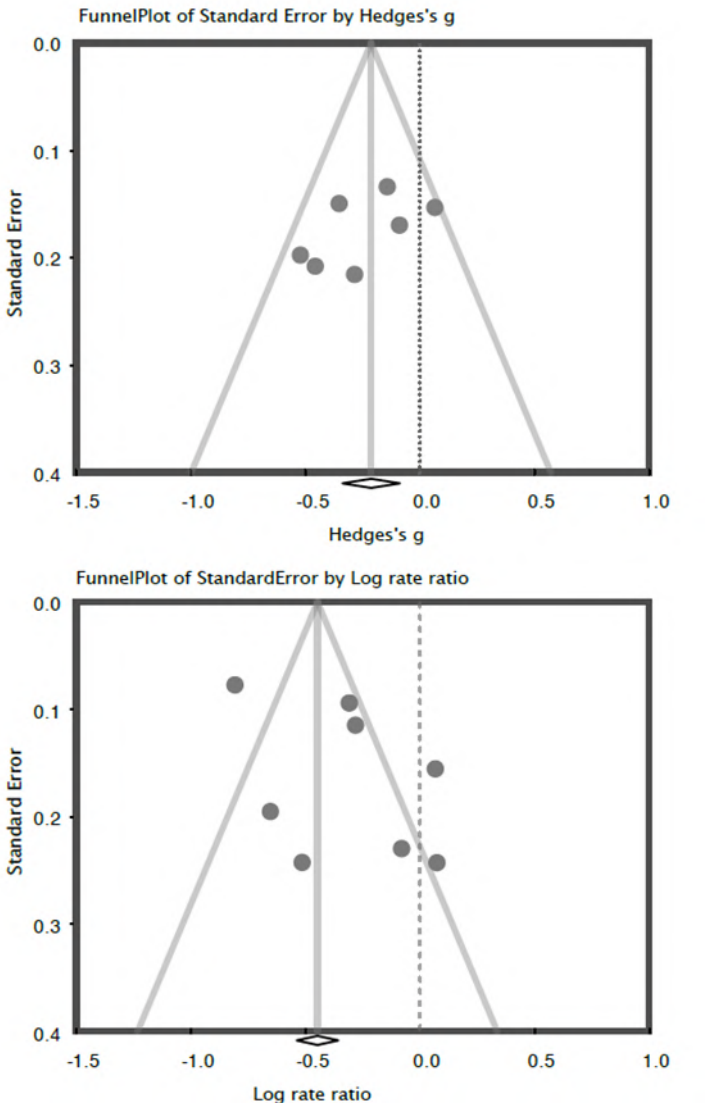

Figure 6.5 Funnel plot of SE by Hedges' g and IRR

Safety

Serious adverse events were not reported in any of the trials. The mild adverse events reported included gastrointestinal symptoms such as nausea, headache, sleeping problems, fatigue, rash, nosebleeds, and psychological symptoms. These adverse events were not significantly more common in the active condition compared to the control group—one exception was the burping of a foul odor in one trial, probably due to omega-3 FA (De Bles et al., 2022).

DISCUSSION

In the present meta-analysis, we included eleven trials and calculated two pooled effect sizes. For the count data outcome, the pooled IRR from eight trials was 0.72, p = .011, which can be interpreted as 28% fewer incidents in the group of active supplements compared to the placebo group. Hedges' g from ten pooled effect sizes of the continuous data was -0.23, p < .004.

The result of this meta-analysis showed a small effect of vitamins and minerals on aggression incidents. Though no meta-analysis has been performed on the effect of multivitamins and minerals on aggression, our conclusions corroborate those of two other meta-analyses on the effect of dietary supplements on problem of behavior. Latter trials used more stringent inclusion criteria. As a result, these trials could examine a more homogeneous study population but were unable to include enough trials to calculate a pooled effect size (Johnstone et al., 2020; Qureshi et al., 2021). Our meta-analysis included more trials by collecting additional information about the outcome data (see Sections 3.1 and 3.2). Another comparable meta-analysis is the study by Gajos and Beaver (2016) on the effect of omega-3 FAs on aggression, which included 30 trials. Their pooled Hedges' g (random effect) was -0.24, which is close to the effect size from our study.

Heterogeneity

In the Results section, we found a difference in heterogeneity between the count data (I^2 = 84.35) and continuous outcome (I^2 = 32.13). Heterogeneity of effect sizes for the count data was relatively high, which could be the result of a smaller number of subjects included in these trials and the different measures and designs. A higher homogeneity of the trial designs, composition and dosages of supplements, and exclusion of behavioral medication would likely have ensured a higher internal validity.

Measuring aggressive behavior

There are many operational definitions of aggression with associated measuring instruments (Parrott & Giancola, 2007; Suris et al., 2004). In addition, aggression has a large overlap with other constructs such as antisocial behavior, challenging behavior, disruptive behavior, externalizing behavior, and violence. By utilizing a broad definition of aggression, we were able to investigate whether there was an effect on aggression in the broadest sense of the word (in terms of aggression topography and characteristics of included samples and settings). Furthermore, we did not select a specific research population, but included all target groups. The individual trials selected their participants using the following inclusion categories, among others: age (Tammam et al., 2016), prison or school setting (Schoenthaler et al., 2021), psychiatric diagnosis (Adams, 2015; De Bles et al., 2022; Rucklidge et al., 2018), people with ID (Gast et al., 2022). Follow-up trials are needed to explore whether differential effects can be found in different target groups, and subtypes of aggression related behavior.

Strength and limitations

The strength of our study is the inclusion of relatively many studies on the effect of supplements on aggressive behavior. However, this meta-analysis also comes with serious limitations. Firstly, uncertainty about the quality of the trials. Only one RCT featured a low risk of bias (De Bles et al., 2022), and it had a null finding. The risks of bias included imperfect blinding and selective reporting. Including trial results with high risk of bias may lead to the quality of evidence being lower than if these trials were excluded. The question therefore remains whether studies with stronger designs would find the same effect than the studies we used in the meta-analysis. Secondly, we used a broad definition of aggressive behavior as inclusion criterium. The outcome measures of the different studies overlapped but were also partly different. For example, rule-offending behavior in prison (e.g., behavior involving substance use or possession of a mobile telephone) may not be related to aggression. Another limitation is that several outcome measures had to be recalculated; for example, we had to combine two intervention arms. These recalculations may have changed the standard error of the effect size estimate, thereby affecting the weight of the trial in the pooled effect size calculation. However, the effect of this recalculation was conservative in nature and may have resulted in a slightly smaller effect size. Finally, the effect has been studied in young and mainly male population, so more research in adults older than 25 years and women is needed.

Future studies

An efficient, safe, affordable, and easy-to-implement intervention is needed in a number of settings and populations. Examples of these subgroups are people with intellectual disabilities, psychiatric patients, male adolescents, and young adult prisoners. For the first two target groups, the evidence of efficacy of supplements is lacking or less clear. Due to the great diversity and the limited number of trials, we could not perform subgroup analyses. The quality of evidence is still largely inconclusive, due to uncertainty about the risk of bias in many trials. Therefore, additional high-quality RCTs are needed. In view of the minor safety risks of this intervention, this meta-analysis would support a high quality Phase 4 trial of the intervention with multivitamins, minerals, and omega-3 FAs supplements. Whether such beneficial effects could also be reached with a healthier and more balanced diet needs to be explored.

Conclusion

Multivitamin/mineral supplements versus placebo showed a small but significant pooled beneficial effect size on aggressive behavior. Due to heterogeneity in the data and a large uncertainty about the risk of bias, these results will have to be replicated in good quality intervention studies.

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APPENDIX

Search strings within the various databases:

Pubmed

("Omega-3"[tw] OR "fatty acids"[tw] OR "fatty acid"[tw] OR "n3"[tw] OR "n-3"[tw] OR "PUFA"[tw] OR "Fish Oils"[tw] OR "Fish Oil"[tw] OR "Dietary Supplements"[tw] OR "Dietary Supplement"[tw] OR "Dietary Supplementation"[tw] OR "Dietary Supplementations"[tw] OR "Food Supplements"[tw] OR "Food Supplement"[tw] OR "food supplementation"[tw] OR "food supplementations"[tw] OR "Nutraceutical"[tw] OR "Nutraceuticals"[tw] OR "Nutriceutical"[tw] OR "Nutriceuticals"[tw] OR "Vitamins"[tw] OR "Vitamin"[tw] OR "Vitamins" OR "Cholecalciferol"[tw] OR "Niacin"[tw] OR "Niacinamine"[tw] OR "Niacinamin"[tw] OR "Niacinamide"[tw] OR "Pyridoxal"[tw] OR "Pyridoxamine"[tw] OR "Pyridoxamin"[tw] OR "Pyridoxine"[tw] OR "Folic Acid"[tw] OR "Folic Acids"[tw] OR "multivitamin"[tw] OR "multivitamins"[tw] OR "megavitamin"[tw] OR "megavitamins"[tw] OR "Minerals"[tw] OR "Mineral"[tw] OR "Selenium"[tw] OR "micronutrients"[tw] OR "micronutrition"[tw] OR "micronutritional"[tw] OR "micronutrient"[tw] OR "micro nutrients"[tw] OR "micro nutrition"[tw] OR "micro nutritional"[tw] OR "micro nutrient"[tw]) AND ("Externalizing Behavior"[tw] OR "Externalising Behaviour"[tw] OR "external behaving"[tw] OR "antisocial Behavior"[tw] OR "antisocial Behaviour"[tw] OR "antisocial behaving"[tw] OR "aggression"[tw] OR "aggressive"[tw] OR "Self-Control"[tw] OR "selfcontrol"[tw] OR "self controlling"[tw] OR "selfcontrolling"[tw] OR "behavior problem"[tw] OR "behaviour problem"[tw] OR "behavior problems"[tw] OR "behaviour problems"[tw] OR "Impulsive Behavior"[tw] OR "Impulsive Behaviour"[tw] OR "Impulsive Behaviors"[tw] OR "Impulsive Behaviours"[tw] OR "impulsiveness"[tw] OR "Impulsivity"[tw] OR "Impulsivities"[tw] OR "Mood Disorders"[tw] OR "Mood Disorder"[tw] OR "Affective Disorder"[tw] OR "Affective Disorders"[tw] OR "Irritable Mood"[Mesh] OR "Irritable Mood"[tw] OR "Irritable Moods"[tw] OR "Conduct Disorder"[tw] OR "Conduct Disorders"[tw] OR "Violence"[tw] OR "Violent"[tw] OR "Assaultive Behavior"[tw] OR "Assaultive Behaviour"[tw] OR "Assaultive Behaviors"[tw] OR "Assaultive Behaviours"[tw] OR "Assaultive Behaving"[tw] OR "Assaultive Behaving"[tw] OR "socially non-acceptable"[tw] OR "hostility"[tw] OR "hostilities"[tw] OR "hostile"[tw]) AND (“trial” [tw] OR “rct” [tw])

WoS:

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EMBASE

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PsycInfo

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Chapter 7

LESSONS LEARNED FROM TWO CLINICAL TRIALS ON NUTRITIONAL SUPPLEMENTS TO REDUCE AGGRESSIVE BEHAVIOR

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ABSTRACT

Background: Setting up and conducting a randomized controlled trial (RCT) has many challenges–particularly trials that include vulnerable individuals with behavioral problems or who reside in facilities that focus on care as opposed to research. These populations are underrepresented in RCTs.

Approach: In our paper, we describe the challenges and practical lessons learned from two RCTs in two care settings involving long‐stay psychiatric inpatients and people with intellectual disabilities (IDs). We describe five main difficulties and how these were overcome: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioral outcomes, and (5) collecting bio samples.

Conclusion: By sharing these practical experiences, we hope to inform other researchers how to optimally design their trials, while avoiding and minimizing the difficulties that we encountered, and to facilitate the implementation of a trial. Both trials were registered in the Clinical Trials Register (RCT A: NCT02498106; RCT B: NCT03212092).

INTRODUCTION

Conducting clinical trials presents many challenges. We performed two pragmatic randomized clinical trials (RCTs) to determine the effectiveness of nutritional supplements to reduce aggression among two populations: (1) psychiatric patients who resided at long-stay wards within mental health care organizations (RCT A) and (2) people who received care for their intellectual disabilities (RCT B). We hope that by sharing the difficulties that we encountered and the ways in which we dealt with these challenges, we may help future researchers who want to set up similar trials.

RCTs are considered to provide evidence for the effectiveness of a particular treatment (Hariton & Locascio, 2018). Unfortunately, vulnerable individuals with behavioral problems are underrepresented in RCTs, resulting in a lack of evidence-based care for these groups (Shepherd, 2020). For example, the prescription of antipsychotics as behavioral medication among people with IDs is widespread. However, the evidence for the efficacy of this policy is meager and has been extrapolated from research on other populations (Scheifes, Egberts, Stolker, Nijman, & Heerdink, 2016; Sheehan & Hassiotis, 2017). Another example is the guidelines for treatment of aggression among patients with schizophrenia; these guidelines are based on RCTs whose generalizability is questionable (Steinert & Hamann, 2012). Because treatments for aggressive behavior are used on vulnerable populations within long-term care, the RCTs should also take place within these populations and settings (Daffern & Howells, 2002).

Aggressive behavior frequently occurs among psychiatric patients (Bowers et al., 2011) and people with IDs (Didden et al., 2016). A substantial number of individuals admitted to long-term facilities (e.g., psychiatric patients or people with IDs) may express aggressive behaviors not only as the reason for admission but also as a consequence thereof. Aggressive acts range from mild verbal incidents, such as screaming or swearing, to more severe incidents, such as physical violence and self-harm (Dack, Ross, Papadopoulos, Stewart, & Bowers, 2013; Ose, Lilleeng, Pettersen, Ruud, & van Weeghel, 2017; Robertson et al., 2004). The burden of these incidents lies not only with care professionals, often causing distress and sick leave, but also with other admitted individuals and perpetrators themselves (Edward, Ousey, Warelow, & Lui,

2014; Frueh et al., 2005; Henk Nijman, Bowers, Oud, & Jansen, 2005). There is a need for evidence-based treatment options to reduce aggression among these populations.

To address this need, we designed two RCTs involving long-stay psychiatric inpatients and people with IDs. Facilities where these individuals reside, however, generally focus on care rather than research and often have no existing infrastructure to enable clinical research. While conducting the two studies, we encountered many challenges and arranged these into five main topics: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioral outcomes, and (5) collecting bio samples. In this current study, we describe the challenges we encountered and how these challenges were overcome.

1. MULTISITE SETTING

RCT A and RCT B were set up as multisite randomized double-blind placebo-controlled pragmatic intervention studies, which aimed to include 200 participants each. The multisite setting of both trials was necessary to meet their sample size requirement. In addition, a multisite setting features better external validity, which may result in findings that are more generalizable across different settings and circumstances (Glasgow & Riley, 2013; Smith, Tan, Stephens, Hibler, & Duffy, 2019). Despite the advantages, multisite studies tend to be more complicated to conduct compared to single-site studies. It is necessary to take these complexities into account from the start of the design of a trial.

Challenges and lessons learned

Most sites highly valued both their involvement and our research goals; however, we encountered several barriers, including the recruitment of sites and their internal coordination of the study.

Although it is often hard to recruit participants in regular trials, it can be just as hard (or even harder) to recruit sites (Wüsthoff, Waal, & Gråwe, 2012). First, most sites had no research infrastructure. Thus, some personnel were somewhat reluctant to participate because of the anticipated extra workload. Additionally, the reluctance to participate was sometimes caused by reorganizations within some of the sites. As a consequence, we had to approach far more organizations than we had initially anticipated. In our experience, the time it took from our first

contact with the organization to the time the first participants could be included from that site was one year (or more). This lengthy process was due to the formal paperwork we needed to obtain the approval by management and the research committees.

Once our sites were recruited, an additional challenge was to involve a coordinator from the institution to help us run the study from the inside. To help us reach our goals, it was important that the inside coordinators had a coordinating function but (more important) that they were also helpful, approachable, and motivated to support the execution of the study—a research champion. A previous study (partially) reimbursed the hours local coordinators spent on the trial (Friese et al., 2017). In RCT B, we did this by paying a fixed amount to a few selected sites for every completed data(set), but doing so did not always lead to higher motivation in local personnel. Another way in which we promoted the engagement of local coordinators was by offering co-authorship when a certain number of participants per site were successfully included. Of course, co-authorship was only possible in cases were the co-author also made significant scientific contributions to the final manuscript. Unfortunately, this arrangement did not seem to result in a faster or higher recruitment rate.

During the study, we found that consistent personal contact with the care professionals at the sites was essential to maintain motivation. To this end, the RCT A team travelled to the locations every week, and the RCT B team maintained high-frequency contacts via telephone and e-mail.

There were three main lessons that we learned from our experiences with the multisite settings. First, recruiting multiple sites is time-consuming (Wüsthoff et al., 2012), which should be taken into account in the time-management plan of the trial. Second, it is crucial to invest in local coordinators who are intrinsically motivated—often called “champions” (DeVon, Patmon, Rosenfeld, Fennessy, & Francis, 2013; Empey et al., 2018; Friese et al., 2017; Manojlovich et al., 2020; Ploeg, Davies, Edwards, Gifford, & Miller, 2007). And third, frequent (preferably face-to-face) contact with the champions and with the other care professionals is important to keep the sites engaged.

2. INCLUSION OF VULNERABLE PARTICIPANTS

The inclusion of participants with aggressive behavioral problems poses additional difficulties (Hodgins & Müller-Isberner, 2004). Such individuals tend to be less cooperative and are less

likely to be included in clinical trials (Steinert & Hamann, 2012). Thus, vulnerable individuals with chronic behavioral problems are often neither willing nor able to give informed consent. We aimed to include participants with psychiatric diagnosis, or ID, who had behavioral problems. Moreover, we also included minors in RCT B, which resulted in extra challenges. In general, individuals who lack the capacity to provide autonomous consent to participate in a study have often been excluded from clinical trials (Shepherd, 2020). Yet, the topic deserves our attention because of the effects on the well-being of patients themselves, their potential victims, society at large, and the economic costs (Bowers et al., 2011; de Bles et al., 2021; Lloyd & Kennedy, 2014).

According to the European Guideline for Good Clinical Practice, researchers are required to give the potential participant a declaration of consent (or "informed consent"), which must comply with strict requirements. For instance, the declaration must stipulate the research involved and what the participant is giving permission for (https://english.ccmo.nl/human-subjects/informed-consent). Thus, we had to state the goals of both trials in a manner that suited individuals' level of intellectual ability. For individuals who were (at that moment) incapable of giving consent, a legally authorized representative had to provide consent.

Challenges and lessons learned

During the recruitment, we encountered challenges in recruiting people with aggressive behavior and in gaining their informed consent.

First, we used the words "aggressive behavior" in the title of the study and in the information leaflets; as a direct result, many potential participants refused to participate because they did not associate themselves with aggression. To counteract this negative association, we selected a broader and less stigmatizing term "challenging behavior" instead of "aggression" when communicating with the sites in RCT B.

Second, it is important to realize that recruiting vulnerable participants is time-consuming (Shepherd, 2020). A systematic review of 33 studies on aggressive behavior in schizophrenia reported a recruitment period of 3 years on average, with a mean sample size of 93 (Steinert & Hamann, 2012). A main reason is that individuals with aggressive or challenging behavior generally seem less willing to participate in trials. As a consequence, less aggressive participants were more often included in RCT A than their more aggressive counterparts, leading to a large proportion of participants showing less than three aggression incidents during the trial (46%). Unlike the RCT A trial, participants in the RCT B study were screened

for their aggression levels in the run-in phase of the study and were excluded for randomization if they did not show an aggression frequency above a certain threshold.

A third challenge was the process of informed consent and how to transfer knowledge to the potential participants, whose cognitive abilities were often poor. For RCT B, we designed an animation (https://www.youtube.com/watch?v=49wDsOYIxsY) to explain the aim of the study in a way that was understandable to participants with mild IDs and borderline intellectual functioning (IQ 50-85). Even so, not all participants had the capacity to provide written informed consent. In RCT A, the treating psychiatrist assessed a patient's capacity. In cases where a participant was unable to give informed consent, a relative or legal representative was needed to give consent (https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/wmo-protection-human-subjects-central/consent). In RCT B, a relative or legal representative had to provide written informed consent in most cases. All procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Both trial protocols were approved by the Medical Ethical Committee of the Leiden University Medical Centre (LUMC).

Three main lessons can be learned from our experiences with recruiting vulnerable participants. First, we recommend avoiding the use of potentially stigmatizing terms, such as "aggression" or "violence," in the study's description or communication. Researchers in a study on interpersonal violence recommended framing the research question in a nonstigmatizing way (i.e., using a nonthreatening and positive theme) (Hardesty, Haselschwerdt, & Crossman, 2019). Second, we advise researchers to screen participants for entry level of the outcome variable to avoid recruiting participants who show little to no aggression; be aware that the recruitment of more aggressive participants is time consuming. Third, researchers should compose information materials tailored to participants with IDs and should including patient representatives and local care professionals during the design phase.

3. NUTRITIONAL SUPPLEMENTS AND PLACEBOS

Nutritional supplements are a special type of intervention for RCTs. RCTs require successful blinding, and the choice of the placebo is not as straightforward as it may seem (Fergusson,

Glass, Waring, & Shapiro, 2004). To achieve its purpose, a placebo needs to match the sensory characteristics of the active supplements. This includes visual aspects of the capsules (i.e., shape, size, color, and texture) as well as their weight, taste, and odor. Any sensory differences between the two capsules may impede the blinding (Mocking et al., 2016). To address this issue, we used placebo and verum that were made using the same procedures in the same factory (MCO Health for RCT A; Bonusan for RCT B). This resulted in a placebo that was largely indistinguishable from the verum in terms of appearance.

Another aspect in the selection of a nutritional supplement and its placebo concerns the characteristics of the supplements, such as size and shape (swallowability), which can cause participants to drop out of the study (van der Wurff, Meyer, & de Groot, 2017). Therefore, we used soft gel capsules to deliver the supplements in RCT A; gel capsules are known to be relatively easy to swallow and may help to mask unpleasant tastes and odors (Benza & Munyendo, 2011). In RCT B, the multivitamin and mineral capsules from the factory were large, and during the preparation of the trial, they proved difficult to swallow for some participants. To increase swallowability, we crushed the tablets and filled the content of a single tablet into two opal-colored placebo capsules (Size 0). The 2-week run-in phase before randomization (using placebo capsules) helped us to select participants who were willing and able to swallow the supplements.

Challenges and lessons learned

We encountered several challenges before achieving successful blinding and a low dropout rate. First, both trials aimed to use indistinguishable supplements, but this was only partly possible. We succeeded in designing similar supplements regarding the visual characteristics (texture and weight); however, the odor and taste of some of the active ingredients proved difficult to mask (Delompre, Guichard, Briand, & Salles, 2019). To match the odor of the placebo with the active supplements in RCT B, we added vanilla-scented silica gel sachets to all of the jars.

A second challenge was that the active ingredients could have caused physical changes in participants, which could have hampered the blinding. One of the most common and unpleasant sensations in trials with omega-3 is dysgeusia due to the fishy taste (Chang et al., 2018). This could explain why a relatively high percent of participants were able to guess their randomization group in many previous studies on the effects of fish oil (Tammam, Steinsaltz, Bester, Semb-Andenaes, & Stein, 2016; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak,

2010). Furthermore, vitamin B2 (riboflavin) may give urine a typical dark yellow/orange color (Moriyama, 2011). Odor and urine discoloration can be simulated by adding a small amount of riboflavin to the placebo (Rucklidge, Frampton, Gorman, & Boggis, 2014). Therefore, the RCT B multivitamin placebo contained 10% (0.8 mg) of the riboflavin dose of an active capsule. At the end of RCT B, the participants and care professionals were not able to guess the group assignment above chance level. In RCT A, we did not take these precautions to improve the blinding. As a result, burping was slightly (though significantly) more often reported by participants in the intervention group compared to the placebo group, but the majority of participants and nurses could not guess the condition to which the participants had been assigned.

A third problem concerned swallowability. Problems in swallowing the supplements, combined with characteristics such as odor and taste, could cause participants to drop out from the study (Kaplan et al., 2010). The dropout rate among children in a previous fish-oil study ranged from 0% to 58% (van der Wurff et al., 2017). We used a 2-week run-in phase to lower such initial dropout rates due to swallowing problems. In addition, we reminded participants in the protocol that the supplements should be taken with meals, which reduced the chance of a fishy aftertaste (Lee, O'Keefe, Lavie, Marchioli, & Harris, 2008). We noticed during the trial that some participants had difficulty taking the supplements daily. During the trial, however, we could not change the intervention. We therefore recommend a feasibility study to test how best to administer the supplement for the specific target population. There are several options besides capsules, such as liquids (Adams et al., 2011), chewable tablets with a tasty flavor , or food products containing the active ingredients (e.g., drinks, margarine, eggs), which are also called “functional foods” (Wu, Zhou, Ma, Yuan, & Peng, 2015).

Problems concerning blinding methodology and selective dropout are common in diet-related research (Hebert et al., 2016). Based on our experiences, there were three main methods to tackle these problems. First, adding vanilla-scented silica gel sachets to the jars containing the supplements helped to mask the odor. Second, researchers should select the appropriate supplement form to aid the administration to the target population. Third, researchers should advise participants to take the capsules during their meals. An option that we could have considered was to offer participants a swallowing course (Forough et al., 2018).

4. ASSESSMENT OF BEHAVIORAL OUTCOMES

The main objective of both trials was to assess whether nutritional supplementation could reduce aggression incidents. There are different ways to measure aggression, and it is important that the measurement tools are valid and reliable. Both studies defined aggression as "any verbal, non-verbal, or physical behavior that was threatening (to self, others, or property) or physical behavior that actually did harm (to self, others, or property)" (Morrison, 1990). Aggression can be assessed through self- and observer-rated scales. Most of our participants suffered from limited intellectual and self-reflective capacities and were therefore less capable of completing self-report scales accurately. Thus, as a primary outcome, we chose observer-rated scales, which is the preferred method to investigate state aggression (Suris et al., 2004). In RCT A, we assessed the number of aggression incidents using the Staff Observation Aggression Scale – Revised (SOAS-R) (Henk Nijman et al., 1999). The SOAS-R is a quick and easy-to-use tool and is used in psychiatric settings worldwide (HLI Nijman, Palmstierna, Almvik, & Stolker, 2005). In RCT B, we assessed aggression using the Modified Overt Aggression Scale (MOAS) (Kay, Wolkenfeld, & Murrill, 1988), which is used to monitor different types of aggressive behaviors in studies among adults with IDs (Oliver, Crawford, Rao, Reece, & Tyrer, 2007).

Challenges and lessons learned

There were three main challenges regarding the assessment of behavioral outcomes, including the operational observation of aggression, unreported incidents, and the high turnover of staff. First, although both trials specified the definition of aggression, care professionals are regularly exposed to aggressive behavior and may be desensitized to more subtle aggression. It may not be apparent to a seasoned care professional to consider an incident a form of aggression. A problem with measuring aggression in RCT B was that care professionals looked at the objective behavior as well as the intention of the behavior. They believed that behavior without intention to cause harm should not be considered aggression. However, intentions are not always clear among participants with IDs, and some behavior could be a way of seeking attention instead of harming someone (e.g., throwing crockery). During the pretraining, we emphasized that care professionals had to report the objective behavior, not their interpretation of the behavior.

Second, we noticed that a worrisome amount of aggression incidents were not documented. We posit two main reasons why these incidents were underreported. First, care professionals may have become hardened by the frequent occurrence of mild to moderate incidents and thus were less likely to report them. Second, care professionals indicated that when their workload increased, sometimes as a consequence of aggression, reporting incidents could be given a lower priority (Ferns, 2006). These unreported incidents were difficult to monitor in RCT A due to the use of the incident-based SOAS-R. When no incidents were recorded during a certain time interval, we could not assess whether this was because no incidents had taken place or because nothing had been reported. In RCT B, we used the time-based MOAS scale, which allowed us to monitor whether all time intervals were reported (Drieschner, Marrozos, & Regenboog, 2013). To reduce underreporting in each trial, research assistants performed weekly monitoring by visiting the local site (RCT A) or by contacting the site via phone or email (RCT B). Because the risk of underreporting is highest for mild-to-moderate verbal aggression (Volavka, 1999), we asked care professionals specifically whether these incidents had occurred since our last contact. If the answer was yes, care professionals were asked to fill in the SOAS-R or MOAS for that incident.

Last, the high turnover of care professionals was a problem (Sahs, Nicasio, Storey, Guarnaccia, & Lewis-Fernández, 2017) because information acquired through an observational scale is based on the capacities, experiences, and opinions of care professionals and thus vulnerable to subjectivity and measurement error. To ensure validity and accuracy, we provided (new) care professionals in each study with an interactive SOAS-R or MOAS training module before the start of the trial to improve accuracy and precision. In RCT B, we even created an e-learning platform to provide new personnel with a standard form of training.

There are three main lessons to be learned from our experiences regarding the assessment of behavioral outcomes. First, researchers should use a scale that can easily monitor aggressive behavior and that is validated to assess the outcome in the specific study population. Second, setting up a monitoring plan at regular intervals can help researchers to detect and to reduce underreporting of incidents. Third, we encourage researchers to train (new) care professionals continuously throughout the trial phase to calibrate the assessments of the care professionals (Willard-Grace et al., 2019).

5. COLLECTING BIO SAMPLES

In both studies, we collected a series of bio samples. In RCT A, we collected blood samples to determine compliance. In RCT B, we collected fecal samples to assess the effects on participants' microbiomes.

Biomarkers are more reliable than self-reports in measuring compliance (Leyse-Wallace, 2013). In RCT A, we collected blood samples to measure the concentration of vitamins, minerals, and a fatty acid spectrum, which yielded participants' n-3 FA levels. We collected two tubes (1 serum separator [SST]and 1 EDTA tube) before and after the trial. The blood samples were taken by trained care professionals from the local laboratory appointed to each institution. Most sites had a fixed morning once a week during which blood was collected. In RCT A, the blood samples were sent to the laboratory via regular mail within 24 hours. Mailing blood samples offered a cost-effective approach, which we found to be true in a previous study from our group (Giltay, Geleijnse, Schouten, Katan, & Kromhout, 2003). During the two studies in question, we reliably found the essential n-3 PUFAs in EDTA plasma after next-working-day mail delivery. Indeed, vitamins have been shown to be stable after delayed whole-blood processing among various temperatures and storage time (Albahrani, Rotarou, Roche, & Greaves, 2016; Drammeh et al., 2008).

In RCT B, we took fecal samples before and after the trial to measure the effect of nutritional supplements on the microbiome and to assess whether the changes of the microbiome mediated the effect of nutritional supplements on aggressive behavior. For the collection of the fecal samples, we developed a sample manual with simple text and images. The samples were frozen on site (–20 °C), after which the researcher used a small portable freezer to transfer the samples to a –80 °C freezer at the LUMC, where they were stored until analysis. Sequencing the 16s rRNA gene is still the most widely used method for gut microbiome analysis because the financial costs are lower than that of whole-genome metagenomic analysis (Panek et al., 2018). The disadvantage is that the cheaper method provides less information regarding the level of genus, species, and strains, but only of the higher taxa such as family, order, class, and phyla.

Table 7.1. Practical recommendations for future research

Topic	Recommendation
1. Multisite setting	• Take the recruitment of sites into account in the time-management plan. • Choose a key contact within the organization based not only on that person's function but also someone who is helpful, approachable, and motivated to support the execution of the study. • Invest time at each site (once a week or more), preferably face to face. Develop a remote consent and enrollment process for situations where face-to-face contact is not possible.
1. Recruitment of vulnerable participants	• Use subtle terminology. Instead of "aggression," use "challenging behavior" and other words and phrases with more neutral connotations. • Screen participants for at least some level of aggression to avoid recruiting participants who show little to no aggression • Tailor information materials to participants according to their intellectual abilities and include patient representatives and local care professionals.
2. Nutritional supplements and placebos	• Add vanilla-scented sachets to the jars of supplements. • Choose an appropriate form of the supplements to aid administration to the target population. • Advise participants to take the capsules during the meal.
3. Assessment of behavioral outcomes	• Use a scale that can easily monitor aggressive behavior and that is validated to assess the study population. • Set up a plan to monitor participants at regular intervals in order to reduce underreporting of incidents. • Train (new) care professionals continuously throughout the trial phase.
4. Collecting bio samples	• Invest in strong collaboration with the local laboratory. • Develop a simple and illustrated manual that can be understood by the participants. • If possible, choose a bio-sample that can be transported reliably and easily to a central laboratory.

Challenges and lessons learned

For biomarkers, there were several challenges regarding the sampling procedure and the transport of the samples. Separate consent was required for the collection of bio samples, but participants who did not consent to donating bio-samples were still eligible to participate.

First, the blood samples did not always arrive at our laboratory on time, which was due to several reasons. Because of the high turnover of care professionals, the envelope with blood samples (RCT A) was regularly forgotten by care professionals. To reduce this error, it was important to contact care professionals from the site where the participant resided and to communicate directly with the local laboratory. Furthermore, it was important that blood was collected Monday through Thursday because samples needed to be processed on working days. When the baseline samples did not arrive on time, the participant had to postpone the start of

the trial and wait for the next opportunity. Belgian institutions could not participate in blood collection because the mail delivery from Belgium took more than 24 hours to reach the laboratory.

Second, freezing feces (RCT B) directly at -20 ° Celsius regularly resulted in practical challenges because the participants resided at 69 different locations (far more than we had anticipated), and each participant had to produce two samples. Using portable freezers to reach every location was not feasible, so we had to use freezers that were available on site, which was often difficult to arrange. So, even with proper preparation, the logistics of fecal-sample collection can be complex and time consuming. Therefore, we advise researchers to opt for methods that are straightforward.

Based on our experiences, there were three main lessons in collecting biomarker outcomes. Investing in strong collaboration with the local laboratory and care professionals is important when taking blood samples. When collecting fecal samples, it is essential to distribute a manual that the target group can understand. And when choosing a specific bio sample, it is important to consider the feasibility of the necessary logistics.

Conclusions

Conducting a successful RCT among vulnerable populations presents unique challenges, which we have discussed in detail. These trials were conducted in long-term wards for psychiatric inpatients and people with IDs. Such studies are essential to help develop new evidence-based treatment options. Facilities where these individuals reside, however, generally focus on care rather than research and often have no existing infrastructure to enable clinical research. Yet, both RCT A and RCT B successfully recruited participants to determine the effectiveness of nutritional supplements to reduce aggression among two different populations. We stumbled upon numerous difficulties and found ways to modify our practices successfully regarding the following aspects: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioral outcomes, and (5) collecting bio samples—all of which were essential for the success of both projects (Table 7.1). We hope that by sharing our practical experiences, we may enable future researchers to more effectively conduct clinical trials in these populations who could still gain much from improved clinical care.

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Chapter 8

SUMMARY AND GENERAL DISCUSSION

SUMMARY

The aim of this thesis was to investigate whether an intervention with dietary supplements can be used in clinical practice to reduce aggressive behavior in people with ID. Therefore, we conducted several studies with different designs. We performed an observational study on diet quality in people with ID to test the hypothesis that the diet quality would be lower in people with ID than in controls. The underlying assumption was that a low diet quality increases the likelihood of an intervention with dietary supplements being effective. In order to implement the intervention, we wanted to know what determined the acceptance of the intervention by individuals of the target group. To this purpose, we conducted a focus group study into the adoption of the intervention by clients with ID, their representatives, and their healthcare professionals. The research project on the effect of dietary supplements on aggressive behavior consisted of three studies: 1) the analyzes of the data of a randomized placebo-controlled intervention study among inmates in Californian correctional facilities, 2) a pragmatic triple-blind randomized intervention trial with dietary supplements, investigating their effect on aggressive behavior in people with ID, and 3) a meta-analysis of the effect of supplements on aggressive behavior. Finally, we collected and commented on the challenges associated with conducting an intervention study with dietary supplements in vulnerable populations.

Diet quality

In **chapter 2** we investigated the diet quality in people with ID who lived in a residential facility or worked at a sheltered workspace. To measure diet quality, we used the "Eetscorelijst" and compared the results of participants with ID (n = 151) with participants without ID (n = 169) who participated in the "Eet, Weet en Meet-study" (WUR, 2022). We also examined which individual characteristics were associated with diet quality. Overall, we found that there was a lot of room for improvement of diet quality in people with ID. The main differences between people with ID versus controls were an excessive consumption of sugar, processed meat, and other unhealthy products, and insufficient consumption of omega-3 fatty acids in the first group. These are characteristics of the so-called Western dietary pattern, which is associated with multiple health risks, such as obesity and metabolic syndrome. In addition, we found a

lower mean diet quality in people with ID than in the control group. Participants with a MID/ BIF had a lower diet quality and a higher BMI than people with a severe to profound ID. Given the sub-optimal diet quality, which is also confirmed in other studies, a nutritional intervention appears to be indicated for people with ID.

Adoption of supplements

In **chapter 3** we questioned to what extent people with ID and their caregivers would accept an intervention with dietary supplements. To answer this question, we investigated in a qualitative focus group study which factors influenced the adoption of the intervention with supplements. For three reasons, we decided to investigate the effect of an intervention with dietary supplements as a proxy for a change in eating pattern. First, an intervention with dietary supplements makes it possible to introduce a control group with placebo. Second, it is more feasible for the participants with ID and their caregivers to take daily supplements than to make a dietary change. Third, the results from other studies showed that an intervention with dietary supplements could have an effect on behavior (Benton, 2007; Frensham, Bryan, & Parletta, 2012; Rucklidge & Kaplan, 2013). Of course, the use of dietary supplements as a proxy has strong limitations compared to a healthy diet, for example it does not add dietary fiber, it has far fewer ingredients and it is a completely different story in terms of sensory experience.

In total we conducted seven focus group sessions, three with people with ID and four with healthcare professionals and client representatives. We analyzed the transcribed texts according to the steps of 'constant comparison analysis'. Five themes emerged: (1) the relationship with other interventions, (2) the professional roles, (3) characteristics of the intervention with supplements, (4) information provision about the intervention, and (5) supplements and healthy diet. We also found that acceptance of the intervention by people with ID would be promoted by involving them in the choice of the intervention. Finally, evidence of the effectiveness and safety of the intervention was stated as an important precondition for implementation. Therefore, we investigated the effect and safety of the intervention with dietary supplements (see below). During the implementation of the intervention with dietary supplements in the clinical practice, we should give sufficient attention to the above mentioned themes.

Interventions with dietary supplements on aggressive behavior

To map the effect of dietary supplements on aggressive behavior, we analyzed three studies. First a study among inmates, then we performed an RCT among people with ID and finally a meta-analysis into the effect of dietary supplements on aggressive behaviors.

The effect of dietary supplements in correctional facilities

In **chapter 4,** we investigated the effect of multivitamin-mineral supplements on serious rule violations in young adult male inmates from Californian correctional facilities. We analyzed a hitherto unpublished dataset from a 1990s three-arm RCT. For 15 weeks, participants were offered a daily dose of either lower dose supplements, higher dose supplements, or placebo. The main outcome parameter was the number of serious rule violations. In the group of the lower dosed supplements there were 39% less serious rule violations compared to the placebo. However, in the group with higher-dose supplements there was no statistically significant difference, which was unexpected. The results of this study thus provided some support for the hypothesis that dietary supplements could be effective in reducing aggressive behavior among inmates.

The effect of dietary supplements among people with ID

In **chapter 5,** we investigated whether supplementation with multivitamins, minerals and omega-3 fatty acids had an effect on aggressive behavior in people with ID. Therefore, we conducted a randomized, triple-blind, placebo-controlled, pragmatic intervention trial of 16 weeks, of whom some also participated in a cross-over arm. We included people between the ages of 12 and 40 who were living in a residential facility or visited a day care center and who showed aggressive behavior on a regular basis. The participants received daily dietary supplements or a placebo. Aggressive behavior was measured daily with the Modified Overt Aggression Scale (MOAS). At the end of the study, participants were invited to join the cross-over study without breaking the blind. In total, there were 113 participants, 24 of whom participated in the cross-over part of the study. There was no significant difference in the mean number of aggression incidents between the active and placebo arm. During this study phase, the COVID-19 pandemic took place with its associated restrictions, which had a profound effect on the behavior of people with ID. This may have affected our results, which may have increased the imprecision of our main effect estimate. A replication of this study in a period without a pandemic would therefore be recommended.

Meta-analysis

In **chapter 6**, we conducted a systematic review on the effect of multivitamin and mineral supplements on aggressive behavior, including eleven randomized placebo-controlled trials (RCTs). We performed a meta-analysis in which we calculated two pooled effect sizes: one with the standardized mean differences (Hedges g) of continuous measurements and one with the incident rate ratio (IRR) of incidents counted. The target groups of the studies were young adult inmates, school-age youth, students, psychiatric patients and people with ID. Aggressive behavior decreased in the active groups relative to the placebo groups (Hedges' g -0.23, 95% CI [-0.38, -0.07] and IRR of 0.72, 95% CI [0.56, 0.93]). Multivitamin mineral supplements versus placebo showed a small but significant effect on aggressive behavior. However, there was evidence of heterogeneity with large differences in the treatment effects between studies and the risk of bias was unclear or high for many studies. Therefore, we argue for a large and high-quality RCT to test the hypothesis that dietary supplements may reduce aggressive behavior.
In **chapter 7**, we reflected on the challenges we encountered in designing and conducting RCTs with vulnerable participants with problem behavior. These participants often receive a lot of medication, but are underrepresented in RCTs. From our experience with two RCTs, that is one in psychiatric patients and the other in people with ID, we described some of the pitfalls within five themes: (1) multisite setting, (2) inclusion of vulnerable participants, (3) dietary supplements and placebo, (4) aggressive behavior as an outcome measure, and (5) collecting bio-samples. The purpose of sharing practical experiences with the encountered problems and challenges was to inform and provide tips to other researchers when designing and conducting their own research.

METHODOLOGICAL CONSIDERATIONS

In this thesis, different research methods were applied to answer the main question to what extent dietary supplements can be used in clinical practice as an intervention to reduce aggressive behavior in people with ID. Each methodology we used had its specific strengths and limitations which we have discussed in detail in the discussion sections of chapters two through six. In chapter seven, we further described the methodological challenges encountered when conducting a dietary supplement intervention study for aggressive behavior in people with ID. In this chapter, we provide an overview of the overarching strengths and limitations.

Strengths

To assess if dietary supplements are an effective strategy to reduce aggressive behavior in people with ID, we used a combination of different study designs. Qualitative and quantitative studies may complement each other to create a more coherent and comprehensive overview of the research domain (Hadi & Closs, 2015). Quantitative research has the power to demonstrate an effect, but does not assess the problems and opportunities in practice. Qualitative research may investigate the need for an intervention in practice, but lacks the power to demonstrate whether the intervention is effective. In this thesis, our qualitative focus group study (chapter 4) and the quantitative RCT (chapter 5 and 6) complemented each other. For example, our focus group study showed that healthcare professionals consider it important that there is scientific evidence for the effectiveness and safety of an intervention for challenging behavior. While data on the safety and efficacy were provided by the two RCTs in this thesis.

Limitations

The results of these studies should be assessed in the context of a number of overarching limitations. First, the concept of aggressive behavior has not been unambiguously defined across the different studies and has also been operationalized differently, leaving the question of how far we have utilized the same construct in our studies (Suris et al., 2004). This applies to the two RCTs, but also to the focus group study. Second, the interventions used in both RCTs differed in the number of ingredients and their dosages. There are many formulas of multivitamins and omega-3 supplements available on the market. These also change composition over time due to new insights, so that studies in comparable populations have used different ones as their verum intervention (Cortie et al., 2020; Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Hambly et al., 2017; Schoenthaler et al., 1997; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak, 2010). Third, durations of the intervention in our RCT were 15 (chapter 4) and 16 weeks (chapter 5), respectively, while the effects on aggressive behavior through a dietary intervention may require a longer treatment period. However, an RCT with a longer intervention duration is difficult to organize because of drop out, the higher costs, and the burden on the client and healthcare professionals. Fourth, we have been unable to find an unambiguous relationship between the change in vitamin and mineral blood values and aggressive behavior. A relationship between those physiological markers and behavioral outcomes would have supported the evidence of the efficacy of the micronutrients.

PRACTICAL IMPLICATIONS

We found no significant effect of dietary supplements on aggressive behavior among people with ID and we found no significant difference in adverse effects between the active- and placebo group (Chapter 5). It should be noted, however, that there is some evidence of efficacy of the intervention in other study populations and settings (Chapter 6). Our findings do not warrant a large-scale implementation of dietary supplements as an intervention for aggressive behavior among people with ID. However, a limited application may remain as aggressive behavior may persist despite the use of available evidence-based therapies. Evidence-based psychological (e.g., behavioral therapy and CBT/AMT) and contextual interventions are the treatments of choice (Didden et al., 2016; Didden, Nijman, Delforterie, & Keulen-De Vos, 2019). In clinical practice, these interventions are not always sufficiently effective. In the absence of evidence-based therapies, different types of psychotropic drugs are often prescribed off-label for the treatment of aggression, especially antipsychotics (Deutsch & Burket, 2021; Embregts et al., 2019; Henderson et al., 2020; Deb, 2016; Ramerman, De Kuijper, et al., 2019). To date, there is no evidence of the efficacy of long-term use of neither dietary supplements nor off-label use of antipsychotics on aggressive behavior in adults with intellectual disabilities. However, at doses of approximately 100% RDA, the health risks of multivitamins/minerals and omega-3 FA supplementation are very small (EFSA, 2012; EFSA, 2006), while long-term use of antipsychotics is associated with lower quality of life and serious health risks (Espadas et al., 2020; Ramerman, Hoekstra, & De Kuijper, 2019; Sheehan et al., 2017). In addition to evidence of efficacy, care professionals consider evidence of safety important for the use of an intervention in people with intellectual disabilities (Chapter 3). For this reason, in some cases, it might be rational for clinicians to prescribe dietary supplements rather than prescribing off-label psychotropic drugs. The same restraint in prescribing dietary supplements as intervention for aggressive behavior can be maintained as recommended for the off-label use of psychotropic drugs (Embregts et al., 2019).

Healthy diet

Furthermore, we found that diet quality of people with MID/BIF is low and in particular a low intake of omega-3 stands out. Unhealthy diet is associated with multiple health outcomes, such as metabolic syndrome, diabetes mellitus, cardiovascular disease (Christ, Lauterbach, & Latz,

2019; Hosseini, Whiting, & Vatanparast, 2016). These are medical conditions with a relative high prevalence among people with ID (Haveman et al., 2010). For that reason, a focus on improving diet quality among people with MID/BIF is needed. It is not yet known if and to what extent improving diet quality has an effect on aggressive behavior.

Recommendations for future studies

In Chapter 5, we stated that the results of our RCT may have been adversely influenced by the COVID-19 pandemic. Although the overall null finding persisted after adjustment for COVID-19 as a confounder, there was a (non-significant) change in the direction of the effect before and during the COVID-19 pandemic. We therefore recommend that our research is replicated in a time period without such disruptive events. In designing the study, the recommendations we made in Chapter 7 are hopefully helpful, such as: a more positive connotation (with respect to "aggression") in the title and aims description of the study and the use of local "champions" in the recruitment, use of acceptable supplements by the target population, and the choice of a monitorable instrument for measuring aggression. In addition, measuring the participants' blood levels of micronutrient would be valuable to monitor (latent) deficiencies. The outcome of an intervention is partly determined by the placebo effect, also in people with ID (Jensen et al., 2017). Placebo effect may be as strong as the effect of haloperidol and risperidone, as is shown by an RCT on the effect of an antipsychotics on aggressive behavior among people with ID (Tyrer et al., 2008). How the placebo effect can be maximized and the nocebo effect minimized in the treatment of problem behavior is an interesting and clinically relevant question (Evers et al., 2018). Insight in such potential effects can be gained from including a second control group without (placebo) intervention in the design of an RCT. The final recommendation for future research is in line with the findings from our focus group study. A substantial proportion of healthcare professionals argue in favor of investing more energy in increasing diet quality. Therefore, we recommend a study into the effect of a healthy diet on challenging behavior as well as on somatic and mental well-being. This study could be part of a larger study into healthy lifestyle on well-being and behavior.

CONCLUSION

From the results of the above studies, we can conclude that there is too little evidence for the efficacy of an intervention with dietary supplementation for aggressive behavior in people with intellectual disabilities to justify a large-scale implementation. However, if evidence-based psychological and contextual interventions do not work sufficiently, the practitioner may consider prescribing safe doses of multivitamins and minerals and/ or omega-3 supplements, to improve nutritional status and with an added potential of (placebo) behavioral effects.

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ADDENDUM

Nederlandse samenvatting

List of Publications

Curriculum vitae

Dankwoord

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift is om te onderzoeken of een interventie met voedingssupplementen in de praktijk gebruikt kan worden om agressie bij mensen met een verstandelijke beperking te verminderen. Om dat doel te bereiken hebben we een reeks van elkaar aanvullende onderzoeken uitgevoerd. We deden een kwaliteit van eetpatronen onderzoek bij mensen met een verstandelijke beperking, zodat we konden controleren of het eetpatroon van invloed was op het effect van de behandeling met voedingssupplementen. Voor het implementeren van de interventie in de gehandicaptenzorg was het belangrijk om te weten welke factoren bepalend waren voor de acceptatie van de interventie door die doelgroep. Daarom deden we een focusgroep onderzoek onder cliënten, clientvertegenwoordigers en zorgprofessionals. Het onderzoek naar de vraag of voedingssupplementen effectief waren tegen agressief gedrag bestond uit drie delen: 1) de analyse van een interventiestudie met voedingssupplementen bij gedetineerden in California 2) een studie naar het effect van een interventie met supplementen op agressief gedrag bij mensen met een verstandelijke beperking 3) een meta-analyse naar het overal effect van voedingssupplementen op agressief gedrag. Tot slot hebben we de uitdagingen die we tegenkwamen bij ons onderzoek met voedingssupplementen verzameld en van kanttekeningen voorzien, zodat onze leermomenten gebruikt kunnen worden voor toekomstig onderzoek.

Kwaliteit van eetpatronen

We onderzochten in **hoofdstuk 2** de kwaliteit van eetpatronen bij mensen met een verstandelijke beperking, die in een woonvoorziening woonden of op een activiteitencentrum werkten. Voor het meten van de kwaliteit van voeding gebruikten we de “Eetscorelijst” en vergeleken we de resultaten van de deelnemers met verstandelijke beperking, met deelnemers zonder verstandelijke beperking uit de “Eet, weet en meet studie”. We onderzochten ook of een aantal variabelen de kwaliteit van eetpatronen konden voorspelen, zoals geslacht, leeftijd en ernst van verstandelijke beperking. We vonden dat bij mensen met een verstandelijke beperking de kwaliteit van eetpatronen laag was. Aandachtspunten daarbij waren een te hoge consumptie van suiker, bewerkt vlees en andere ongezonde producten en een te lage consumptie van omega-3 vetzuren. Dit zijn kenmerken van een zogeheten Westerse eetpatroon

die met gezondheidsrisico's wordt geassocieerd, zoals obesitas en metabool syndroom. Daarnaast vonden we bij mensen met een verstandelijke beperking een gemiddeld lagere kwaliteit van voeding (M = 80,9), dan bij de controlegroep (M = 111,2). Deelnemers met lichte verstandelijke beperking/ zwakbegaafdheid hadden een lagere kwaliteit van eetpatroon en een hogere BMI dan mensen met een ernstige tot zeer ernstige verstandelijke beperking. Gezien het suboptimale eetpatroon bij de doelgroep en de overal lage inname van omega-3 vetzuren was een voedingsinterventie een rationele keuze.

Acceptatie van een interventie met voedingssupplementen.

Met een focusgroep onderzoek onderzochten we in **hoofdstuk 3** welke factoren van invloed waren op de acceptatie van een interventie met voedingssupplementen. We hielden in totaal zeven focusgroepsessies, drie met mensen met een verstandelijke beperking en vier met zorgprofessionals en cliëntvertegenwoordigers. De teksten werden opgenomen en uitgeschreven en geanalyseerd volgens de methode van de "grounded theory". Daaruit kwamen vijf onderwerpen naar voren: (1) de verhouding met andere interventies, (2) de rollen van de zorgprofessionals, (3) kenmerken van de interventie, (4) informatievoorziening rondom de interventie (5) de verhouding supplementen en gezonde voeding. Het bleek dat de acceptatie van de interventie met voedingssupplementen door zorgprofessionals kon worden gefaciliteerd door duidelijk te benoemen welke professionele rollen aan de interventie zijn gekoppeld en wie die rollen vervullen. Een voorwaarde voor de implementatie was dat er voldoende wetenschappelijke onderbouwing zou zijn voor de effectiviteit en veiligheid van de interventie. Acceptatie van de interventie door mensen met een verstandelijke beperking kon worden bevorderd door hen te betrekken in de keuze van de interventie. Tot slot waren er zorgen bij zorgprofessionals dat een interventie met voedingssupplementen ten koste zou gaan van aandacht voor gezonde voeding.

Het effect van supplementen op agressief gedrag

Om het effect van voedingssupplementen op agressief gedrag in kaart te brengen hebben we drie elkaar aanvullende onderzoeken uitgevoerd:

In **hoofdstuk 4** onderzochten we het effect van multivitaminen-mineralen supplementen op ernstige regelovertredingen bij jongvolwassen mannelijke gedetineerden. Daarvoor gebruikten we een ongepubliceerde dataset van een driearmige, gerandomiseerde, placebogecontroleerde, dubbelblinde studie uit de jaren negentig. Gedurende 15 weken kregen de deelnemers dagelijkse een supplement aangeboden van: of ongeveer 100% van de

aanbevolen dagelijkse hoeveelheid (adh) van een groot aantal vitaminen en mineralen (n=149), of een hogere dosering (n=150), of placebo (n=150). De hoofduitkomst was het aantal ernstige regelovertredingen zoals door het gevangenispersoneel werd geregistreerd. In de groep met de lager gedoseerde supplementen was er een daling van 39% regelovertredingen ten opzichte van de placebo groep (p=.01). In de groep met hoger gedoseerde supplementen was er geen statistisch significant verschil met de placebogroep gevonden.

In **hoofdstuk 5** onderzochten we of suppletie van multivitaminen-mineralen en omega-3-vetzuren een effect had op agressief gedrag bij mensen met een verstandelijke beperking. We deden dit door middel van een gerandomiseerde interventiestudie van 16 weken. Aan het einde van het onderzoek konden de deelnemers voor een tweede keer aan het onderzoek deelnemen, maar dan kregen de deelnemers die in placebogroep zaten de actieve supplementen en vice versa, dit zonder de blindering te verbreken (cross-over). We wierven mensen van tussen de 12 en 40 jaar die in een woonvoorziening voor verstandelijke beperking woonden of dagbesteding ontvingen, en agressief gedrag vertoonden. De deelnemers kregen dagelijks een voedingssupplement, of een placebo, en agressie incidenten werden dagelijks gemeten met de Modified Overt Agression Scale (MOAS). In totaal waren er 113 deelnemers, waarvan er 24 deelnamen aan het cross-over deel van de studie. We vonden geen significant verschil tussen het gemiddelde aantal agressie-incidenten in de actieve- en placebogroep. De COVID-19-pandemie en bijbehorende maatregelen interfereerden met dit onderzoek. Een replicatie van dit onderzoek zonder grote verstorende factoren zou daarom wenselijk zijn.

In **hoofdstuk 6** onderzochten we met behulp van een systematische review naar het effect van multivitamine- en mineralensupplementen op agressief gedrag, daarbij konden we 11 gerandomiseerde placebo gecontroleerde onderzoeken (RCT's) includeren. We deden een meta-analyses waarin we twee effect sizes berekenden: één met de standarized mean differences (Hedges g) uit continue maten en één met de incident rate ratio (IRR) uit data die bestond uit het tellen van incidenten. De deelnemers in die onderzoeken waren jongvolwassen gedetineerden, schoolgaande jongeren, studenten, psychiatrische patiënten en mensen met een verstandelijke beperking. Agressief gedrag verminderde in de actieve groepen ten opzichte van de placebo groepen (Hedges' g -.23, 95% CI [-.38; -.07], en IRR van .72, 95% BI [.56; .93]). Multivitamine-mineralensupplementen versus placebo liet een klein maar significant effect op agressief gedrag zien. De diversiteit tussen de studies was echter hoog en het risico op bias was voor veel studies onduidelijk of hoog.

In **hoofdstuk 7** reflecteerden we op de problemen die we tegenkwamen bij het opzetten en uitvoeren van interventiestudies met voedingssupplementen bij kwetsbare deelnemers met probleemgedrag. Deze deelnemers kregen vaak veel medicatie, maar zijn ondervertegenwoordigd in medisch onderzoek. Uit onze ervaringen met twee interventiestudies, de een bij psychiatrische patiënten, en de ander bij mensen met verstandelijke beperking, beschreven we de volgende vijf thema's : (1) onderzoek op meerdere locaties, (2) inclusie van kwetsbare deelnemers, (3) voedingssupplementen en placebo's, (4) agressie als uitkomstmaat en (5) verzamelen van bio-monsters. Het doel van het delen van deze praktijkervaring was om andere onderzoekers te informeren hoe ze bij het ontwerpen en uitvoeren van hun studie rekening kunnen houden met de moeilijkheden die we tegenkwamen.

Conclusie

Uit de resultaten van bovenstaande onderzoeken kunnen we concluderen dat er te weinig bewijs is voor de werkzaamheid van voedingssuppletie bij agressief gedrag bij mensen met een verstandelijke beperking om grootschalige implementatie te rechtvaardigen.

LIST OF PUBLICATIONS

D.A.A. Gast, G.L. de Wit, A. van Hoof, J.H. de Vries, A.M. van Hemert, R. Didden & E.J. Giltay (2021). Diet quality among people with intellectual disabilities and borderline intellectual functioning. *Journal of Applied Research in Intellectual Disabilities*, 35(2), 488-494.

D.A.A. Gast, E.J. Giltay, A.J.C. van der Slot, J.K. de Wit, J. Heijstek-van Grootheest, A.M. van Hemert & R. Didden. Adoption of dietary supplements to reduce challenging behaviour in people with intellectual disability: A qualitative study (submitted for publication)

S. Schoenthaler*, D.A.A. Gast*, E.J. Giltay, & S. Amos (2021). The effects of vitamin-mineral supplements on serious rule violations in correctional facilities for young adult male inmates: A randomized controlled trial. *Crime & Delinquency*

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D.A.A. Gast, R. Didden, J. J. Westera, O. van de Rest, A.M. van Hemert & E.J. Giltay (2022). Dietary Supplements for Aggressive Behavior in People With Intellectual Disabilities: A Randomized Controlled Crossover Trial. *Journal of Applied Research in Intellectual Disabilities,* 1-10.

D.A.A. Gast, T.A. Wissink, A.M. van Hemert, R. Didden & E.J. Giltay. Effectiveness of multivitamin and mineral supplementation on aggressive behavior: a systematic review and meta-analysis (submitted for publication)

N.J. de Bles*, D.A.A. Gast*, A.J.C. van der Slot, R. Didden, A.M. van Hemert, N. Rius‐Ottenheim & E.J. Giltay (2022). Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behavior. *Journal of Evaluation in Clinical Practice*, 28, 607-614.

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CURRICULUM VITAE

David Gast was born on July 7th 1968 in Amsterdam. After high school, he studied three years history and philosophy at the Vrije Universiteit Amsterdam. From 1995-2021 he worked for various (youth) care organizations in the Netherlands and Romania. He was a daily staff worker at Zorgboerderij Gouda (Gemiva-SVG) from 2000 to 2017. In addition, he graduated as a naturopathic practitioner at the hogere school voor natuurgeneeskunde Arnhem (HvNA) in 2004 and had a practice as naturopath from 2005 to 2013. Subsequently, he lectured phytotherapy at the complementary and alternative medicine department of Saxion Next, University of Applied Sciences, from 2009 to 2013. He obtained his bachelor's degree in Psychology at the Open University of the Netherlands in 2013, followed by a master's degree in 2014. In 2016, he explored whether a study into the effect of dietary supplements on aggressive behavior of people with ID would be feasible. In the same year he sought affiliation with the LUMC to start the multisite project. He coordinated the project and supervised working students and interns from various universities and disciplines. In 2022 he started his job as a researcher/ lecturer at the social work and applied psychology department of the University of Applied Sciences in Leiden.

DANKWOORD

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