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## **Dietary supplements for aggressive behavior: studies in people with intellectual disability**

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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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