The relationship between Non-Celiac Gluten Sensitivity and Psychological Functioning

A Correlational Study on Children with Down Syndrome

Daniel Bryne and Mikkel Glimsdal

Submitted as thesis at the Institute of Psychology

Fall 2020

Abstract

Authors: Daniel Bryne and Mikkel Glimsdal

Title: The relationship between Non-Celiac Gluten Sensitivity and Psychological Functioning: A Correlational Study on Children with Down Syndrome

Main supervisor: Egil Nygaard; **Contributing supervisor:** Knut Lundin

Author involvement: This thesis is based on the ongoing research project "Gluten sensitivity and development in children with Down syndrome" by Egil Nygaard, where we worked as research assistants. We researched and selected measures, created the assessment procedure, got changes approved ethically by REK, pilot tested the study, recruited participants, collected the data, and selected and performed statistical analysis.

Background: Over the last decade, an increasing body of research has indicated that celiac disease and non-celiac gluten sensitivity (NCGS) is related to various aspects of psychological as well as gastrointestinal functioning. People with Down syndrome struggle with impaired psychological functioning and increased prevalence of gluten-related disorders. Nygaard et al. (2001) found anti-gliadin IgA and IgG, two possible indicators of NCGS, to be related to cognitive/motor functioning in children with Down syndrome. However, more research is needed on how NCGS affects psychological functioning.

Method: We assessed cognitive/motor functioning of 21 children with Down syndrome and their prevalence of anti-gliadin IgA and IgG. Parents assessed parenting stress and their child's gastrointestinal symptoms, behavioral/emotional problems, health-related quality of life, and curiosity through questionnaires. The relationship between NCGS and facets of psychological functioning were investigated using non-parametric and parametric correlational methods, and linear models. Path analysis was used to investigate whether the relationship between NCGS and cognitive/motor functioning was mediated by curiosity.

Results: No significant relationship were found between NCGS and psychological functioning. Effect sizes indicated that anti-gliadin IgA and IgG are considerable negatively related to cognitive-motor functioning. Incoherent results were found for the relationship between NCGS and behavioral/emotional problems, health related quality of life, parenting stress and curiosity. Curiosity was not found to mediate the relationship between NCGS and cognitive-motor functioning.

Conclusion: This thesis finds partial support for the negative relationship between NCGS and facets of psychological functioning. Cognitive-motor functioning was found to be negatively related to anti-gliadin IgA and IgG, implying a possible effect of NCGS. A larger sample size and more studies are needed to further investigate the proposed relationship.

Acknowledgments

We want to thank our main supervisor, Egil Nygaard, for hiring us and giving us this opportunity. He has given us invaluable advice and always kept the door open. He guided us and this thesis through a chaotic pandemic and the countless challenges that came with it. He provided a scaffolding that gave us the opportunity to develop as scientists, giving us invaluable experience. We have both learned a great deal from you. Thank you.

We also want to thank our contributing supervisor Knut Lundin for helping us to separate the wheat from the chaff of gastrointestinal literature, and patiently entertaining our cluelessness. We want to thank the rest of the research group Kari-Anne Bottegaard Næss, Christine Olbjørn, Carina Hinrich, Marte Valde and Stine Rosenqvist Lund. Thank you for helping us get the data in time for the deadline of the thesis. Without all of you this project would not be possible.

We both want to thank Katrine for the patient support you have given us, spending countless hours helping us make sense of R and for lending us your graphical expertise. Mikkel also wants to say that he is very sorry for immediately eloping with the thesis after saying yes to your marriage proposal.

We are very grateful for the scholarship given us by the Research Council of Norway, allowing us to dedicate our time to this project.

A big thanks to all the health professionals and habilitations services that have given us invaluable aid throughout the project, and all the user organizations that helped us recruit families for this study. We also want to thank Barnebo kindergarten for helping us conduct the pilot study.

Many thanks to Per Daniel for reading through and reviewing the thesis.

Last but not least, we would like to thank all the families who have participated in the project. Thank you.

Table of contents

1. Introduction

Celiac disease (CD; see Appendix A for all abbreviations) is a gluten-induced disorder in which gluten consumption causes the body to mount an immune response that attacks the small intestine (Ludvigsson et al., 2013). Other individuals lack the characteristic serological and histological markers of CD but still report a wide range of celiac-like symptoms that disappear once gluten-containing cereals are removed from the diet. The causes and mechanisms of this syndrome, known as non-celiac gluten sensitivity (NCGS), are still largely unknown (Catassi et al., 2015). Over the last decade, an increasing body of research has indicated that CD and NCGS not only affect gastrointestinal functioning, but may impair various aspects of psychological functioning, as well (Daulatzai, 2015; Pennisi et al., 2017).

Studies have shown that people with Down syndrome (DS) have both an increased prevalence of gluten-related disorders and impaired psychological functioning (Folkehelseinstituttet, 2015; Marild et al., 2013). Nygaard et al. (2001) found anti-gliadin IgA and IgG to be related to cognitive/motor functioning in children with DS, and the present study intends to further investigate this relationship. The aim of the thesis is to investigate whether there is a relationship between NCGS and psychological functioning in children with DS, thereby contributing to the understanding of NCGS in general and how it affects those with DS.

1.1 What is Celiac disease?

Celiac disease is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals (Ludvigsson et al., 2013). When gluten is consumed, the small intestinal mucosa becomes inflamed, the intestinal villi are damaged, and the ability to absorb nutrients is impaired. The only known effective treatment is a lifelong gluten-free diet.

Traditionally, CD patients have presented symptoms of malabsorption such as diarrhea, weight loss, steatorrhea, and failure to thrive. Over time, that has changed: the proportions of patients diagnosed with symptoms of malabsorption has decreased, and CD patients with a variety of other types of symptoms have received more attention. These symptoms include gastrointestinal symptoms, ataxia, neuropathy, depression, and anemia (Al-Toma et al., 2019).

These diverse symptoms seem to be caused by gluten eliciting an autoimmune reaction. Gluten is a mix of proteins, the most prominent being gliadin, which is found in wheat, rye, and barley. When these proteins are consumed, they are broken down in the gut into smaller parts. The smaller gluten peptides can cross the intestinal wall in the small

intestine and enter the submucosa. In the submucosa, the enzyme transglutaminase 2 (TG2) deaminates the gluten peptides making it easier for them to bind to the HLA-DQ2 and HLA-DQ8 molecules on the surface of antigen presenting cells (Ludvigsson et al., 2013). This binding activates the T-helper cells (specifically $CD4^+$), releasing cytokines that triggers activation of inflammatory cells in patients with CD (Ludvigsson et al., 2013). This causes other immune cells to migrate to the area and damage the intestinal wall. The cytokines also trigger the activation of B cells that produce specific gluten antibodies such as anti-gliadin IgA and IgG and anti-TG2 IgA (Alaedini & Green, 2005).

Genetic studies have shown that CD is associated with the expression of HLA-DQ2 and HLA-DQ8. They are estimated to contribute 25%-40% of the genetic variation of CD. HLA-DQ2 is carried by 95% of CD patients, with a minority carrying HLA-DQ8 or a different HLA-DQ2 variant. These gene variants are quite common with up to 40% of Europeans testing positive for HLA-DQ2 or HLA-DQ8. Of these 40%, only 3% develop CD. This indicate that the HLA variants are necessary but not sufficient for the development of CD (Withoff et al., 2016).

Most patients with CD typically have signs of IgA antibodies against the TG2 enzyme, as well as IgG and IgA antibodies against deaminated gliadin peptide when exposed to gluten (Ludvigsson et al., 2014). Currently, these serological tests are not sufficient to establish a CD diagnosis, as a duodenal biopsy while the patient is on a gluten-containing diet is required (Ludvigsson et al., 2014). However, the guidelines of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition suggest that a biopsy might not be necessary if the antibody levels are high enough in children and the patient responds to a gluten-free diet (Husby et al., 2012).

1.2 Non-celiac gluten sensitivity

Double-blind placebo-control challenge studies over the last decade have shown some patients benefiting from a gluten-free diet without showing the serological, histological or genetical markers of CD or a wheat allergy (Biesiekierski et al., 2011; Carroccio et al., 2012; Shahbazkhani et al., 2015; Volta & De Giorgio, 2012). These patients typically suffer from both intestinal symptoms such as bloating, abdominal pain and diarrhea; and extra-intestinal symptoms such as fatigue, headache, anxiety and cognitive difficulties including foggy mind (Catassi et al., 2015; Volta et al., 2014). Based on studies like these, the current consensus definition of NCGS is “a syndrome characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food, in subjects that are not affected by either

celiac disease (CD) or wheat allergy (WA)" (Catassi et al., 2015, p. 4968); this reflects the fact that the syndrome has largely been diagnosed through exclusion criteria.

It is unclear whether it is the gluten itself that triggers the symptoms, or other proteins found in gluten-containing cereals. A review by Dale et al. (2019) of recent gluten challenge studies on patients suspected of NCGS notes, "The lack of difference in symptoms between placebo and gluten challenges found in most studies is a significant problem, giving strength to the assumption that gluten may not be the main trigger of symptoms in most patients" (p. 34). It is possible the disorder could be better explained by other possible triggers such as amylase-trypsin inhibitors, known as wheat ATIs (Fasano et al., 2015), or fructans instead (Pinto-Sanchez & Verdu, 2018; Skodje et al., 2018). Some papers therefore argue that n*on-celiac wheat sensitivity* is a more appropriate term (Catassi et al., 2015). Other papers have used the term *gluten sensitivity*, but that is considered too broad as it seemingly includes CD (Ludvigsson et al., 2013).

Irritable bowel syndrome (IBS) is a common functional intestinal disorder causing abdominal pain, bloating, gas, diarrhea, and constipation. IBS and NCGS were long thought to have different pathogenesis, with overlapping gastrointestinal symptoms (Volta et al., 2014). As NCGS might be triggered by wheat-related components other than gluten, and gluten and wheat components may trigger IBS symptoms, the relationship between the disorders is currently unclear (Catassi et al., 2017). Several studies have found a large overlap in patients with IBS who react to a gluten-free diet (Shahbazkhani et al., 2015) and fructan-inducing symptoms in patients with NCGS (Skodje et al., 2018). This might be explained by subgroups of IBS-patients having NCGS and vice versa, but the jury is still out (Fasano et al., 2015).

One other trait IBS and NCGS have in common that makes the differentiating them more difficult, is the lack of validated biomarkers, although promising advances are currently underway with NCGS. Uhde et al. (2016) have found increased serum levels of soluble CD14 (sCD14), lipopolysaccharide-binding protein (LBP), and antibody reactivity to microbial antigens in patients with NCGS compared to both healthy controls and CD, which indicates systemic immune activation. This activation also correlated with levels of fatty acid-binding protein 2 (FABP2), suggesting the impairment of intestinal barrier integrity and increased small intestinal permeability in patients with NCGS (Volta et al., 2017). Anti-gliadin antibodies have also been suggested as a potential biomarker for NCGS, with Volta and De Giorgio (2012) finding an anti-gliadin IgG prevalence of 56.4% in NCGS. A review by Infantino et al. (2017) notes that though the correlation between anti-gliadin IgG and NCGS

turned out to be significant in most studies, it does not seem to be a suffiecnt marker on its own.

Estimates of the prevalence of NCGS typically range from 0.5% to 6% (Fasano et al., 2015; Lundin, 2014). However, the current lack of biomarkers and unclear diagnostic criteria make conducting prevalence studies difficult, and double-blind placebo-control challenge studies can only diagnose approximately 20% of suspected NCGS patients (Molina-Infante & Carroccio, 2017; Volta et al., 2017).

1.3 CD, NCGS and psychological functioning

Patients with CD frequently report some temporary cognitive impairments, or "brain fog," to memory, processing speed, executive function, and attention (Yelland, 2017). In the last several years, a limited number of studies has examined the possible relationship between CD and psychological functioning. One study has demonstrated improved cognitive function in 11 newly diagnosed adults with CD after going on a gluten-free diet (Lichtwark et al., 2014). Additionally, a study of 18 seniors have found that participants with CD had worse cognitive function compared to similarly aged people without CD, even though the CD patients had been on a gluten-free diet for a long time (Casella et al., 2012). A study using a questionnaire have found that 401 adults with CD and 173 adults with IBS had a greater risk of peripheral neurological problems than a control group (Pennisi et al., 2017).

Studies have also shown that CD can influence other parts of psychological functioning. Two studies used Achenbach's child behavior checklist to detect behavioral and emotional problems in children with CD. In a study of 4,151 mothers, L. B. Smith et al. (2017) found that CD was associated with increased reports of 3.5-year-old children's depression, anxiety, aggressive behavior, and sleep problems when mothers are unaware of their child's CD status, but no differences were found when the children were 4.5 years old. Mazzone et al. (2011) found an increased rate of emotional and behavioral problems in 100 children with CD, compared to 100 in the control group. Epifanio et al. (2013) have compared 66 children with CD to 66 healthy controls and found that CD influences parent stress levels as measured by Parenting Stress Index, but not the patient's health-related quality of life. Two other studies from Spain and Sweden also found no effect of CD on children's health-related quality of life (HRQoL) using the KIDSCREEN-52 measure (Barrio et al., 2018; Myléus et al., 2014).

Several studies have examined the relationship between psychological function and NCGS. In a double-blind study, Peters et al. (2012) have found that three days of gluten consumption was associated with higher levels on the Spielberger State Trait Personality

Inventory depression scores in 22 people with IBS but without CD when compared to a control group. A randomized study of 45 children with ADHD-related problems have found that a gluten-free diet played a role in lowering the children's levels of hyperactivity over the course of six months (Lykogeorgou et al., 2014). Gluten sensitivity has also been found related to ataxia (Hadjivassiliou et al., 2003).

The nature of the relationship between CD/NCGS and psychological functioning is still unclear, as the few available studies often have a limited number of participants and have other methodological problems (Yelland, 2017). It is also uncertain if this possible relationship can be explained as a direct negative consequence of gluten or if there are more indirect relationships.

The possible relationship among CD, NCGS, and psychological functioning can be explained through dysfunction in the gut-brain bidirectional pathway. There is significant evidence that the gut microbiota communicates with the central nervous system through neural, endocrine, and immune pathways (Daulatzai, 2015). This has led to the suggestion of two separate, but not necessarily exclusive, pathways.

The first suggested pathway is through inflammation. Studies have shown that gluten causes increased gut permeability in CD, and some studies have found similar effects in NCGS (Hollon et al., 2015). The increased gut permeability encourages the migration of toxins and undigested food particles to sites where they can alert the immune system. This triggers the release of cytokines, inciting systemic inflammation. There is growing evidence this systemic inflammation is a precursor of neuroinflammation (Daulatzai, 2015; Yelland, 2017). This may cause widespread disruption of many key areas in both the brainstem and neocortex, including the hippocampus, entorhinal cortex, basal forebrain, prefrontal cortex, locus coeruleus, hypothalamus, and amygdala, leading to cognitive impairment (Daulatzai, 2015). This hypothesized pathway is supported by other studies that have found increased concentrations of cytokines to be associated with changes in behavior, cognition and mood (Daulatzai, 2015; Lichtwark et al., 2014; Yelland, 2017).

The other suggested pathway is through the release of gluten fragments called exorphins. A permeable gut wall in CD and NCGS patients makes it easier for exorphins to leave the gut, binding to opioid receptors throughout the body. Although the blood-brain barrier is expected to protect the brain from opioid peptides like exorphins, studies have suggested that they seem to be able to cross it if it is disrupted (Bressan & Kramer, 2016). The presence of exorphins in the brain are linked to changes in behavior (Fasano, 2017) and could influence the development of the central nervous system (Nygaard et al., 2001).

However, this hypothesis has not been investigated, especially with human participants (Yelland, 2017).

Other possible mechanisms have also been suggested. Studies have shown that nutrients such as iron, vitamin D, and folate are associated with cognitive impairment (Lichtwark et al., 2014). This is a possible mechanism in CD, as some patients show malabsorption of micronutrients. However, Lichtwark et al. (2014) did not find a link between levels of iron, Vitamin D and cognitive performance in CD for those put on a gluten-free diet. Patients with NCGS did not show the same symptoms of malabsorption as in CD patients (Biesiekierski & Iven, 2015). It is also possible that the relationship can be partially explained by the somatic symptoms. NCGS and CD cause physical discomfort and fatigue (Losurdo et al., 2018; Ludvigsson et al., 2014), which might affect general functioning.

If there is a relationship between NCGS, CD and psychological functions, it is likely that it will start affecting a child rather quickly once he or she begins a diet containing gluten. This could affect the child negatively in important development phases in its life and have lasting consequences.

1.4 Down syndrome

Down syndrome is caused by the partial or total trisomy of chromosome 21 and is the most common known source of intellectual disability. There are three known types of DS. The most commons called trisomy 21, which means those with this type have three sets of chromosome 21; it affects 90%-95% of the population with DS. Approximately 2%-4% have translocation, meaning they have parts of an extra chromosome 21 localized on another chromosome. In people with the third type, mosaicism, only some cells have an extra chromosome, while others are normal. Mosaicism accounts for about 2%-4% of all cases of DS (Papavassiliou et al., 2015).

People with DS share some common characteristic physical features. In addition to their characteristic appearance, many with DS have additional conditions, e.g., heart defects, hearing defects, vision problems, immune system deficits, digestive problems, and CD. (National Institutes of Health, 2017, January 31). Most children with DS have delayed development, but there are large individual differences within the population (Folkehelseinstituttet, 2015).

The physician John Langdon Down clinically described the existence of DS in 1866, but it was well known before this. The first indication of the existence of the disease is found in 2500-year-old sculptures resembling people with trisomy 21 (Kazemi et al., 2016). It is likely that DS has existed for as long as there have been humans. It seems that the overall

prevalence of DS pregnancies is relatively similar among European countries. However, the proportion of live-born children with DS varies more. It is likely that this can be explained by the differences in pregnancy screening test and societal attitudes among countries (Folkehelseinstituttet, 2016).

We still have limited knowledge of why some people are born with this extra chromosome or parts of it. However, there is a strong connection between the age of the mother at inception and the frequency of trisomy 21, which increase with the age of the mother. A large European population-based study using the EUROCAT registries has found that mothers aged 40+ had a prevalence rate that was 17 times higher than mothers aged 25-29 (Loane et al., 2012). There is now ample of research investigating the parental origin of the extra chromosome 21. Studies have indicated that approximately 90% of the meiotic errors are maternal and are related to the nondisjunction of chromosome 21 (Vundinti & Ghosh, 2011). The effects of paternal age are still undetermined; some studies have suggested a small effect that is seemingly mediated by the maternal age (Fisch et al., 2003).

1.5 Down syndrome and gluten-related disorders

Children with DS have a considerably heightened risk for CD. A nationwide, population-based case-control study in Sweden found a six-fold increased risk of CD in individuals affected with DS (Marild et al., 2013). This fits well with a recent meta-analysis by Du et al. (2018), who found a biopsy-confirmed prevalence of approximately 6% in patients with DS, compared to estimates of approximately 1% in the general population (Fasano & Catassi, 2012; Singh et al., 2018).

The relationship between DS and NCGS is still unclear, and, to the best of our knowledge, there are currently no direct estimates of NCGS among people with DS. A study by Gomes et al. (2016) of 77 children with DS found that 64% had gastrointestinal symptoms and 43% had constipation, while blood samples indicated potential CD in 27%, and biopsy confirmed CD in 13% of the children. Such results may indicate a greatly heightened risk of NCGS among children with DS, as well. The difficulty of effectively diagnosing NCGS makes it challenging to study this relationship (Catassi et al., 2015), but recent advances in the identification of biomarkers open new avenues. Two DS studies have found heightened levels of anti-gliadin IgG in 58% and 16% of their samples (AlRuwaily et al., 2017; Nygaard et al., 2001), which could imply considerably heightened NCGS prevalence in people with DS. However, more research is needed, as the two estimates varied greatly, and anti-gliadin IgG is limited as a predictor of NCGS.

The findings of Nygaard et al. (2001) are of special interest to this study, as it is the only study investigating how gluten is related to psychological functioning in children with DS. They studied 55 children with DS and found significant negative correlations (r = -0.13 to -0.51) between antibody response to certain food proteins (IgA and IgG activity against gliadin and gluten), and psychological functioning (cognitive and motor function). The strongest correlations found (r=-0.44 to 0.51, $p \leq .005$) was between IgA and IgG antibody response to gluten and gliadin and the novelty preference measured by Fagan Test of Infant Intelligence. The article used the results of the Fagan test as an indicator of the biological basis for psychological development, being a strong indicator of future intelligence (McCall & Carriger, 1993). However, as the results of the delayed recollection condition were excluded from analysis, the results of the Fagan test might also reflect individual differences in curiosity. Novelty preference is a form of visual exploratory behavior, and is generally considered to be motivated by curiosity (Berlyne, 1950; Muentener et al., 2018; Spielberger & Starr, 1994). It is possible the results of Nygaard et al. (2001) can be explained by a mediation effect of curiosity on intelligence.

Research into CD and NCGS in Autism spectrum disorders (ASD) may help shine more light on gluten's influence on children with DS. Several studies have found a relationship between the disorders for example DiGuiseppi et al. (2010), who found a substantially higher prevalence of ASD in 123 children with DS aged 2 to 11 years than in the general population. The focus on CD and NCGS in ASD has culminated in the popularity of the gluten-free casein-free diet intervention for children with ASD, and it has been an increasingly popular area of study in the last two decades (Czaja-Bulsa, 2015; Pennesi & Klein, 2012). A review article on gastrointestinal symptoms in ASD from 2020 found that 83% of the articles highlighted increased symptoms in ASD patients, and it found suggested associations between cognitive and behavioral deficits and gastrointestinal symptoms in certain groups of individuals with ASD (Lefter et al., 2020).

It is disputed whether a gluten-free diet increases psychological functioning in children with ASD. Navarro et al. (2015) have found no support for a change in behavioral problems after putting 12 children with ASD on a gluten-free, casein-free diet. Ghalichi et al. (2016) put 40 out of 80 children with ASD on a gluten-free diet and found a significant decrease in both gastrointestinal symptoms and behavioral disorders. R. W. Y. Lee et al. (2018) have found an increase in psychological functioning in 15 children after three months on a ketogenic, gluten-free diet. Studies have found increased intestinal permeability in children with ASD (de Magistris et al., 2010). Considering the relationship between DS and

ASD, it is possible that similar relationships between CD/NCGS and psychological functioning can be found in children with DS. Furthermore, the possible link between CD/NCGS and ASD on the one hand and ASD and DS on the other may explain some of the findings in people with DS.

Different national associations' guidelines vary on the subject of screening children with DS for CD, from not recommending it at all to recommending it for all patients (Pavlovic et al., 2017). In Norway, the official guidelines dictate that children with DS should be tested for risk factors (HLA-DQ2/DQ8 serotype) at 15 months of age, with yearly blood samples recommended if positive (Regionsenter for habiliteringstjenesten for barn og unge, 2017). As far as we are aware, there are no current guidelines concerning NCGS and children with DS. This is problematic, as many children with DS still have nonspecific gastrointestinal symptoms without CD. These symptoms are often simply attributed to DS (Davidson, 2008), and remain untreated. This has led to disagreement and uncertainty among parents and health professionals regarding what consequences gluten has on the development of the children with DS and whether they should be on a gluten-free diet. At the time of writing, there is neither sufficient research evidence to understand the nature of their gastrointestinal symptoms nor to confirm or reject the possible effect of gluten on the children's development. This thesis hopes to provide more insight into these phenomena and the relationships among them, and thus contribute to the future decision basis for parents and health professionals.

1.6 Aims and research questions

This thesis is based on a cross-sectional study investigating the relationship between NCGS and psychological functioning in children with DS between 5 and 11 years old. The present study measures NCGS through blood samples and parent-reported symptoms, and it measures psychological functioning through neurocognitive test results and the child's parent-reported behavior.

The aim of the thesis is to investigate whether there is a connection between NCGS and psychological functioning in children with DS. This is important knowledge to support the need for further study of possible consequences of NCGS, and thus lay a foundation for evaluating the benefits of possible measures and interventions. Such knowledge is especially important for children with DS due to their over-frequency of both gluten-related disorders and their poorer psychological functioning relative to the general population.

This thesis' primary hypothesis:

There is a negative relationship between NCGS and psychological functioning. Psychological functioning is defined in this study as: cognitive functioning, quality of life, and behavioral signs of anxiety, sadness, and anger.

The thesis also investigates the following secondary hypothesis:

The relationship between NCGS and cognitive-motor functioning is partially mediated by curiosity.

2. Method

2.1 Sample

The study consisted of 21 participants. The average age of the children in the study was 8.5 years, with an SD of 1.88. There were eight (38.1%) boys and 13 (61.9%) girls. In contrast to the expected 10.3% in the population (Statistisk sentralbyrå, 2020), 38.8% of the parents had a university or college degree (more than four years). Two participants were born outside of Norway. Possible biological markers of NCGS were analyzed for seven participants.

A total of 19 children had medical complications or conditions that could have affected their cognitive as well as motor functioning. These included hearing impairment (four children), visual impairment (18), different types of motor difficulties (six), gastroesophageal reflux (two), Hirschsprung's disease (one), milk allergy (two), other allergies (four), and cardiac illnesses (12). Four participants reported using medication against constipation (Movicol and Laxoberal). Two of the participants were on a gluten-free diet; these participants were not excluded. Eight of the 13 participants with available celiac diagnostics had one or more HLA-DQ2/DQ8 genotypes, and two out of 12 had levels of Anti-deamidated gliadin IgG (anti-DGP IgG) over the reference range. Four participants were excluded, two due to previously diagnosed CD, and two due to the amount of missing data, which made the statistical software unable to impute their data.

2.2 Procedures

2.2.1 Author involvement in the study

We were hired in a 10% research assistant position with the study between April 2019 and May 2020 and took over the development of the study. We researched and selected measures, created the assessment procedure, got changes approved ethically by Regional Committees for Medical and Health Research Ethics (REK), pilot tested the study, recruited participants, collected the data, and selected and performed statistical analysis. We aim to publish an article based on the study when the data collection is completed later this year.

2.2.2 Pilot study

A pilot study was conducted to assess the feasibility of the psychometric tests, standardize the procedure, and give the test administrators the practice needed to produce reliable test results. Five participants between the ages of 3 and 5 were recruited through a kindergarten in Oslo. The parents received written invitations with information about the pilot and a permission slip. Seven adults piloted the questionnaire, leading to minor improvements

in language and format. The data gathered during the pilot test was destroyed after the end of the pilot and was neither used nor discussed in this thesis.

The pilot study revealed a need for rewards to motivate and help the children stay focused. Accordingly, a system using stickers for each completed task and a small toy at the end were added. The task *Stockings of Cambridge* from the Cambridge neuropsychological test automated battery (CANTAB) was excluded from the battery, as it was ultimately too complicated and time consuming for the participants. The simple variant of the *Reaction Time Index* subtest was also dropped as the participants seemed tired and uninterested and did not want to finish the task. None of the participants in the pilot had any problems with the more complicated five-choice variant. Small adjustments were made to clarify the instructions of the *Nine-Hole Pegboard Test* (9-HTP) and the CANTAB.

2.2.3 Recruitment

The participants of the study had to be between 5 and 11 years old and diagnosed with DS. They had to live within the study's geographical recruiting area of south-eastern Norway, and both parents needed to give their informed consent. Children previously diagnosed with CD were excluded, as were children with other conditions that made them unsuited to participate in the study; this assessment was based on the judgement of the responsible pediatrician. No participants were excluded based on this exclusion criterion.

The number of participants recruited was based on statistical strength calculation from the only comparable previous study (Nygaard et al., 2001). That study found an average correlation of 0.38 between four gluten related biological markers and two psychological targets. This indicated that 52 participants were needed to be sufficiently safe to avoid type I (α=0.05) and type II (β=0.20) errors in bivariate correlation analyses. Because of economic and practical constraints, it was decided that recruitment would stop at 70 participants.

The recruitment was done by sending written invitations with information about the project and consent forms to parents of children with DS in the age group (see Appendix B), and the parents had to sign up of their own volition. This was done through two different types of partners. The 10 habilitation services of southern and eastern Norway were offered pre-packaged letters to send the parents, with invitations and stamped return envelopes to make it easy to sign up. Six of the habilitation services sent our prepared letters, while two sent the invitations of their own initiative (without return envelopes). The following user organizations helped share the study's website ("Kognisjon og psykisk helse hos barn med Downs syndrom med glutensensitivitet," 2019) and other information about the study through social media and e-mail: Norsk Nettverk for Down Syndrom (NNDS), Ups&Downs Bærum,

Ups&Downs Hedemark, Ups&Downs Oslo, Ups&Downs Romerike, Ups&Downs Telemark, Ups&Downs Vestfold and Ups&Downs Østfold. An offer was also made to hold a presentation of the study at parent gatherings, but due to COVID-19 all such meetings were cancelled. The Norwegian Association for Persons with Intellectual Disabilities (NFU) shared information about this study to the local branches in the recruitment area.

2.2.4 Test administration

The location of the test administration varied according to agreements with individual participants, which were based on their needs. Eleven administrations for the participants living in the area around Oslo took place at the University of Oslo (UiO). For participants who lived farther away, the testing was primarily done at their local Habilitation Service, at eight in total. Two participants were tested in their own homes.

The test administration consisted of an assessment of the child's cognitive and motor functions. This was done at a desk with chairs that could be adjusted according to their height. While the parent could borrow an iPad to complete the questionnaire during the assessment, some of the parents had to attend to their child and received a URL to complete it at home instead.

2.3 Measures

2.3.1 Assessment of cognitive and motor functions

Cambridge neuropsychological test automated battery (CANTAB) is a battery consisting of 18 optional non-verbal cognitive tests intended ages 4 to 90 and is administrated on tablets (d'Ardhuy et al., 2015). CANTAB tasks are widely used with DS (Edgin et al., 2010), and they have previously been used on a clinical Norwegian population (Torgersen et al., 2012). The following CANTAB tasks were chosen based on test time, the suitability of their difficulty level for the study's participants, and the cognitive areas the study explored:

The motor screening task (MOT) provides a screening for visual, movement, and comprehension limitations, as well as introducing the CANTAB tests to the participants. The task involves selecting colored crosses presented on the screen as quickly as possible. No results from this subtest were used in the statistical analysis.

The reaction time (RTI) five-choice variant tests motor and mental response speed. The task involves holding down a button at the bottom of the screen. A yellow dot then flashes in one of the five circles presented above. The participant then reacts as quickly as possible, releasing the button and pressing the circle with the yellow dot. Two scores from the subtest were used. *RTI Median Five-Choice Reaction Time* is the median duration it took to release the button after the flash of a yellow dot, and *RTI Median Five-Choice Reaction Time*

is the median time taken to release the button and select the yellow dot after a flash and is measured in seconds.

Spatial span (SSP) is an assessment of visuospatial working memory capacity. Squares are shown on the screen, some of which briefly change color in a variable sequence. The participant must copy the sequence displayed by the computer. The number of boxes in the sequence increases from two at the beginning to nine at the end, unless the stop criterion of four failed sequences in a row is met. The score used from the subtest is *SSP Forward Span Reached*, which is the longest sequence of boxes the subject successfully reached, with a minimum score of two and a maximum of eight.

Paired associated learning (PAL) assesses new learning and visual memory. Boxes are displayed on a screen, and some are empty, while others contain a hidden pattern. The content of the boxes is shown in a randomized order. The participant is then prompted to pair the patterns with the box that contained them. The patterns are repeated in a new randomized order if the participant makes an error. The stop criteria are met if this happens four times in a row. The difficulty increases by adding more boxes and patterns to memorize. Two scores from the subtest were used. The *PAL First Attempt Memory Score* is the number of times the subject selected the correct boxes on first attempt, whereas the *PAL Total Errors (Adjusted)* reflects the number of times the subject chose an incorrect box, with an adjustment for trials not reached.

We translated the original instructions as there was no available Norwegian translation. The instructions were modified based on experience from the pilot study to increase compliance (see Appendix C). A three-month test-retest study from 2020 found that none of the CANTAB subtests in the study reached the acceptable test-retest correlation of $r \geq .75$ (Karlsen et al., 2020). They found a Spearman's rank correlation coefficient of .72 for RTI, .69 for SSP, and .73 for PAL, whereas MOT was not included. These findings are consistent with previous studies (Gau & Shang, 2010; Lowe & Rabbitt, 1998; Syväoja et al., 2015). To our knowledge, the study of Syväoja et al. (2015) is the only one that has inspected the test-retest reliability of the CANTAB battery in children, and it found Pearson's correlations between assessments for RTI five-choice movement time ($r = .50$, $p < .001$) and RTI five choice reaction time ($r = .63$, $p < .001$). Several studies have investigated the construct and criterion validity of the CANTAB battery. The studies found weak to moderate correlations between CANTAB and other neuropsychological tests (Matos Gonçalves et al., 2018; P. J. Smith et al., 2013). In contrast, Torgersen et al. (2012) have found that PAL correlated with a wide range of other established memory and intelligence tests, with

correlations between .52 and .78. The most consistent correlation found was between PAL and different general measures of memory.

The Stanford Binet 5 Abbreviated IQ (SB5 ABIQ) is a shortened version of the Stanford Binet Intelligence Scale, Fifth Edition (SB5), and can be used on participants between ages 2 and 85 (Bain & Allin, 2005). SB5-ABIQ consists of two subtests: a non-verbal subtest (Object Series/Matrices*)* and a verbal subtest (Vocabulary). The raw scores from each subtest were summed to create a matrix score and a verbal score, which were used in the data analysis. The raw scores were also standardized and combined to create an estimate of IQ for sample description purposes.

Object Series/Matrices requires the participant to identify patterns of series of objects and pictures. The first eight tasks are done with physical objects, and the participants must figure determine what object from a pool of several continues the pattern shown to them. In later tasks, the participants must identify patterns in matrices instead of objects. The task continues until all tasks are completed or the stop criterion of four failed tasks in a row is met. There are 36 items, the matrix sum score is created from these items with a score ranging from 0 to 36.

The Vocabulary subtest requires examinees to use their verbal knowledge. It increases in difficulty with each task. The first five tasks involve pointing to different body parts on themselves and pictures. It continues with four tasks in which the participants must name physical objects, followed by five tasks in which they describe actions in pictures. The rest of the tasks involves defining words of increasing difficulty. There are 44 items in total; the verbal sum score is created from these items and has a possible score between 0 to 74. It continues until all tasks are completed or the stop criterion of four failed tasks in a row is met.

The Norwegian instructions used in this study were translated by the Norwegian Institute of Public Health (FHI) in its ADHD study, which is a part of the Norwegian mother, father child study (MoBa; Rohrer-Baumgartner et al., 2014). A book review from Bain and Allin (2005) found that the split-half reliability of the ABIQ score ranged between .91 and .98. The review also found that the test-retest reliability ranged from .84 to .95. Bain and Allin (2005) have reported a concurrent validity between SB5 ABIQ and SB5 FSIQ of .87 for people over the age of 6 and .81 for children between 2 and 5 years old. The correlations between SB5-ABIQ and the Wechsler Adult Intelligence Scale third edition (WAIS-III), and the Wechsler Intelligence Scale for Children (WISC-III) were .81, and .69, respectively.

The Nine-Hole Peg Test (9-HPT) measures fine motor skill. The participants must take nine pegs from a container, one by one, and place them into the holes on the board, as quickly as possible. They must then remove the pegs individually and put them back in the container. The test is scored based on the time needed to place and remove all nine pegs. This task is repeated for both hands. The test has moderately high test-retest reliability (R_s = .81 and .79) and high interrater agreement (Y. A. Smith et al., 2000). Studies have shown that 9-HPT can discriminate manual dexterity between healthy controls and populations with minimal hand dysfunctions (Feys et al., 2017). A recent has study found evidence supporting construct validity of the 9-HPT by comparing the scores of participants with Parkinson with varying hand dexterity loss (Proud et al., 2020). We translated the instructions to Norwegian. The 9-HPT-score used in this thesis is the time used to complete the task with the dominant hand.

2.3.2 Questionnaires

One parent of each participant had to complete a questionnaire. The questionnaire had a short introduction with practical information, followed by nine forms (Appendix D).

Socio-demographical information was gathered through a form created for the study. It included items on the participants sex, age, weight, height, birth country, parents' educational level and the participating guardian's relationship with the child.

The Brief Problem Monitor (BPM) is a short version of the Achenbach System of Empirical Based Assessment (ASEBA) and consist of 19 items selected from three longer scales (CBCL, YSR, and TRF). The instrument was developed to easily assess children's and adolescent's (ages 6 to 18) development of internalizing, attentional, and externalizing problems. There are three different versions, and the present study used the parent-report version (BPM-P). The items are rated on a 3-point Likert scale from "not true*"* (1) to "very true*"* (3)*,* with the option to comment on each item. While the items can be divided into three subscales (one for each problem area), the score used in this study was the overall problem score calculated by averaging all items. As a part of this study's sample are not in school, the wording "at school" in item 9 was changed to "in the kindergarten/at school."

The original scales of the items were translated into Norwegian by Torunn S. Nøvik and Sonja Heyerdahl and published in 1986/88, 1993 and 2002 (Kornør & Martinussen, 2012). A study investigating the psychometric properties of the Norwegian version of the BPM found good construct and content (convergent) validity (Richter, 2015). Another article has concluded that although the reliability of the total problem score is good, more Norwegian or Scandinavian studies are needed to ensure its overall validity (Backer-

Grøndahl & Martinussen, 2018). Good psychometric properties have been found in the Spanish and English version (Penelo et al., 2017; Piper et al., 2014).

The Parenting Stress Index Fourth Edition Short Form (PSI-4-SF) is a questionnaire used to survey stress in the relationship between parent and child and is designed for use with parents of children ranging in age from 1 month to 12 years. Its 36 items are divided into three domains: Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child, which together create a Total Stress scale. Items are rated on a 5-point Likert scale from "strongly agree" (1) to "strongly disagree" (5) and then averaged by each scale. Higher scores indicate less stress as parents disagree with statements indicating stress.

This research team translated both the PSI-4 and PSI-4-SF into Norwegian, and the translations were derived from the earlier Norwegian translation of the third edition by John A. Rønning (Kaaresen et al., 2006). The translation was back translated by an independent translation company, Akasie Språktjenester AS, and approved by the publisher, Psychological Assessment Resources, Inc. (PAR). Psychometric tests have demonstrated the good reliability and validity of the Norwegian translation of the third editions, and the index has been found to predict dysfunctional parenting and deviant development across different populations (Kornør & Martinussen, 2011). Studies have found strong psychometric properties of the PSI-4-SF in English and Spanish (Barroso et al., 2016; S. J. Lee et al., 2016).

KIDSCREEN-10 is a questionnaire measuring HRQoL for children and adolescents (ages 8 to 18). The KIDSCREEN-10 is a 10-item index version of the longer KIDSCREEN-52. The parent report version of the form was chosen for this study. Parents are asked to estimate how many HRQoL statements fit their child's behavior on 5-point Likert scale from "not at all*"* (1) to *"*extremely" (5). As not all the children in the present study are of school age, "kindergarten" was added to items 9 and 10. The answers were averaged to a general HRQoL index.

The Norwegian version was translated by Haraldstad, Eide and Helseth in 2006. The Norwegian KIDSCREEN-52 has been found to be reasonably valid (Haraldstad et al., 2011). A pan-European study with 22,830 children and 16,237 parents across 13 European countries found that KIDSCREEN-10 provides a valid measure of a general HRQoL factor in children and adolescents (Ravens-Sieberer et al., 2010). A review by Haraldstad and Richter (2014) has concluded that more studies are needed of the Norwegian parent report version.

I/D-Young Children (I/D-YC) is a parent report questionnaire measuring epistemic curiosity in children. Epistemic curiosity is the desire for new information that motivates knowledge acquisition and exploration. This is measured through two scales in the I/D-YC.

The I-type scale measures *interest*-type curiosity, which is positive feelings of intellectual interest associated with the anticipation of learning new knowledge. The D-type scale measures curiosity stemming from the need to reduce unpleasant experiences of being *deprived* of information (Piotrowski et al., 2014). Both scales consist of five items answered on a 4-point Likert scale from "almost never" (1) to "almost always" (4), which are averaged. The creators found the scale to produce valid and reliable measures of individual differences in early expressions of curiosity (Piotrowski et al., 2014). This research team translated the measure to Norwegian, and Jessica Taylor Piotrowski approved the back translation by Akasie Språktjenester AS on behalf of the creators.

The children's diet questionnaire is based on an earlier questionnaire used in a study of children with a cow's milk allergy (Kvammen et al., 2018), and it was adapted to the current study's focus on NCGS. The questionnaire consisted of 16 items concerning the development of the child's eating behaviors, current diet, use of supplements, and the child's compliance with its own growth curve. Item 5 ("What foodstuff do you NOT give the child?") was used to measure the number of participants on a gluten-free diet through option 1 ("Gluten-containing cereals / flour [wheat, spelt, rye, barley]"). The questionnaire has not previously been validated.

Gastrointestinal Symptom Rating Scale (GSRS) is a self-administered, 15-item questionnaire used to measure gastrointestinal symptoms. It is the recommended measure of symptoms in NCGS (Catassi et al., 2015). As the researchers found no readily available parent report measures of gastrointestinal symptoms, the decision was made to adapt the GSRS to this study's population. This meant rewriting the start of the items from "Have you been bothered by…" to "Have you noticed your child being bothered by…". As such the version used is not currently validated. The items were answered on a 7-point Likert scale, "no discomfort at all" (1) to "very severe discomfort" (7). The items were averaged for a GSRS total symptom scale. The publishers, AstraZeneca, granted permission to use and modify the Norwegian version of the GSRS. Akasie Språktjenester AS back-translated the modified version, and the publishers approved it.

Sleep was measured through three items from the questionnaires used in the Norwegian mother, father and child study (MoBa; Jin, 2016a; MoBa; Jin, 2016b). The results from the sleep measure were not used in this thesis.

Bodily diseases was the eighth and last form and the researchers made it to map the child's somatic health. The participating guardian was asked to report the child's somatic problems; somatic impairments within motor functions, hearing, and sight; and the child's use

of medicines. The items were selected based on clinical experience and general knowledge of possible confounding variables and risk factors. These items were used to screen for other conditions that threatened the validity and reliability of the results.

2.3.3 Blood samples

The participants received a requisition for blood samples at the end of the assessment session (see Appendix E). The blood samples were taken at a time and place of the participants' choosing, often done where the child was accustomed to being medically examined. One tube of EDTA blood and one tube of serum were sent to Fürst Medisiniske Laboratorium for analysis, while a tube of serum was sent to the Department of Gastroenterology, Oslo University Hospital (OUH).

Fürst analyzed the samples for the established serological markers for CD: Anti-TG2 IgA, anti-DGP IgG, and major histocompatibility complex for serotypes HLA-DQ2.2, HLA-DQ2.5, and HLA-DQ8. They also analyzed additional general measures, including hemoglobin, MCH, MCV, ferritin, WBC count and differential, thrombocytes, CRP, TSH and free T4, ASAT, and ALAT.

The tube of serum sent to the Department of Gastroenterology, OUH was used for analysis of experimental NCGS-biomarkers: anti-gliadin IgA and anti-gliadin IgG, anti-flagellin IgG and IgM, intestinal fatty acid-binding protein (I-FABP), lipopolysaccharide-binding protein (LBP), and soluble CD14 (sCD14). The Department of Gastroenterology, OUH performed the analysis of anti-gliadin IgA and IgG. The original intent was for Alaedini Lab at Columbia University (Alaedini Lab, 2020) to perform the rest of the experimental analyses, as they have the necessary equipment. However, due to difficulties obtaining a material transfer agreement with Columbia University, it was decided that the Department of Gastroenterology, OUH would acquire the necessary equipment.

Both anti-gliadin IgA and IgG were determined by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (α-gliatest SIgA and SIgG, Eurospital). The cut-off levels were set at 50 and 15 arbitrary units (AU) for IgG and IgA, respectively, as the manufacturer suggested. HLA-DQ2.2, HLA-DQ2.5, and HLA-DQ8 were scored as either positive or negative. Anti-tTG IgA, Anti-DGP IgG, and CRP were scored as a specific value if the value was over a set minimum value, which is usually set to <1.0 U/ml for Anti-tTG IgA and Anti-DGP IgG, and <1.0 U/mg for CRP. All other biological values reflect its ratio per sample, with a minimum score of 0.

To better predict NCGS, a biomarker composite score was made (see section 2.6.1), with higher scores predicting higher sensitivity. The biomarker composite was intended to

contain all seven experimental NCGS biomarkers. However, only anti-gliadin IgA and IgG were available in time for this thesis. All biomarkers will be included in the future article. The main study also aims to assess measures of NCGS by analyzing each individual proposed biomarker. As this thesis's focus is psychological functioning, individual biomarkers will be addressed in another article.

2.4 Ethics

The Regional Ethical Committee South-East Norway (REK), REK nr. 2018/1122 (see Appendix F), approved the project. To ensure that the parents and children did not feel pressured into joining the study, all contact occurred through existing contact persons, and parents had to sign their children up on their own initiative. The invitation contained information about the project, including its background and purpose, what it entailed, possible advantages and disadvantages, and the storage and use of personal data (see Appendix B3). Signed declarations of consent had to be provided from both parents before the child joined the study. The parents were informed that they could withdraw from the study at any time.

The information recorded included answers from the questionnaire, the child's cognitive test results and results from the analysis of blood samples. UiO was responsible for data processing. Only people authorized by the project manager had access to the data, and only for the time they needed it. Everyone with access had a duty of confidentiality. The data was stored electronically in an area specifically designed for the storage and processing of sensitive data (TSD) at the UiO (University of Oslo (UiO), 2020a). TSD is certified for storing sensitive health information. All statistical analysis of the data took place within TSD's high-security system.

The following procedures were implemented to secure the storage of sensitive data. All sensitive data was stored either in TSD's high security system or the lockable filing cabinet. Of this stored data, only the signed consent forms, answers from the questionnaire and the contact information document had personal information. Separate IDs were used with the contact information and the data gathered. The cypher connecting the participant number and contact information ID was stored in the filing cabinet, while the contact information was stored on TSD. The manual record forms for the SB5 and 9-HPT results were stored in the filing cabinet and shredded after being transferred into TSD. All results are presented on a group basis, and thus no participants can be recognized.

The results from the analyses of the blood samples are stored in the participants' patient records at Oslo University Hospital, Rikshospitalet. The analyses was performed at

Rikshospitalet and Fürst Medisiniske Laboratorium, and the blood samples are stored in an approved research biobank (the research biobank "Intestinal Diseases", ref. No. 2012/341) at the Oslo University Hospital, Rikshospitalet. We manually transferred the results from the blood samples to TSD, and all paper information used in this process was destroyed after the information was electronically stored in TSD.

UiO's electronic questionnaire service "Nettskjema" was used to collect the information from the parents. The data (answers to electronic questionnaires) were sent directly to TSD and encrypted. This solution is approved for the collection of health data and other very sensitive information. The computerized CANTAB test results did not contain any personal information besides the participant ID and were stored on CANTAB's cloud services until we transferred them via secure lines to this projects TSD database.

2.5 Impact of the COVID-19 pandemic

As a consequence of the COVID-19 pandemic spreading to Norway in late February (Solsvik, 2020), all research activity on the premises of UiO was closed on March 12 (University of Oslo, 2020b), leading to a shutdown of testing. At this time, approximately 20 participants had been recruited and one tested. Further recruitment was also effectively suspended, as the capacity of health services was burdened, including habilitation services. User organizations also suspended relevant activity, and all planned presentations were cancelled.

To restart the activity of our study, we had to make a thorough evaluation of the risk involved for the participants, and comply with national guidelines for COVID-19. Although DS was not identified as a significant risk factor for the virus (Norwegian Institute of Public Health, 2020), some comorbid conditions made parts of the population fall within high risk groups (De Cauwer & Spaepen, 2020; Down Syndrome Medical Interest Group, 2020; Espinosa, 2020). Thus, it was important to be prudent with the timing of resuming testing. Habilitation services continued with their assessments of children with DS by early May, but as this work was less urgent, a decision was made to wait until the consequences of the broader gradual reopening were clearer.

By mid-June, the spread of COVID-19 was considered to be low and stable enough for testing to resume, and an infection control protocol was created based on guidelines by the Norwegian Institute of Public Health (FHI), guidelines used by other research projects, and input from professionals from habilitation services (see Appendix C). The infection control protocol focused on disinfection, hygiene, screening of symptoms, and social distancing with COVID-19. The testing procedure was changed to make it easier to uphold

the social distance of one meter. One participant withdrew from the study following the pandemic, citing a lack of time before turning 12 and fear of contamination.

The four-month delay of data collection and recruitment had several consequences for the study and this thesis. The study experienced a loss of participants due to withdrawal and cancelled recruitment opportunities. The time available for data collection was reduced from five to two months, and the time for data analysis and the subsequent finalization of the thesis was reduced to one month. It was impossible to reach the targeted 70 participants in time for the deadline of this thesis. There was also a loss of biological data. First, because of infection control procedures in hospitals, some participants could not take the blood sample in time for the thesis deadline, e.g., if they had a persistent cold. Second, it was not possible to complete five of the experimental serum analyses in time. Furthermore, the delay of data made it necessary to prepare and codify all analyses before the data was available, while being unable to test the feasibility of these statistical analyses on the reduced data.

2.6 Data analyses

Statistical analyses were originally conducted using IBM SPSS Statistics version 26.0.0.1 (IBM Corp., 2018). However, due to its limitations with the analysis of multiply imputed data, the multiple imputation itself and all later analyses were conducted using R version 4.0.2 (R. Core Team, 2019). This includes the computation of composite and standardized scores, reliability analysis, confirmatory factor analysis (CFA), correlations, linear regression, and mediator analysis. The raw data was not handled prior to being imported into SPSS. One syntax was created to organize the data and one to perform preliminary analyses in SPSS (see Appendix G), and three scripts were created to perform the analyses in R (see Appendix G). These were created prior to collecting and receiving the data.

2.6.1 Preliminary analyses

Data from the blood samples, SB5-ABIQ and 9-HPT were manually entered. To minimize the risk of error all data was entered twice by two different researchers. SPSS was then used to match the two datasets and look for inconsistencies between them. The minimum and maximum values of all variables were also manually checked for impossible values.

All the raw scores from the test battery and the parent questionnaire used in the analyses were inspected for outliers, floor and ceiling effects, and normality. This analysis of raw data was conducted using the explore function in SPSS. Outliers were detected using the interquartile range (IQR) method, defined as observations falling below Q1-3*IQR or above Q3+3*IQR (Schwertman et al., 2004). All outliers detected were addressed using

winsorization (Liao et al., 2017). Floor and ceiling effects were examined by looking at the data spread. The Shapiro-Wilks test was conducted together with Q–Q plots and histograms to determine whether the data were normal distributed.

Littles test of missing completely at random was conducted to determine whether our data was missing completely at random (MCAR) (Li, 2013). Missing data was dealt adressed multiple imputation (MI), 20 imputations with 10 iterations each were performed using the package mice (v3.11.0; van Buuren & Groothuis-Oudshoorn, 2011).

A composite cognitive-motor score (CM-score) was made to predict cognitive abilities, with higher scores predicting better once. In order to weigh all six motor-cognitive subtests equally, the two scores of RTI and PAL were Z-scored and averaged, respectively, to create separate subtest mean scores. PAL total errors (adjusted) were reversed to create the PAL mean score. The CM-score was created using the averaged Z-scores of the following variables: sum scores of the SB5 matrix and verbal subtests, 9-HPT-score (reversed), RTI mean (reversed), SSP Forward Span Reached, and PAL mean.

The biomarker composite in this thesis consisted of anti-gliadin IgA and anti-gliadin IgG as the other biomarkers were not available. Three different biomarker composites were created due to the expected non-normal distribution of the biological measures: the first by averaging the Z-scores of the biomarkers, the second by transforming the biomarkers into ranked scores and then averaging them, and the third by logarithmically transforming the biomarkers before Z-scoring and averaging. The three versions of the biomarker composite and the CM-score were analyzed for normality both visually with histograms and Q–Q plots and with the Shapiro-Wilks test (Razali & Yap, 2011) using the packages dplyr (v0.7.8; Wickham et al., 2020) and ggpubr (v0.4.0; Kassambara, 2020). The results from Shapiro-Wilks and the plots could not be pooled, so all 20 imputations were analyzed separately.

All the scales from the study were examined for internal validity with Cronbach's Alpha using the package psych (v2.0.8; Revelle, 2020). The alpha score was calculated and then averaged across all imputations. CFA was used to investigate the relationship between the observed variables and the underlying latent constructs and was performed using the package lavaan (v0.6-7; Rosseel, 2012). The chi-square value, an index to describe incremental fit (Tucker–Lewis index), and a residual-based measure (root mean square error of approximation) were used to evaluate the model (Jackson et al., 2009). The modification of the GSRS made some items potentially unobservable (Items 1, 2, 3, 4, 5, and 7, see Appendix D). While all items were used in the main analyses, the potentially unobservable items were excluded in an additional CFA to investigate their influence on the GSRS-score.

2.6.2 Statistical analyses

The distribution of residuals in the planned linear models was checked for each of the three potential biomarker composites, using the Shapiro-Wilks test and histograms from the R-package car (v3.0-8; Fox & Weisberg, 2019). This indicated that the ranked transformed biomarker composite had the best fit and was thus selected for the statistical analyses. Combined with GSRS, this meant the study had two measures of NCGS and the following five measures of psychological functioning: the CM-score, the BPM problem score, the I/D-Young Children score, the KIDSCREEN-10 total score, the I/D-YC epistemic curiosity score, and the PSI-4-SF total stress scale.

The relationship between key biological and psychological measures and known confounding variables (age, gender, and parents' level of education) was investigated using Pearson's product-moment correlation through the r package miceadds (v3.10-28; Robitzsch & Grund, 2020). Both Pearson's product-moment correlation and Spearman's rank correlation were calculated on the imputed data to investigate the relationship between measures of psychological functioning and symptoms of NCGS. These correlations were partial and controlled for the three confounding variables. Identical partial correlation analyses were also done on the seven participants with complete anti-gliadin IgA and anti-gliadin IgG data as a sensitivity analysis.

The intended multivariate analysis technique was structural equation modeling, using the R package lavaan (v0.6-7; Rosseel, 2012). This approach did not work on the current data, likely due to the low sample size (Wolf et al., 2013). Linear regression was therefore selected to model the relationship between NCGS and psychological functioning on the multiply imputed data, using the package mice (v3.11.0; van Buuren & Groothuis-Oudshoorn, 2011). Five linear models were created with GSRS and the biomarker composite as predictor variables. Each model used one of the five measures of psychological functioning as the outcome variable (CM-score, BPM, I/D-YC, KIDSCREEN-10 and PSI-4-SF). All linear models included age, gender, and parents' level of education as covariates to control for their effect. To remove the effects of the covariates on the r2, separate linear models were created to estimate their r2 on each facet of psychological functioning (see Table H1, Appendix H). The covariate r2 was then subtracted from the main analyses to calculate the r2 of the NCGS measures. The composite scores from GSRS, BPM, PSI, KIDSCREEN, and I/D-YC were Z-scored, as standardized beta coefficients cannot be pooled across imputed datasets because there is no available statistical method to do so (van Ginkel, 2020).

As it is not possible to run regression diagnostics on pooled estimates from the imputed datasets, the following diagnostics was checked on each of the 20 imputed datasets using the package car (v3.0-8; Fox & Weisberg, 2019). The linear relationships between predictor and outcome variables in the linear models were checked using partial residual plots, normal distribution of residuals using the Shapiro-Wilks test and histograms, and multicollinearity using the variance influence factor. Homoscedasticity was analyzed using the White test from the R package skedastic (v1.0.1; Farrar, 2020).

Mediation analysis was performed using a structural equation model in R with the package lavaan (v0.6-7; Rosseel, 2012). The analysis was modelled with GSRS and the biomarker composite as predictor variables, the CM-score as the outcome variable, and the I/D-YC epistemic curiosity score as the mediator, while controlling for age, gender and parental education. The Monte Carlo Method for Assessing Mediation (Selig, 2008) was used with the package MASS (v7.3-53; Venables & Ripley, 2002) to test the significance of the indirect effect. For the simulation at 95% confidence interval 20,000 repetitions were used. The plan was to use structural equation modeling to infer a latent NCGS-variable using the biomarker composite and GSRS and then run the mediation analysis. This was not possible as lavaan was unable to create latent variables based on our current data. Instead, a mediation model with two paths was used and tested the effect of biomarker composite and GSRS separately. The kappa-squared method (κ 2) was used to calculate the mediation effect sizes (Preacher & Kelley, 2011). The calculations were done using an online calculator (Rothmann, 2011).

3. Results

3.1 Preliminary analyses

3.1.1 Distribution and missing data

The frequencies and percentages of demographic variables are presented in Table 1.

Table 1: *Descriptive statistics of demographic variables*

Variables	Frequency	Percent
Age [a] *(x̄:8.5) SD (1.88)*		
• 5-7	9	43%
• 8-9	8	38%
• 10-11	4	19%
Diet		
Participants on gluten-free diet	4	19%
Participants not on diet	17	81%
Gender		
Female	13	61.9%
Male	8	38.1%
Parental education		
Professional degree (Fagskole) or lower	6	14.3 %
University or college, undergraduate degree (up to four years)	17	40.5%
University or college, graduate degree (more than four years)	16	38.1%
Unknown [b]	3	7.1%

Note. N = 21. High school or lower= primary school, high school or professional degree (Fagskole)

[a] In years, [b] Three questioners answered with "I do not know" when asked for the father's degree.

The descriptive statistics of the test battery, questionnaire, and biomarker composite are presented in Table 2. The children had an average IQ of 51.95. Six out of seven participants had anti-gliadin IgG scores above the upper normal limit (50 AU/ml). No participants reached anti-gliadin IgA scores above the upper normal limit (15 AU/ml), but two participants were in the range of the border area (8.0-15.0 AU/ml).

Table 2: *Descriptive statistics of the test battery, questionnaire, and biomarker composite*

	N	$\bar{x}$	*SD*	*Min-max*
SB5				
Stanford Binet 5 Abbreviated IQ	21	52.0	8.4	47-79
Sum score from Vocabulary subtest	21	14.5	3.4	8-22
Sum score from Object Series/Matrices	21	7.4	2.0	4-12
9-HTP-score	21	54.6	16.2	30.0-88.0
CANTAB				
RTI Median Five-Choice Movement Time	15	456.9	156.0	262-677
RTI Median Five-Choice Reaction Time	15	743.5	196.5	391-1043
SSP Forward Span Reached	19	2.5	0.7	2-4
PAL First Attempt Memory Score	19	2.6	2.7	0-8
PAL Total Errors (Adjusted)	19	59.6	9.0	41-69
Questionnaires				
KIDSCREEN-10	21	3.7	0.6	2.73-4.55
Parenting Stress Index Fourth Edition Short Form	21	3.8	0.5	2.64-4.53
Brief Problem Monitor	21	1.6	0.2	1.26-2.05
I/D-Young Children	21	2.4	0.5	1.6-3.2
Gastrointestinal Symptom Rating Scale	21	1.8	0.7	1.00-3.20
Biomarker composite				
Anti-gliadin IgA	7	5.356	5.220	1.71-14.63
Anti-gliadin IgG	7	81.213	35.592	23.64-134.07

Note. RTI = reaction time; SSP = spatial span; PAL = paired associates learning. The Stanford Binet 5 Abbreviated IQ is normed; all other variables use raw scores.

The data has 6.93% missing values from all raw scores used in the statistical analysis. Little's test was not significant, indicating that our missing data is missing completely at random. Two outliers were detected and winsorized: one in PAL Total Errors (Adjusted) and one in RTI Median Five-Choice Movement Time. Seven (33%) participants hadthe minimum PAL First Attempt Memory Score of zero, and 11 (52%) had the minimum SSP Forward Span Reached score of two, indicating floor effects in these two subtests.

Two of the questionnaires had significant Shapiro-Wilk test results and skewed plots, suggesting that GSRS and BPM are unlikely to have been created by a normal distribution.

Due to missing data, the CM-score and biomarker composite were checked for normality on each of the 20 imputations. The CM-score had no significant Shapiro-Wilks results, indicating a normal distribution. The ranked biomarker composite had 1/20 significant Shapiro-Wilks results. This, combined with the assessment of Q-Q-plots, indicates a reasonably good normal distribution for the rank transformed biomarker composite.

3.1.2 Cronbach's alpha and confirmatory factor analysis

Internal reliability of scales was checked using Cronbach's alpha. As Table 3 shows, all scales, except the biomarker composite showed strong internal consistency ($\alpha > 0.70$), with PSI-4-SF showing excellent consistency ($\alpha = 0.90$-0.95).

Table 3: *Standardized Cronbach's alpha of scales and confirmatory factor analysis model fit*

		Confirmatory factor analysis			
	α [a]	df	χ^2	RMSEA	TLI
Biomarker composite [b]	.52	NA	NA	NA	NA
Gastrointestinal Symptom Rating Scale	.82	90	154.50**	.189	.705
CM-score	.79	9	8.31	.00	1
Brief Problem Monitor	.72	NA	NA	NA	NA
KIDSCREEN-10	.84	44	62.06*	.14	.92
Parenting Stress Index 4th Edition Short Form	.94	NA	NA	NA	NA
I/D-Young Children	.85	35	86.35**	.271	.932

Note. All numbers are standardized. NA= Not able to run/no data; RMSEA = Root mean square error of approximation; TLI = Tucker–Lewis index

[a] Mean Cronbach's alpha across all 20 imputations. [b] Ranked transformed

* $p < .05$. ** $p < .01$.

CFA was used to investigate the relationship between our observed variables and the underlying latent constructs made. KIDSCREEN-10, I/D-YC and GSRS had significant chi-square results, suggesting bad model fit. The CM-score reached an accepted model fit level on the root mean square error of approximation (less than .06) and the Tucker–Lewis index (higher than .95), suggesting that the CM-score had good model fit (Jackson et al., 2009). No other scales reached acceptable levels. Table 3 shows the CFA estimation of model fits. The statistical software was unable to compute the CFA for BPM, PSI-4-SF, and biomarker composite. Table H2 in Appendix H shows the available factor loadings for novel composites. The standardized factor loadings of the items in the CM-score varied from .57 to .67.

3.2 Statistical analyses

3.2.1 Correlations

The Pearson Product-Moment correlations between the control variables age, gender, and parent's level of education and measures of NCGS and psychological functioning can be found in Table H3 in Appendix H. The only significant correlation was between gender and CM-score (r = .45, p = .042).

Spearman's p and Pearson's r between key psychological and biological measures are presented in Table 4. The CM-score correlated most strongly with the biomarker composite (r = -.46; ρ = -.34) but had a low correlation with GSRS in an unexpected direction (r = .13; ρ = .09). Both GSRS and the biomarker composite had generally low and not significant correlations with the other measures of psychological functioning, with varying directions of effects. Some significant intercorrelation between the questionnaire measures of psychological functioning can be noted, both in expected (BPM with KIDSCREEN and BPM with I/D-YC) and unexpected (KIDSCREEN with PSI-4-SF) directions.

A sensitivity analysis with the same procedure was performed on the seven participants with biological data, and can be found Table H4 in Appendix H; it shows notably higher correlations between the biological and psychometric measures. All the relationships of the biomarker composite had the expected direction of correlations in the sensitivity analysis, and the correlations with KIDSCREEN-10 (r = -.93, p = .042) and PSI-4-SF (r = -.94, p = .04) were significant.

Table 4: *Pearson product moment correlation coefficients and Spearman's rank correlation coefficient between measures of NCGS and psychological functioning based on multiply imputed data.*

	1	2	3	4	5	6	7	8	9
1. Biomarker composite[a]	-	.79**	.81**	-.03	-.34	-.11	.09	.08	-.07
2. Anti-gliadin IgA[a]	.82**	-	.33	-.09	-.29	.00	.10	.05	-.08
3. Anti-gliadin IgG[a]	.81**	.31	-	.06	-.25	-.20	.05	.08	-.01
4. Gastrointestinal symptom rating scale[b]	-.12	-.17	.00	-	.09	-.21	.01	.28	.17
5. CM-score[bc]	-.46	-.41	-.34	.13	-	-.11	-.04	-.13	.19
6. Brief Problem Monitor [bd]	-.08	-.01	-.13	-.11	-.07	-	-.61**	-.55	-.48*
7. KIDSCREEN-10[bc]	.18	.16	.12	-.10	-.08	-.57**	-	.69**	.27
8. Parenting Stress Index 4 Short form[bc]	.12	.06	.13	.38	-.05	-.38	.58**	-	.38
9. I/D-Young Children[bc]	-.14	-.16	-.06	.25	.16	-.51*	.27	.34	-

Note. N = 21. Spearman's ρ correlations are in the top right section of the matrix (grey). Pearson's *r* correlations are in the bottom left section (white). Age, gender, and parents' level of education were included as partial correlations when calculating all correlations.

[a] Ranked version of variables used in both correlation analyses.

[b] Ranked version of variables used only when calculating Spearman's ρ.

[c] Higher score indicates better psychological functioning

[d] Lower score indicates better psychological functioning

* p < .05. ** p <.01.

3.2.2 Linear regressions

Regression diagnostics were conducted on all models of the relationship between facets of psychological functioning and NCGS in each of the 20 imputations. The only model with a significant Shapiro-Wilks test, which implies the non-normal distribution of residuals was the model of NCGS and PSI-4-SF (Model 4) on 11/20 imputations. Q–Q plots and histograms of seven randomly selected imputations supported the results of the Shapiro-Wilks tests. The partial residual plots on the participants with complete data showed close to completely linear relationships between predictor and outcome variables for all models. These relationships stayed reasonably linear on the seven randomly selected imputations. None of the models had a variance inflation factor over 4 signifying a problem with multicollinearity. The White test was insignificant for all models and imputations, supporting homoscedasticity for the models. In summary, there were no indications of any models violating the assumptions of linear modeling, except the model of NCGS and PSI-4-SF (Model 4).

Table 5 summarizes the linear modelling of the relationship between the measures of psychological functioning and NCGS when controlled for the known potential confounders age, gender, and parents' level of education. None of the models had any significant results, and the most significant relationships identified were between the biomarker composite and CM-score in the expected direction ($\beta = -0.35$, $p = .164$) and between GSRS and PSI-4-SF in the opposite direction of expected ($\beta = 0.39$, $p = .135$). This was also reflected in model 1 and model 4 having the highest coefficient of determination, with an Δr^2 of respectively .18 and .17, respectively. The same unexpected direction of effects found in the correlation analyses (Table 4) can be seen in the linear models, as well.

Table 5: *Summary of the linear models of the relationship between NCGS, as operationalized through both GSRS and the biomarker composite, and measures of psychological functioning on the multiply imputed data.*

		95% CI					
	β	*LL*	*UL*	*SE*	*df*	*p*	Model Δr^2
Model 1: CM-score [a]							.18
Intercept	-0.25	-0.97	0.46	0.32	10.24	.452	
Biomarker Composite	-0.35	-0.88	0.18	0.23	7.82	.164	
GSRS	0.06	-0.32	0.43	0.17	11.81	.754	
Model 2: Brief Problem Monitor [b]							.06
Intercept	1.01	-1.85	3.87	1.29	10.51	.452	
Biomarker Composite	-0.10	-1.10	0.90	0.41	6.36	.813	
GSRS	-0.10	-0.70	0.49	0.28	12.39	.714	
Model 3: KIDSCREEN-10 [a]							.07
Intercept	0.06	-1.04	1.17	0.50	11.20	.904	
Biomarker composite	0.19	-0.77	1.15	0.40	6.67	.648	
GSRS	-0.10	-0.69	0.49	0.27	12.57	.725	
Model 4: Parenting Stress Index 4 Short form [a]							.17
Intercept	-0.74	-1.69	0.22	0.44	12.20	.119	
Biomarker composite	0.18	-0.66	1.03	0.36	6.94	.623	
GSRS	0.39	-0.14	0.92	0.24	12.72	.135	
Model 5: I/D-Young Children [a]							.12
Intercept	0.05	-1.06	1.16	0.50	10.83	.919	
Biomarker composite	-0.13	-1.17	0.91	0.42	5.80	.769	
GSRS	0.23	-0.38	0.83	0.28	11.69	.431	

Note. N = 21. CI = confidence interval; *LL* = lower limit; *UL* = upper limit; β = standardized estimates created by Z-scoring predictor and outcome variables; GSRS = gastrointestinal symptom rating scale. All models included age, gender, and parents' level of education as covariates, which are excluded from this summary. The r^2 from models with the three covariates are subtracted from each model's Δr^2.

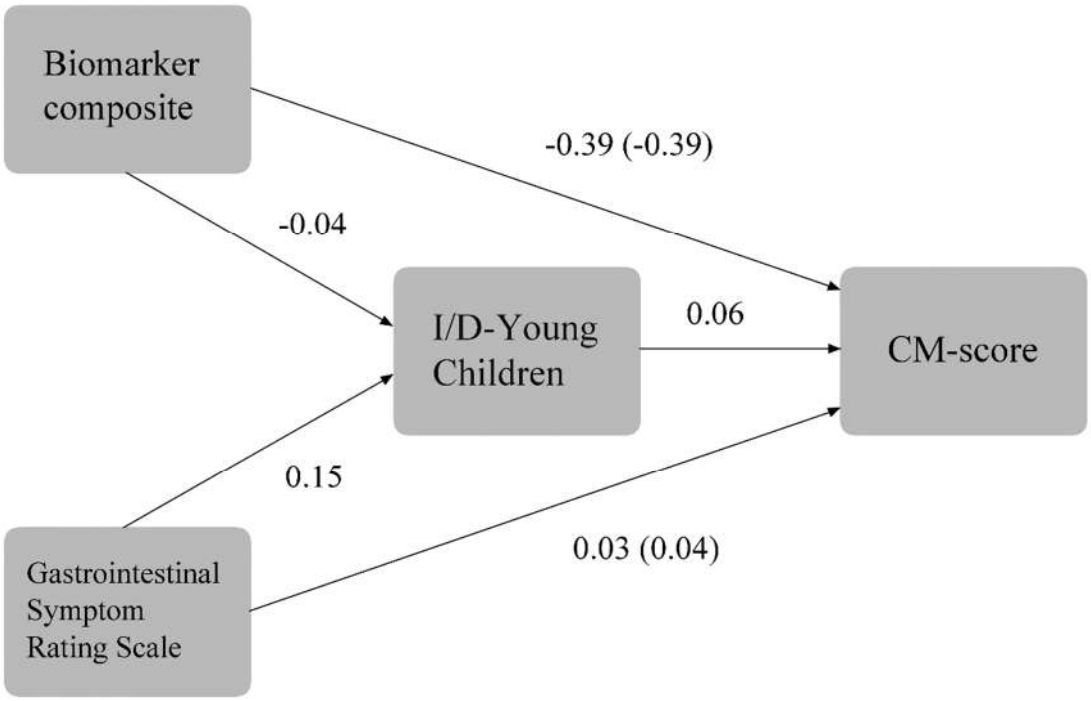
[a] Higher score indicates better psychological functioning

[b] Lower score indicates better psychological functioning

3.2.3 Mediation analysis

As Figure 1 illustrates, the standardized path coefficients between the biomarker composite, GSRS, and I/D-YC as predictors and the CM-score as outcome variable were non-significant. The standardized path coefficients between the biomarker composite and GSRS as predictors and I/D-YC as outcome variable were also not significant. GSRS had an unexpected positive relationship with CM-score and I/D-YC. Using the Monte Carlo method for assessing mediation, the 95% confidence intervals were estimated for biomarker composite (-0.01 to 0.01) and GSRS (-0.11 to 0.17). The null hypotheses could not be rejected, as the hypothesized values of a*b did not fall outside the confidence intervals, indicating that no mediations were present. The kappa squared of the indirect effect of the biomarker composite was κ^2=0.003 and for GSRS κ^2=0.009, indicating insubstantial (<0.01) effect sizes (Preacher & Kelley, 2011).

Figure 1: *Mediation analysis of the effect of the biomarker composite and GSRS on CM-score as mediated by I/D-YC*



Note. The standardized path coefficient between GSRS/biomarker composite and CM-score, controlled for I/D-Young Children, is in parentheses. The three control variables used: age, gender, and parental education, are left out of the model for clarity. None of the paths were significant ($p < .05$.)

4. Discussion

Due to the COVID-19 pandemic this thesis is based on data with considerably fewer subjects than the power analysis estimated to be necessary to avoid type I and type II errors. . As the lack of participants increases p-values and thus risk of type II error, this discussion focuses on the effect estimates, Δr^2 and correlations, found in the study. This is in line with recent statistical literature advocating a greater focus on effect sizes in research (Field, 2013; Fritz et al., 2012; Sullivan & Feinn, 2012). The most important predictor of NCGS in this study is the experimental blood values. These analyses were severely limited in this thesis, as we received only seven of 21 participants' complete blood values and two experimental measures of the intended seven. The decision was made to use multiple imputation to impute the lacking biological measures, even though we are fully aware that the 67% missing data for anti-gliadin IgA and IgG further limits the validity of these measures. We have decided to downplay this lacking validity in the following discussion for two reasons: first, to be able better to show the possible ways to interpret the results, and second, to keep the discussion as close to the future article as possible.

4.1 Hypotheses

4.1.1 Primary hypothesis

The primary hypothesis of this thesis was as follows:

"There is a negative relationship between NCGS and psychological functioning. Psychological functioning is defined in this study as: cognitive functioning, quality of life, and behavioral signs of anxiety, sadness, and anger."

The results from the correlations in Table 4 and linear models in Table 5, which both used multiply imputed data, partially support the primary hypothesis. Six medium or larger correlations were found between measures of NCGS and psychological functioning, using the effect size descriptions of Funder and Ozer (2019; very small ≥ .05, small ≥ .10, medium ≥ .20, large ≥ .30, very large ≥ .40). However, none were significant, and the direction of effects varied greatly, with some contradicting the hypothesis by implying that NCGS has a positive relationship with psychological functioning

The analyses found a contradictory relationship between NCGS and the CM-score. On the one hand, the biomarker composite correlated negatively with the CM-score (r = -.46; ρ = -.34), implying that NCGS has a negative relationship with cognitive-motor functioning. On the other hand, the correlation with GSRS is positive (r = .13; ρ = .09), implying that more gastrointestinal symptoms have a positive relationship with cognitive-motor functioning. While the relationships are contradictory, the linear model predicting CM-score

(Model 1) still had the largest Δr^2 of the models ($\Delta r^2 = .18$), likely due to the very large correlation coefficient of the biomarker composite. Thus, while none of the estimates were significant, the results might imply an overall negative relationship between NCGS and the CM-score.

Studies on patients with CD indicating that gluten has an impact on cognitive functioning support this potential negative effect of NCGS on the CM-score (Casella et al., 2012; Lichtwark et al., 2014; Pennisi et al., 2017). Some caution is warranted when comparing these findings to NCGS given the different natures of the disorders, as the differences in serological, histological, and genetical markers make clear. On the other hand, both CD and NCGS have extra-intestinal symptoms (Losurdo et al., 2018), and similar gut-brain pathways have been suggested for them (Bressan & Kramer, 2016; Daulatzai, 2015; Yelland, 2017), indicating that studies on one disorder may be relevant for the other.

The study of Nygaard et al. (2001) found significant relationships between IgA and IgG reactivity to both gliadin and gluten with psychological functioning. These findings are of special interest in the context of this study as they found significant correlations between anti-gliadin IgA and IgG and SB5-subtests ($r = .27$ and $r = .29$ respectively) in children with DS, but with a larger sample size (N = 51). Considering the even higher correlations with the biomarker composite in the present study, it seems plausible that the current lack of significant results is due to the low sample size. However, this high correlation might be overestimated due to the small sample size, as well, considering how effect sizes of this order in the context of psychology often imply an overestimation (Funder & Ozer, 2019). Yelland (2017) in a summary of the existing literature on the relationship between cognitive functioning and gluten intolerance, found that it was inconclusive, and the few studies available often have a limited number of participants and other methodological problems.

The present findings partially imply a positive relationship between NCGS and the three parental reported measures of psychological functioning (BPM, Kidscreen-10, and PSI-4-SF). The implied direction of effects is contrary to the current hypothesis; however, none of the estimates are significant. The positive correlations of the biomarker composite ($r = -.08$; $\rho = -.11$) and GSRS ($r = -.11$; $\rho = -.21$) with BPM both imply that NCGS leads to fewer behavioral and emotional problems, with Model 2 finding an Δr^2 of .06. The existing literature using the questionnaire BPM to investigate parental reports of behavioral and emotional problems in children with CD is inconclusive. L. B. Smith et al. (2017) have found differences when the children were 3.5 years old, but not at 4.5 years. Mazzone et al. (2011) have found significant differences in an older sample (7.41+/-4.08 years). The results of

Peters et al. (2014) imply that gluten might induce feelings of depression in NCGS patients, and a review found depression to be more common in adult patients with CD than in healthy controls (D. F. Smith & Gerdes, 2012).

The contradictory relationships of the biomarker composite (r = .18; ρ = .09) and GSRS (r = -.10; ρ = .01) with KIDSCREEN-10 give no clear implications of the relationship between NCGS and HRQoL. While we are not aware of any studies that imply a positive effect of gluten related disorders on HRQoL, it is uncertain what relationship should be expected. Two studies using KIDSCREEN-52 have found no effect of CD on HRQoL (Barrio et al., 2018; Myléus et al., 2014). Other studies imply lower QoL in patients with CD compared to the general population, and an increase in QoL on a gluten-free diet (Ludvigsson et al., 2014). This could support the very low effect size found in Model 3 (Δr^2 = .07).

The relationship of both the biomarker composite (r = .12; ρ = .08) and GSRS (r = .38; ρ = .28) with PSI-4-SF implies that more NCGS leads to less parenting stress, and Model 4 also had the second largest identified coefficient of determination (Δr^2 = .17). This contradicts the findings of Epifanio et al. (2013), who found higher parenting stress in parents of children with CD compared to controls. It is important to note that Model 4 failed the Shapiro-Wilks test on 11 of20 imputations and had a skewed distribution of residuals on most of the histograms; however, the non-parametric Spearman's ρ found the same direction of effects.

Interestingly, the biomarker composite had the expected relationship with the three parental reported measures of psychological functioning in the sensitivity analysis of the seven participants with biomarker values (Table H4 in Appendix H). This might indicate that that the imputation influences the relationships of the biomarker composite in the main analyses. However, despite GSRS having no imputed data, its relationships with BPM and PSI-4-SF also changed direction to expected in the sensitivity analysis sample. This highlights the lacking generalizability of the present results due to sample size and the proportion of imputed key variables.

The relationship between the measures of NCGS and I/D-YC showed the same contradictory pattern as between NCGS and the CM-score. I/D-YC had a negative relationship with the biomarker composite (r = -.14; ρ = -.07) and a positive relationship with GSRS (r = .25; ρ = .17), with a Δr^2 of .12. Although none of these estimates were significant, this indicates that more NCGS biomarkers decrease curiosity, while more experienced NCGS symptoms increase curiosity. As far as we are aware, the study by Nygaard et al. (2001) has examined curiosity in people with CD and NCGS. They have found strong correlations

between IgA and IgG antibody response to gluten and gliadin and the novelty preference (r = -.44 to -.51, $p \leq .05$). These results were not replicated between I/D-YC and the biomarker composite in this study, even though the direction was the same. One possible explanation for the dissimilar results is that the Fagan test and I/D-YC measures different aspects of curiosity. Whereas I/D-YC is a parent report questionnaire measuring complex behaviors, the Fagan test directly measures novelty preference.

All the relationships described through the models rests upon the operationalization of NCGS. This disorder can only be diagnosed through a double-blind placebo control challenge (Ludvigsson et al., 2013) which would require an experimental design outside the scope of this study. Instead, NCGS was defined through a combination of several criteria. The first was the exclusion of participants with a wheat allergy and CD. The second was through the presence of gastrointestinal symptoms as reported through GSRS, and the third was through the presence of the seven (two in the present thesis) biomarkers that Uhde et al. (2016) have found to be significantly different in the NCGS group compared to both the CD group and the control group.

A common theme in the results was the unexpected relationships between GSRS and the facets of psychological functioning. The relationships were generally weak, and several of the relationships found had a direction that was opposite from what was theoretically expected. A possible explanation is that the current adaption of GSRS lacks specificity as a measure of NCGS. Some participants might have gastrointestinal symptoms caused by other disorders without the same extra-intestinal symptoms as NCGS, such as IBS or other gastrointestinal disorders connected to DS (Ravel et al., 2020). If so, the suggested gut-brain pathways might not be involved, and the biological basis for the effect on psychological functioning disappears despite symptoms reported through GSRS. Additionally, if the prevalence of NCGS in DS is similar to that of CD (6%), then it is likely that very few or none of the participants in the current sample has NCGS. This low specificity could potentially undermine GSRS's ability to predict the influence of NCGS on psychological functioning, leading to type I errors. However, this still does not explain the directional issue. Possible explanations are the small sample size, measurement error due to methodological issues with GSRS as used in the study or unforeseen effects caused by an interaction with DS.

Another limitation of the current operationalization of NCGS is the scarcity of available biological measures. The lack of participants with complete blood values and the loss of five suggested biomarkers limits the biomarker composites ability to predict NCGS.

The multiple imputation of the biomarker composite seems to have influenced the modeled relationship between NCGS and psychological functioning. The sensitivity analysis of the relationship with BPM shows that this influence could be considerable.

Considering the limited number of biomarkers available and the biomarkers' high proportion imputed data, the biomarker composite's current validity in measuring NCGS is uncertain. The same can be said of GSRS with its limited specificity towards NCGS, in addition to being an indirect parent report measure of gastrointestinal symptoms (see section 4.2.2 Questionnaires). Combining these two types of measures was intended to help strengthen the thesis's operationalization of NCGS, but the low correlation between the measures and their contradictory relationship with measures of psychological functioning complicates this. As some research suggests anti-gliadin IgG to be the most prevalent positive antibodies in the NCGS population (Infantino et al., 2015), and GSRS is limited by being a more indirect measure, the biomarker composite may be a more reliable estimate of NCGS than GSRS.

Although the current results find ambiguous relationships between NCGS and facets of psychological functioning, the implicated negative relationship between the biomarker composite and cognitive-motor abilities might be partially explained by the suggested gut-brain pathways. The low correlations with positive direction between the CM-score and GSRS (r = .13; ρ = .09) imply that the effect of NCGS on the CM-score can be explained by symptomatic discomfort only to a limited degree, allowing for biological mechanisms. These gut-brain pathways are further supported by the high presence of NCGS associated anti-gliadin IgG in the sample (6 of 7 over upper normal levels). The high presence of gluten antibodies in the blood implies increased immune reactivity, which could have possible extra-intestinal effects. Thus, the current findings offer some support for potential gut-brain pathways.

In summary, some support was found for a negative relationship between NCGS and facets of psychological functioning. The results imply a negative relationship between NCGS and the CM-score. The relationship between CM-score and the biomarker composite was considerably stronger than with GSRS, implying that biological mechanisms might be involved. On the other hand, the findings from the other facets of psychological functioning are inconclusive. As the results are incoherent and contradictory, it is too early to say if they reflect lacking relationships, or whether they are the results of methodological issues.

4.1.2 Secondary hypothesis

The secondary hypothesis of this thesis was as follows:

"The relationship between NCGS and cognitive-motor functioning will be partially mediated by curiosity."

The results from the mediation analysis presented in Figure 1 do not support this hypothesis. The effect sizes of the indirect effects between the two measures of NCGS and CM-score when controlled for curiosity were insubstantial ($\kappa^2 = 0.003$ for the biomarker path and $\kappa^2 = 0.009$ for the GSRS path). Neither the indirect effects nor any of the path coefficients from Figure 1 were significant. Overall, this indicates that no mediation effect is present in the current data.

It was hypothesized that the strong correlations found between Fagan Novelty Preference and anti-gliadin IgA and IgG in Nygaard et al. (2001) might reflect a mediation effect of curiosity on the effect of NCGS on cognitive abilities. The present mediation analysis offers no support for this hypothesis. The fact that the correlations between the Fagan Novelty Preference test and Stanford Binet-5 scores from Nygaard et al. (2001) are not known, makes it difficult to say whether these results should be expected. As discussed previously, the lack of comparable findings may be related to the considerably different measures of curiosity.

The previously discussed methodological problems of small sample size, data limitations in the biomarker composite and the unexpected positive relationships between GSRS and several psychological measures might explain why no mediation effect was found. There is also a possible theoretical explanation for the present results. Curiosity is generally considered to be an important motivator for learning and cognitive development, however relatively little research has investigated the relationship between curiosity and cognitive abilities (Kidd & Hayden, 2015).

The relationship between curiosity and cognitive-motor ability might not be a direct effect, which could explain why no mediation effect is present. The low, non-significant, correlations ($r = .16$) found between curiosity and CM-score indicate that this might be the case. This explanation is also supported by a correlational study of preschoolers that found no significant effect between curiosity and intelligence (Henderson & Wilson, 1991). The study's authors argued that curiosity might only predict changes in intelligence, as the relationship is not concurrent. Curiosity might affect the CM-score as a factor that motivates children to seek more experiences, thus influencing their cognitive and motor ability. Thus, two children with the same CM-score but differing in levels of curiosity would differ in CM-score at a later age. This kind of relationship would be difficult to discover without measuring cognitive-motor abilities and curiosity over time, which would make it possible to see if

curiosity could predict changes in cognitive-motor abilities. This has been done in a longitudinal study (Muentener et al., 2018) that investigated the stability of exploratory play in infancy and how it related to cognitive development in early childhood. The study found a significant positive correlation ($r = 0.37$, $p = .028$) of medium effect size between exploratory play and higher IQ at later testing. Another longitudinal study reported many years ago by Kagan et al. (1958) also concluded that curious children seem more likely to show positive changes in IQ over time.

In summary no support was found for the secondary hypothesis. This might be caused by an actual lack of mediation effect, low sample size in the present study, or a limited operationalization of the relationship between cognitive-motor abilities and curiosity

4.2 Methodological considerations

4.2.1 Test battery

The SB5 ABIQ is a well validated and reliable measure, and several factors indicate that it was well-adjusted for the study's population: No floor or ceiling effects were found and there were no missing data from the two SB5 subtests. Another benefit of the SB5-ABIQ is the inclusion of an IQ measure, which makes it possible to compare this study's results with others. The Norwegian translation of the verbal subtest might have had a small effect on the study's IQ estimates, as some words changed in difficulty when translated. However, this should not affect the main analyses since the scores are compared between subjects and not with a normative group.

Several experiences that occurred during the administration of the CANTAB tasks suggest that some issues affect its reliability and validity. Participants' inability to complete all the subtests affect the CANTAB results from this study. This was especially evident for the RTI subtest, which could not be completed in six cases. This was seen in the pilot study as well, and reward procedures were implemented to increase motivation. However, it turned out to be insufficient.

As the test administrators subjectively assessed disappointment after starting the tasks in several of the children, which could stem from unfulfilled expectations. An iPad is often used for games and other entertainment, the repetitive and visually unstimulating tasks of the CANTAB were likely not what they expected. Some participants also pressed the "Home"-button when they did not want to continue, causing the subtest to reset. It should also be noted that the visually unstimulating tasks of the CANTAB were also a strength, as cultural bias is removed, and the monotonous tasks were useful to test sustained attention.

The lack of compliance could be an effect of age. The CANTAB tasks are intended for children as young as 4, but many of the younger participants in this study had difficulties understanding and completing some of the tasks. One potential cause is the abstract nature of the tasks, which could make them confusing and difficult to understand. Many of the participants also struggled with the attention, motor, and coordination skills the CANTAB tasks require. It is possible that this is especially difficult for young children with DS, considering that many have delayed motor development (Ferreira-Vasques & Lamônica, 2015). The floor effects found in two CANTAB subtests combined with the fact that many participants struggled to complete all the tasks, indicate that the CANTAB might be too difficult for the study's population.

It was deemed important to include a test of motor skills because of a previous study showing that motor skills correlated negatively with possible biological markers of gluten sensitivity (Nygaard et al., 2001). A potential limitation of 9-HPT is that it measures fine motor skills and people with DS have motor difficulties and often struggle with finger dexterity (Ferreira-Vasques & Lamônica, 2015). Studies indicating that 9-HPT can effectively discriminate between different levels of fine motor skill difficulties within the same population (Proud et al., 2020), in combination with a lack of indications of floor effects, suggest that this was not an issue.

The subtests from SB5, CANTAB, and 9-HPT were combined into the CM-score, which was created to obtain a more reliable measure of the participants' cognitive and motor abilities. The subtests stem from three different psychometric batteries, but studies demonstrate that the same g-factor is measured across different intelligence batteries (Reynolds et al., 2013). Although tests of motor abilities are not usually added into a composite score together with cognitive abilities, there are studies that find a strong relationship between cognitive and fine motor skills (van der Fels et al., 2015) indicating that the two could have increased statistical power if combined.

This is supported by the strong internal consistency (α =0.79; Table 3) of the CM-score. The CFA analysis also suggests good model fit, indicating that that model fit the data well. However, model fit analyses must be interpreted carefully as they are unreliable when there is a high number of parameters relative to the sample size (Ory & Mokhtarian, 2009). The factor loadings found (ranging from .57 to .67; Table H2 in Appendix H) show similar loadings to other tests of cognitive abilities, indicating good construct validity of cognitive abilities (Floyd et al., 2009). The reliability and validity of the CM-score was important to

determine, given that the test battery was created for this study, and none of the translated test instructions were previously validated.

Testing young children with DS is generally a challenge, and combined with the children's variable motivation (Gilmore & Cuskelly, 2009; J. Wishart, 2001) this could threaten the reliability of the measures. Subjective assessments of the test situation indicate that many children did not achieve their optimal level of function on several of the subtests. However, this measurement error might still reflect differences in the participants psychological functioning, limiting how much it affects the potential conclusions regarding the correlations found.

Another consideration is how the method used to control for age might affect the validity and reliability of the CM-score. The method assumes a linear relationship between the CM-score and age, this is likely not the case considering the large individual differences in development within the population (Folkehelseinstituttet, 2015). The CM-score could have used the already normed IQ scores of SB5-ABIQ-SF instead of raw scores to control for age. A potential problem with using IQ is that the standardization of SB5 is adapted and normed for the general population, but children with DS do not follow the same curve as the general population (Couzens et al., 2011; J. G. Wishart, 1993). This limits the use of existing norms. Another reason is that CANTAB and 9-HTP does not have normative data available. This would have caused SB5 to be age-corrected with a different method than the 9-HTP and CANTAB, or it would lead to SB5 being age-corrected twice (first from raw scores to IQ and then age-controlling the CM-score in the analyses), creating another source of error.

A somewhat surprising finding is the relatively large significant correlation between gender and CM-score ($r = .456$, $p = .042$; Table H3 in Appendix H). Most studies have found small or non-significant effects of gender in intelligence measures (Buczyłowska et al., 2019; Sellers et al., 2002), and these studies usually have a larger sample then the current study. However, some studies have such found effects. A longitudinal study by Lynn and Kanazawa (2011) has found that the same girls, who obtained a higher average IQ than boys at the ages of 7 and 11 years, obtained a lower average IQ than boys at the age 16 years. A possible explanation of the gender effect found in this study is the slower maturation rate of boys compared to girls. This explanation is difficult to confirm, as the relationship found in this study is correlational and indicates say nothing about changes over time. In addition, the delayed development seen in children with DS might affect this relationship in unforeseen ways. As far as we know, no one has studied the effect of gender on cognitive abilities in people with DS. Another possible explanation is that the effect found is due to spurious

effects, caused by the low sample size or other methodological problems present in the current thesis.

4.2.2 Questionnaires

The nature of the subject population made it necessary to gather behavioral data using parent report forms. As many children in this population have delayed language development, self-report was not an option. Their educational situation also varies greatly, making it challenging to use teacher-report forms. For practical reasons, and to reduce potential missing data, it was decided that only one parent would complete the form, and the parents decided who would do so. Mothers could be assumed to have more insight into their children's HRQoL as, on average, they spend more time taking care of their children (Kitterød, 2012). However, a Swedish and a German study have found good agreement between parents HRQoL ratings (ICC of respectively .66–.76 and ≥.80) (Fält et al., 2018; Witt et al., 2019). Studies have typically found greater agreement for HRQoL ratings between parents and their child for observable functioning than unobservable functioning (Eiser & Morse, 2001; Rajmil et al., 2013). KIDSCREEN-10 and our modified GSRS had some problems with items requiring the parents to infer the child's experiences. In general, parent-child agreement on children's HRQoL is moderate to low, with no clear trend for parents to overestimate or underestimate their experiences (Rajmil et al., 2013; Stokes et al., 2011).

Though several questionnaires used in the analyses were abbreviated measures, they still showed good internal consistencies ($\alpha \geq .70$). This is important, as these abbreviated measures are often less validated, and as the combination of fewer items and low sample size increases the error in the study. The model fit estimates from the CFA for GSRS, KIDSCREEN-10, and I/D-YC indicated a bad construct validity for the measures, possibly caused by the low sample size (Ory & Mokhtarian, 2009). CFA could not be calculated for two measures. BPM had intercorrelations between items that were too high, likely caused by the low sample size and the 3-point Likert scale. PSI-4-SF had more items than there were subjects in the study.

BPM, KIDSCREEN-10, and PSI-4-SF are well-validated instruments with good psychometric properties. It is unlikely that the minor adjustments to BPM and KIDSCREEN influenced their validity, especially as the results are not normed. We translated the I/D-YC and PSI-4-SF, and the owners approved both back-translations. The validation of I/D-YC, although limited, is promising, and we do not consider it likely that the current unexpected findings are a consequence of its validity.

The excellent psychometric qualities of the GSRS apply only partially to the version used in this study, as it was adapted into a parent report form. Some items require parents to answer questions that are not easily observed, which may affect its validity. On the one hand, it is possible that children with more gastrointestinal symptoms are more bothered by them and make their parents more aware of those issues. On the other, the potentially unobservable items increase the influence of other characteristics of the child and parent, such as personality and communication abilities. To investigate the effect of these items, an additional CFA was performed in which they were excluded. The improved model fit estimates of this CFA might imply that these items had an impact on the construct validity. This could help explain some of the unexpected relationships of GSRS found in our main analyses. However, as the ratio of items per subject is also halved, it is possible that the low sample size is the main cause of the improved results. Thus, it was difficult to test the impact of these unobservable items with the current small sample size, though an increase in measurement error is likely.

4.2.3 Biomarker composite

To make the multitude of biomarkers more manageable in this thesis, a decision was made to create a composite score of the biomarkers connected to NCGS. Based on the promising findings of Uhde et al. (2016), it was assumed that this aggregated measure would be more reliable than the individual biomarkers. As far as we are aware, this has not been done before with potential biomarkers for NCGS. Although some studies have recently found promising results when using a biomarker composite score in predicting diagnosis and key outcomes (Basu et al., 2014; Dickerson et al., 2013; Munkholm et al., 2019), others have not (Bouman et al., 2017).

The use of an untested composite made from experimental markers is a potential limiting factor in its ability to measure NCGS. The predictive ability of each single biomarker will be the subject of another article written based on the data. The validity of the composite is further limited by the lack of available blood samples, which cause a high proportion of imputed values, and that only two of the seven intended biomarkers were available. The low internal consistency implied by the Cronbach's alpha ($\alpha = .52$) might be caused by a combination of the low number of items in the composite (Tavakol & Dennick, 2011) and the small sample size.

No participants had anti-gliadin IgA values over the cut-off, whereas six of seven did for anti-gliadin IgG. Nygaard et al. (2001) study of 55 children found nine participants with anti-gliadin IgG over normal limits and 19 participants with anti-gliadin IgG over normal

limits. This difference is peculiar considering that these participants belonged to the same clinical population. The analysis for the future article will include blood samples from patients with active untreated CD to control for measurement error in the test kits.

4.2.4 Statistical considerations

Several statistical considerations influenced the validity and reliability of the findings. An IQR of 1.5 is generally considered a mild outlier, while an IQR of 3 is considered an extreme outlier (Schwertman et al., 2004). Given the large variation in cognitive development in children with DS (Folkehelseinstituttet, 2015), using 1.5 as the cut-off would likely have been too strict, causing an overestimation of outliers. Instead, the decision was made to use in IQR of 3. Using a less strict criteria for outliers might affect the normality, as most of our variables had several outliers using the 1.5 IQR criteria.

We expected considerable missing data due to the inherent difficulties in testing young children with DS (Edgin et al., 2010; J. G. Wishart, 1993) and the COVID-19 situation. Having a statistically robust method of dealing with missing data was deemed important. The two most robust methods currently used are multiple imputation and the full information estimated maximum likelihood method, which yield similar results (Little et al., 2016). Multiple imputation was chosen because it was more compatible with the analyses of this study. Each of the imputations must be analyzed separately and then pooled according to specific rules, as averaging leads to inaccurate estimates (van Buuren, 2018). Not all statistical methods have established pooling rules, which causes some statistical limitations (van Buuren, 2018). Although it is not recommended, the Cronbach's alphas were averaged across imputations causing lower validity. The averaged estimates were still considered valid enough, as the variation between imputations was low.

As the biological variables were expected to be non-normally distributed, and the use of multiple imputation limits the available nonparametric tests, the decision was made to transform the variables based on best fit. Ranked transforming of the biomarker composite eliminates the problem of skewness because all ranks are equally distanced from each other. This also led to a loss of information, however, as the relative distance between each score is no longer present. Although some of the variables used in the main analyses had non-normal distributions, the impact was considered to be low, as the residuals of all the linear models had normal distributions, except the model with PSI-4-SF and NCGS, as previously discussed.

Both a parametric and a non-parametric correlation method were used, as they have different strengths and limitations. The advantage of using a nonparametric Spearman's rank

correlation is that it has fewer assumptions and is less affected when they are not met. The disadvantage, however, is that all variables need to be ranked, leading to loss of information. Nonparametric tests are also usually less powerful than the corresponding parametric tests when the variables are normally distributed. As most of the variables used were estimated to be normally distributed this could lead to underestimated relationships.

Regression diagnostics could not be pooled across the imputed datasets. Checking all plots on 20 datasets was considered overwhelming and could be a source of researcher bias, especially due to our limited experience with regression diagnostics. Two common solutions are checking the plots on the original, unimputed dataset or drawing a random imputation. Those solutions were deemed unreliable, and instead statistical tests were used on all imputations, while plots were checked on seven randomly selected imputations. Relying on statistical tests for regression diagnostics is often discouraged due to their inherent limitations. In some cases, this could be amended by the choice of statistical test, e.g. the more robust White test replaced the Breusch-Pagan test that can only detect linear forms heteroskedasticity (Williams, 2020). The imputations themselves might also be a strength, functioning similarly to a small bootstrapping of the statistical test.

According to Afifi et al. (2019), structural equation modeling and canonical correlations are the recommended methods for modeling the relationship between several continuous dependent and independent variables. Canonical correlations do not take the direction of the effects into consideration (Kenkel, 2006), and could not test the hypothesis. Structural equation modeling was attempted (see code in Appendix G) using the R package lavaan (v0.6-7; Rosseel, 2012). However, it did not work when latent variables were added to the models, possibly due to the low sample size. Structural equation modeling will be used in the future article.

Due to the lack of available alternatives, linear models were used. Using several outcome variables with the linear model function in the package mice led to the outcome variables being averaged, which created a composite. A composite of psychological functioning was not created, as it is defined quite broadly in this thesis, and combining the measures was deemed too reductive. Thus, the five linear models using the facets of psychological functioning were used. The use of five different models, in addition to both non-parametric and parametric correlations, might influence the validity of the findings, as using several tests on the same variables increases the risk of type I error.

Bootstrapping is the most common method used to significance test the indirect effects of mediation analysis (Kenny, 2018). To our knowledge, there is currently no

statistically sound method to pool bootstrapping estimates with multiple imputations. The Monte Carlo method is considered statistically sound and a good alternative when there is no easy way to bootstrap (Kenny, 2018), and it was used instead.

4.3 Strengths and limitations

4.3.1 Strengths

Studies indicate that children with DS have a high prevalence of NCGS (Gomes et al., 2016). By studying a group with a high proportion of NCGS the number of participants needed to draw conclusions was reduced. This minimized, for example, the possibility of false positive blood tests and the number of children who have to take a biopsy.

The present study is one of the first to examine whether there is a connection between NCGS and psychological functioning in children with DS. By using a multi-disciplinary approach combining psychology and medicine, the study can contribute to the understanding of both NCGS in general and how it affects those with DS in particular. By using recent findings regarding promising biomarkers of NCGS (Ierardi et al., 2018; Uhde et al., 2016), this study also contributes to further understanding its biomarkers and helping to develop new diagnostic criteria. As these biomarkers are experimental, the addition of a parent report form of gastrointestinal symptoms makes the operationalization of NCGS more robust.

The study uses a broad measure of cognitive functioning through seven subtest from two different batteries. As many of the children with DS struggle with delayed verbal abilities, the non-verbal cognitive tests used were essential to obtain valid estimates. Luciana and Nelson (2002) study that found no significant differences between native and nonnative English speakers also support the finding that CANTAB is a useful tool in assessing cognitive function in a population with differing language abilities.

The use of multiple imputation to address missing data is a strength, as it is considered one of the best to do this (Allison, 2003) and should considerably reduce the missing data bias in the data. All the syntaxes and scripts for the analyses were created with dummy data prior to data collection, thus reducing the risk of researcher bias.

4.3.2 Limitations

Due to COVID-19, the data collection is not yet finished. The current sample size is 21, while the power analysis estimated 70. The effects of the low sample size can be seen in the generally large confidence intervals of the effect sizes and thereby also in the lack of significant findings. This thesis is further limited by the lack of a more specific operationalization of NCGS. The data available to this thesis cannot be used to conclude whether the participants have NCGS, and the adaptation of the GSRS to a parent report along

with the lack of biomarker measures makes them less accurate in their prediction of NCGS. Currently, there is no way to know if any of the participants in the study has NCGS at all. This makes interpreting the findings difficult, and the generalizability is limited.

The generalizability of the findings may also be further limited by participant bias. One cause for such an effect could be that the parents of children with lower psychological functioning might be less inclined to enroll their children in studies, as lower psychological functioning may relate to characteristics that would make it more difficult for the child in a test situation or to take blood samples. Studies have found this effect for behavioral challenges, with Stokes et al. (2011) finding that both the children participating and their parents were more socially and cognitively competent on average than those who did not (i.e. the participants had better psychological functioning).

It is assumed that the participant selection from southeastern Norway is representative of the Norwegian population. However, it is uncertain how results would differ in other cultures, where diet and learning environments differ from those of Norway. One should also be careful about generalizing our findings to other age groups.

Even though some support was found for the primary hypothesis, one must be careful with drawing causal conclusions, as the analyses in this thesis are based on correlations. For example, both antibody levels and children's functioning may be related to an underlying biological factor that cannot be affected by a gluten-free diet. Assuming there is causality, much is still unknown. There is, for example, still limited knowledge on the potential mechanisms of how NCGS affects curiosity.

Due to the complexity associated with DS, it is quite certain that gluten cannot improve functioning in children with DS to the extent that they function like other children. Thus, even if the findings of this thesis were to be replicated and strengthened, the expected effect of a gluten-free diet on psychological functioning might still be relatively small compared to the wide-ranging effects of DS.

4.4 Implications for research and practice

The results of this thesis are too limited by the missing data and the small sample size to be more than an indication of a possible relationship. The high p-values, large confidence intervals, and contradictory findings demonstrate that a larger sample size and more biological data are needed for the future article to draw any conclusions concerning the relationship between NCGS and psychological functioning. Assuming the results from the future article support our primary hypothesis and the findings of Nygaard et al. (2001), further research is still needed.

First, to make conclusions concerning this study's ability to measure NCGS, more research is needed on the experimental measures used. This study is insufficient to establish the validity of the planned biomarker composite as an indication of NCGS. Another planned article will focus on the biological data from this study and investigate the relationship between each individual biomarker and NCGS. Such research could also help establish the use of these biomarkers as a screening procedure for the disorder, and further the understanding of the potential gut-brain axis.

Second, as the current study is exploratory and does not provide conclusive results, other studies are needed to be able to draw causal conclusions. To investigate causality an experimental longitudinal study with a dietary intervention is necessary. The current literature and the present findings also indicate that such a design is needed to further investigate the secondary hypothesis, whether the relationship between NCGS and cognitive functioning is partially mediated by curiosity.

Third, as the two studies investigating the relationship between gluten and development were both done on children with DS, further studies are needed on the general population. The relative benefit of a gluten-free diet intervention may differ in the general population. There may also be different or additional mechanisms at play in DS that affect the relationship between NCGS and psychological functioning.

These findings may be an important step towards validating the experiences of many parents who feel gluten influences the everyday functioning of their children despite the lack of a CD diagnosis. We hope this study can motivate more interdisciplinary research, as more knowledge is needed on the relationship between NCGS and psychological functioning.

4.5 Conclusion

This thesis found partial support for negative relationships between NCGS and facets of psychological functioning. Cognitive-motor functioning was found to be negatively related to anti-gliadin IgA and IgG antibodies, which might imply an effect of NCGS. This is in line with previous research on both NCGS and CD. The findings on the relationship between NCGS and curiosity, HRQoL, parenting stress, and behavioral and emotional problems are currently difficult to interpret, as the results are too incoherent. These incoherencies may be caused by statistical noise due to low statistical power or may reflect an actual lack of effect.

We did not find any support for a mediation effect of curiosity on the relationship between measures of NCGS and cognitive functioning. The literature on the effect of curiosity on cognitive functioning suggests that a longitudinal design is required to study this

relationship. However, it is also possible that methodological concerns may cause the current lack of findings, or they may accurately reflect the lacking relationship.

The validity of all findings in this thesis is severely limited by the small sample size and the missing data. Although the relationship between the biomarkers and cognitive-motor functioning that was found is promising, completing this study with its intended sample size and all seven biomarkers will be important to confirm or refute the current findings.

References

Afifi, A., May, S., Donatello, R., & Clark, V. A. (2019). *Practical Multivariate Analysis*: CRC Press.

Al-Toma, A., Volta, U., Auricchio, R., Castillejo, G., Sanders, D. S., Cellier, C., . . . Lundin, K. E. A. (2019). European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterology Journal, 7*(5), 583-613. doi:https://doi.org/10.1177/2050640619844125

Alaedini, A., & Green, P. H. R. (2005). Narrative Review: Celiac Disease: Understanding a Complex Autoimmune Disorder. *Annals of Internal Medicine, 142*(4), 289-298. doi:https://doi.org/10.7326/0003-4819-142-4-200502150-00011

Alaedini Lab. (2020). Aledini Lab at Columbia University. Retrieved from https://www.alaedinilab.org/

Allison, P. D. (2003). Missing Data Techniques for Structural Equation Modeling. *Journal of Abnormal Psychology, 112*(4), 545-557. doi:https://doi.org/10.1037/0021-843X.112.4.545

AlRuwaily, F., Kattan, H. A., AlMehaidib, A. M., & AlDekhail, W. (2017). Prevalence of celiac disease in Saudi children with Down syndrome: A retrospective study. *International Journal of Pediatrics and Adolescent Medicine, 4*(2), 51-53. doi:https://doi.org/10.1016/j.ijpam.2016.12.002

Backer-Grøndahl, A., & Martinussen, M. (2018). Måleegenskaper ved den norske versjonen av Brief Problem Monitor (BPM). *PsykTestBarn*. doi:https://doi.org/10.21337/0057

Bain, S. K., & Allin, J. D. (2005). Book Review: Stanford-Binet Intelligence Scales, Fifth Edition. *Journal of Psychoeducational Assessment, 23*, 87-95. doi:https://doi.org/10.1177/073428290502300108

Barrio, J., Cilleruelo, M. L., Román, E., & Fernández, C. (2018). Health-related quality of life in Spanish coeliac children using the generic KIDSCREEN-52 questionnaire. *European Journal of Pediatrics, 177*(10), 1515-1522. doi:https://doi.org/10.1007/s00431-018-3204-0

Barroso, N. E., Hungerford, G. M., Garcia, D., Graziano, P. A., & Bagner, D. M. (2016). Psychometric properties of the Parenting Stress Index-Short Form (PSI-SF) in a high-risk sample of mothers and their infants. *Psychological Assessment, 28*(10), 1331-1335. doi:https://doi.org/10.1037/pas0000257

Basu, R. K., Wong, H. R., Krawczeski, C. D., Wheeler, D. S., Manning, P. B., Chawla, L. S., . . . Goldstein, S. L. (2014). Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *Journal of the American College of Cardiology, 64*(25), 2753-2762. doi:https://doi.org/10.1016/j.jacc.2014.09.066

Berlyne, D. E. (1950). Novelty and curiosity as determinants of exploratory behavior. *British Journal of Psychology, 41*, 68-80.

Biesiekierski, J. R., & Iven, J. (2015). Non-coeliac gluten sensitivity: piecing the puzzle together. *United European Gastroenterol Journal, 3*(2), 160-165. doi:https://doi.org/10.1177/2050640615578388

Biesiekierski, J. R., Newnham, E. D., Irving, P. M., Barrett, J. S., Haines, M., Doecke, J. D., . . . Gibson, P. R. (2011). Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *American Journal of Gastroenterology, 106*(3), 508-514; quiz 515. doi:https://doi.org/10.1038/ajg.2010.487

Bouman, C. A. M., van der Maas, A., van Herwaarden, N., Sasso, E. H., van den Hoogen, F. H. J., & den Broeder, A. A. (2017). A multi-biomarker score measuring disease

activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes. *Rheumatology, 56*(6), 973-980. doi:https://doi.org/10.1093/rheumatology/kex003

Bressan, P., & Kramer, P. (2016). Bread and Other Edible Agents of Mental Disease. *Frontiers in Human Neuroscience, 10*, 130-130. doi:https://doi.org/10.3389/fnhum.2016.00130

Buczyłowska, D., Ronniger, P., Melzer, J., & Petermann, F. (2019). Sex Similarities and Differences in Intelligence in Children Aged Two to Eight: Analysis of SON-R 2–8 Scores. *Journal of Intelligence, 7*(2), 11. doi:https://doi.org/10.3390/jintelligence7020011

Carroccio, A., Mansueto, P., Iacono, G., Soresi, M., D'Alcamo, A., Cavataio, F., . . . Rini, G. B. (2012). Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *American Journal of Gastroenterology, 107*(12), 1898-1906; quiz 1907. doi:https://doi.org/10.1038/ajg.2012.236

Casella, S., Zanini, B., Lanzarotto, F., Ricci, C., Marengoni, A., Romanelli, G., & Lanzini, A. (2012). Cognitive performance is impaired in coeliac patients on gluten free diet: a case-control study in patients older than 65 years of age. *Digestive & Liver Disease, 44*(9), 729-735. doi:https://doi.org/10.1016/j.dld.2012.03.008

Catassi, C., Alaedini, A., Bojarski, C., Bonaz, B., Bouma, G., Carroccio, A., . . . Sanders, S. D. (2017). The Overlapping Area of Non-Celiac Gluten Sensitivity (NCGS) and Wheat-Sensitive Irritable Bowel Syndrome (IBS): An Update. *Nutrients, 9*(11). doi:https://doi.org/10.3390/nu9111268

Catassi, C., Elli, L., Bonaz, B., Bouma, G., Carroccio, A., Castillejo, G., . . . Fasano, A. (2015). Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. *Nutrients, 7*(6), 4966-4977. doi:https://doi.org/10.3390/nu7064966

Couzens, D., Cuskelly, M., & Haynes, M. (2011). Cognitive Development and Down Syndrome: Age-Related Change on the Stanford-Binet Test (Fourth Edition). *American Journal on Intellectual and Developmental Disabilities, 116*(3), 181-204. doi:https://doi.org/10.1352/1944-7558-116.3.181

Czaja-Bulsa, G. (2015). Non coeliac gluten sensitivity – A new disease with gluten intolerance. *Clinical Nutrition, 34*(2), 189-194. doi:https://doi.org/10.1016/j.clnu.2014.08.012

d'Ardhuy, X. L., Edgin, J. O., Bouis, C., de Sola, S., Goeldner, C., Kishnani, P., . . . Khwaja, O. (2015). Assessment of Cognitive Scales to Examine Memory, Executive Function and Language in Individuals with Down Syndrome: Implications of a 6-month Observational Study. *Frontiers in Behavioral Neuroscience, 9*. doi:https://doi.org/10.3389/fnbeh.2015.00300

Dale, H. F., Biesiekierski, J. R., & Lied, G. A. (2019). Non-coeliac gluten sensitivity and the spectrum of gluten-related disorders: an updated overview. *Nutrition Research Reviews, 32*(1), 28-37. doi:http://doi.org/10.1017/S095442241800015X

Daulatzai, M. A. (2015). Non-celiac gluten sensitivity triggers gut dysbiosis, neuroinflammation, gut-brain axis dysfunction, and vulnerability for dementia. *CNS & Neurological Disorders Drug Targets, 14*(1), 110-131. doi:https://doi.org/10.2174/1871527314666150202152436

Davidson, M. A. (2008). Primary care for children and adolescents with Down syndrome. *Pediatric Clinics of North America, 55*(5), 1099-1111, xi. doi:https://doi.org/10.1016/j.pcl.2008.07.001

De Cauwer, H., & Spaepen, A. (2020). Are patients with Down syndrome vulnerable to life-threatening COVID-19? *Acta Neurologica Belgica*, 1-3. doi:https://doi.org/10.1007/s13760-020-01373-8

de Magistris, L., Familiari, V., Pascotto, A., Sapone, A., Frolli, A., Iardino, P., . . . Riegler, G. (2010). Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. *Journal of Pediatric Gastroenterology and Nutrition, 51*(4), 418-424. doi:https://doi.org/10.1097/MPG.0b013e3181dcc4a5

Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Katsafanas, E., Khushalani, S., & Yolken, R. (2013). A combined marker of inflammation in individuals with mania. *PLoS One, 8*(9), e73520-e73520. doi:https://doi.org/10.1371/journal.pone.0073520

DiGuiseppi, C., Hepburn, S., Davis, J. M., Fidler, D. J., Hartway, S., Lee, N. R., . . . Robinson, C. (2010). Screening for autism spectrum disorders in children with Down syndrome: population prevalence and screening test characteristics. *Journal of Developmental & Behavioral Pediatrics, 31*(3), 181-191. doi:https://doi.org/10.1097/DBP.0b013e3181d5aa6d

Down Syndrome Medical Interest Group. (2020). Covid-19 and Down Syndrome. Retrieved from https://www.dsmig.org.uk/covid-19-and-down-syndrome/

Du, Y., Shan, L. F., Cao, Z. Z., Feng, J. C., & Cheng, Y. (2018). Prevalence of celiac disease in patients with Down syndrome: a meta-analysis. *Oncotarget, 9*(4), 5387-5396. doi:http://doi.org/10.18632/oncotarget.23624

Edgin, J. O., Mason, G. M., Allman, M. J., Capone, G. T., DeLeon, I., Maslen, C., . . . Nadel, L. (2010). Development and validation of the Arizona Cognitive Test Battery for Down syndrome. *Journal of Neurodevelopmental Disorders, 2*(3), 149-164. doi:https://doi.org/10.1007/s11689-010-9054-3

Eiser, C., & Morse, R. (2001). Can parents rate their child's health-related quality of life? Results of a systematic review. *Quality of Life Research, 10*(4), 347-357. doi:https://doi.org/10.1023/A:1012253723272

Epifanio, M. S., Genna, V., Vitello, M. G., Roccella, M., & La Grutta, S. (2013). Parenting stress and impact of illness in parents of children with coeliac disease. *Pediatric Reports, 5*(4), e19-e19. doi:https://doi.org/10.4081/pr.2013.e19

Espinosa, J. M. (2020). Down Syndrome and COVID-19: A Perfect Storm? *Cell Reports Medicine, 1*(2), 100019. doi:https://doi.org/10.1016/j.xcrm.2020.100019

Farrar, T. J. (2020). skedastic: Heteroskedasticity Diagnostics for Linear Regression Models. In.

Fasano, A. (2017). Celiac Disease, Gut-Brain Axis, and Behavior: Cause, Consequence, or Merely Epiphenomenon? *Pediatrics, 139*, e20164323. doi:https://doi.org/10.1542/peds.2016-4323

Fasano, A., & Catassi, C. (2012). Clinical practice. Celiac disease. *New England Journal of Medicine, 367*(25), 2419-2426. doi:https://doi.org/10.1056/NEJMcp1113994

Fasano, A., Sapone, A., Zevallos, V., & Schuppan, D. (2015). Nonceliac Gluten Sensitivity. *Gastroenterology, 148*(6), 1195-1204. doi:https://doi.org/10.1053/j.gastro.2014.12.049

Ferreira-Vasques, A. T., & Lamônica, D. A. C. (2015). Motor, linguistic, personal and social aspects of children with Down syndrome. *Journal of Applied Oral Science, 23*(4), 424-430. doi:https://doi.org/10.1590/1678-775720150102

Feys, P., Lamers, I., Francis, G., Benedict, R., Phillips, G., LaRocca, N., . . . Rudick, R. (2017). The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Multiple Sclerosis Journal, 23*(5), 711-720. doi:https://doi.org/10.1177/1352458517690824

Field, A. (2013). *Discovering Statistics using IBM SPSS Statistics*: Sage Publications Ltd.

Fisch, H., Hyun, G., Golden, R., Hensle, T. W., Olsson, C. A., & Liberson, G. L. (2003). The Influence of Paternal Age on Down Syndrome. *The Journal of Urology, 169*(6), 2275-2278. doi:https://doi.org/10.1097/01.ju.0000067958.36077.d8

Floyd, R. G., McGrew, K. S., Barry, A., Rafael, F., & Rogers, J. (2009). General and Specific Effects on Cattell-Horn-Carroll Broad Ability Composites: Analysis of the Woodcock-Johnson III Normative Update Cattell-Horn-Carroll Factor Clusters Across Development. *School Psychology Review, 38*(2), 249-265. doi:https://doi.org/10.1080/02796015.2009.12087836

Folkehelseinstituttet. (2015, 4th December 2015). Fakta om Down syndrom. Retrieved from https://www.fhi.no/fp/gravide-og-fodende-kvinners-helse/fakta-om-down-syndrom/

Folkehelseinstituttet. (2016, 13th January 2016). Nye tall om Downs syndrom i Norge. Retrieved from https://www.fhi.no/nyheter/2016/nye-tall-om-down-syndrom-i-norge/

Fox, J., & Weisberg, S. (2019). *An R Companion to Applied Regression*: Sage.

Fritz, C. O., Morris, P. E., & Richler, J. J. (2012). Effect size estimates: Current use, calculations, and interpretation. *Journal of Experimental Psychology: General, 141*(1), 2-18. doi:https://doi.org/10.1037/a0024338

Funder, D. C., & Ozer, D. J. (2019). Evaluating Effect Size in Psychological Research: Sense and Nonsense. *Advances in Methods and Practices in Psychological Science, 2*(2), 156-168. doi:https://doi.org/10.1177/2515245919847202

Fält, E., Wallby, T., Sarkadi, A., Salari, R., & Fabian, H. (2018). Agreement between mothers', fathers', and teachers' ratings of behavioural and emotional problems in 3–5-year-old children. *PLoS One, 13*(11), e0206752. doi:https://doi.org/10.1371/journal.pone.0206752

Gau, S. S. F., & Shang, C. Y. (2010). Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB). *Journal of Child Psychology and Psychiatry, 51*(7), 838-849. doi:https://doi.org/10.1111/j.1469-7610.2010.02215.x

Ghalichi, F., Ghaemmaghami, J., Malek, A., & Ostadrahimi, A. (2016). Effect of gluten free diet on gastrointestinal and behavioral indices for children with autism spectrum disorders: a randomized clinical trial. *World Journal of Pediatrics, 12*(4), 436-442. doi:https://doi.org/10.1007/s12519-016-0040-z

Gilmore, L., & Cuskelly, M. (2009). A longitudinal study of motivation and competence in children with Down syndrome: early childhood to early adolescence. *Journal of Intellectual Disability Research, 53*(5), 484-492. doi:https://doi.org/10.1111/j.1365-2788.2009.01166.x

Gomes, R. C., Maia, J. C., Arrais, R. F., Jatoba, C. A. N., Rocha, M. A. C., Brito, M. E. F., . . . Maranhao, H. D. (2016). The celiac iceberg: from the clinical spectrum to serology and histopathology in children and adolescents with type 1 diabetes mellitus and Down syndrome. *Scandinavian Journal of Gastroenterology, 51*(2), 178-185. doi:https://doi.org/10.3109/00365521.2015.1079645

Hadjivassiliou, M., Grunewald, R., Sharrack, B., Sanders, D., Lobo, A., Williamson, C., . . . Davies-Jones, A. (2003). Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain, 126*(Pt 3), 685-691. Retrieved from http://d1gqps90bl2jsp.cloudfront.net//content/brain/126/3/685.full.pdf

Haraldstad, K., Christophersen, K. A., Eide, H., Nativg, G. K., & Helseth, S. (2011). Health related quality of life in children and adolescents: reliability and validity of the Norwegian version of KIDSCREEN-52 questionnaire, a cross sectional study. *International Journal of Nursing Studies, 48*(5), 573-581. doi:https://doi.org/10.1016/j.ijnurstu.2010.10.001

Haraldstad, K., & Richter, J. (2014). *Måleegenskaper ved den norske versjonen av KIDSCREEN*.

Henderson, B. B., & Wilson, S. E. (1991). Intelligence and curiosity in preschool children. *Journal of School Psychology, 29*(2), 167-175. doi:https://doi.org/10.1016/S0022-4405(05)80009-3

Hollon, J., Puppa, E. L., Greenwald, B., Goldberg, E., Guerrerio, A., & Fasano, A. (2015). Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity. *Nutrients, 7*(3), 1565-1576. doi:https://doi.org/10.3390/nu7031565

Husby, S., Koletzko, S., Korponay-Szabo, I. R., Mearin, M. L., Phillips, A., Shamir, R., . . . Nutrition. (2012). European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *Journal of Pediatric Gastroenterology & Nutrition, 54*(1), 136-160. doi:https://doi.org/10.1097/MPG.0b013e31821a23d0

IBM Corp. (2018). IBM SPSS Statistics for Windows (Version 26.0.1). Armonk, NY: IBM Corp.

Ierardi, E., Losurdo, G., Piscitelli, D., Giorgio, F., Amoruso, A., Iannone, A., . . . Di Leo, A. (2018). Biological markers for non-celiac gluten sensitivity: a question awaiting for a convincing answer. *Gastroenterology and hepatology from bed to bench, 11*(3), 203. doi:https://doi.org/10.22037/ghfbb.v0i0.1326

Infantino, M., Manfredi, M., Meacci, F., Grossi, V., Severino, M., Benucci, M., . . . Macchia, D. (2015). Diagnostic accuracy of anti-gliadin antibodies in Non Celiac Gluten Sensitivity (NCGS) patients: A dual statistical approach. *Clinica Chimica Acta, 451*(Pt B), 135-141. doi:http://dor.org/10.1016/j.cca.2015.09.017

Infantino, M., Meacci, F., Grossi, V., Macchia, D., & Manfredi, M. (2017). Anti-gliadin antibodies in non-celiac gluten sensitivity. *Minerva Gastroenterologica e Dietologica, 63*(1), 1-4. doi:https://doi.org/10.23736/s1121-421x.16.02351-5

Jackson, D. L., Gillaspy, J. A., & Purc-Stephenson, R. (2009). Reporting Practices in Confirmatory Factor Analysis: An Overview and Some Recommendations. *Psychological Methods, 14*(1), 6-23. doi:https://doi.org/10.1037/a0014694

Jin, F. (2016a). Questions Documentation 5-year Questionnaire when the child was 5 years old. Retrieved from https://www.fhi.no/globalassets/dokumenterfiler/studier/den-norske-mor-far-og-barn--undersokelsenmoba/instrumentdokumentasjon/instrument-documentation-q-5year.pdf

Jin, F. (2016b). Questions documentation 7-year Questionnaire (Q-7aar) when the child is 7 years old. Retrieved from https://www.fhi.no/globalassets/dokumenterfiler/studier/den-norske-mor-far-og-barn--undersokelsenmoba/instrumentdokumentasjon/instrument-documentation-q-7year.pdf

Kaaresen, P. I., Rønning, J. A., Ulvund, S. E., & Dahl, L. B. (2006). A randomized, controlled trial of the effectiveness of an early-intervention program in reducing parenting stress after preterm birth. *Pediatrics, 118*(1), e9-19. doi:https://doi.org/10.1542/peds.2005-1491

Kagan, J., Sontag, L. W., Baker, C. T., & Nelson, V. L. (1958). Personality and IQ change. *Journal of Abnormal and Social Psychology, 56*(2), 261-266. doi:https://doi.org/10.1037/h0040884

Karlsen, R. H., Karr, J. E., Saksvik, S. B., Lundervold, A. J., Hjemdal, O., Olsen, A., . . . Skandsen, T. (2020). Examining 3-month test-retest reliability and reliable change using the Cambridge Neuropsychological Test Automated Battery. *Applied Neuropsychology: Adult, ahead-of-print*(ahead-of-print), 1-9. doi:https://doi.org/10.1080/23279095.2020.1722126

Kassambara, A. (2020). ggpubr: 'ggplot2' Based Publication Ready Plots. In.

Kazemi, M., Salehi, M., Kheirollahi, M., & Kazemi, M. (2016). Down Syndrome: Current Status, Challenges and Future Perspectives. *International Journal of Molecular and Cellular Medicine, 5*, 125-133. doi:https://doi.org/10.22088/acadpub.BUMS.5.3.125

Kenkel, N. (2006). On selecting an appropriate multivariate analysis. *Canadian Journal of Plant Science, 86*. doi:https://doi.org/10.4141/P05-164

Kenny, D. A. (2018). Mediation. Retrieved from http://davidakenny.net/cm/mediate.htm

Kidd, C., & Hayden, B. Y. (2015). The Psychology and Neuroscience of Curiosity. *Neuron, 88*(3), 449-460. doi:https://doi.org/10.1016/j.neuron.2015.09.010

Kitterød, R. H. (2012). Foreldrenes tidsbruk: Fedre deltar mer i husarbeid og omsorg. *Samfunnsspeilet(2012/4)*.

Kognisjon og psykisk helse hos barn med Downs syndrom med glutensensitivitet. (2019, 8.9.2019). Retrieved from https://www.sv.uio.no/psi/forskning/prosjekter/kognisjon-og-psykisk-helse-hos-barn-med-downs-syndrom/index.html

Kornør, H., & Martinussen, M. (2011). Måleegenskaper ved den norske versjonen av Parenting Stress index, 3. versjon (PSI). *Regionsenter for barn og unges psykiske helse, helseregion øst og sør, 2*(1). doi:https://doi.org/10.21337/0002

Kornør, H., & Martinussen, M. (2012). Måleegenskaper ved den norske versjonen av Child Behavior Checklist- versjon 2-3, 4-18, 11/2-5 og 6-18 (CBCL). *PsykTestBarn, 1:3*. doi:https://doi.org/10.21337/0014

Kvammen, J. A., Thomassen, R. A., Eskerud, M. B., Rugtveit, J., & Henriksen, C. (2018). Micronutrient Status and Nutritional Intake in 0- to 2-Year-old Children Consuming a Cows' Milk Exclusion Diet. *Journal of Pediatric Gastroenterology and Nutrition, 66*(5), 831-837. doi:https://doi.org/10.1097/mpg.0000000000001942

Lee, R. W. Y., Corley, M. J., Pang, A., Arakaki, G., Abbott, L., Nishimoto, M., . . . Wong, M. (2018). A modified ketogenic gluten-free diet with MCT improves behavior in children with autism spectrum disorder. *Physiology & Behavior, 188*, 205-211. doi:https://doi.org/10.1016/j.physbeh.2018.02.006

Lee, S. J., Gopalan, G., & Harrington, D. (2016). Validation of the Parenting Stress Index-Short Form With Minority Caregivers. *Research on social work practice, 26*(4), 429-440. doi:https://doi.org/10.1177/1049731514554854

Lefter, R., Ciobica, A., Timofte, D., Stanciu, C., & Trifan, A. (2020). A Descriptive Review on the Prevalence of Gastrointestinal Disturbances and Their Multiple Associations in Autism Spectrum Disorder. *Medicina, 56*(1), 11.

Li, C. (2013). Little's Test of Missing Completely at Random. *The Stata Journal, 13*(4), 795-809. doi:https://doi.org/10.1177/1536867X1301300407

Liao, H., Li, Y., & Brooks, G. P. (2017). Outlier impact and accommodation on power. *Journal of Modern Applied Statistical Methods, 16*(1), 261-278. doi:https://doi.org/10.22237/jmasm/1493597640

Lichtwark, I. T., Newnham, E. D., Robinson, S. R., Shepherd, S. J., Hosking, P., Gibson, P. R., & Yelland, G. W. (2014). Cognitive impairment in coeliac disease improves on a gluten-free diet and correlates with histological and serological indices of disease severity. *Alimentary Pharmacology & Therapeutics, 40*(2), 160-170. doi:https://doi.org/10.1111/apt.12809

Little, T. D., Lang, K. M., Wu, W., & Rhemtulla, M. (2016). Missing data. In D. In C. (Ed.) (Ed.), *Developmental Psychopathology, vol. 1: Theory and method* (3rd edition ed., pp. 760– 796). New York, NY: Wiley.

Loane, M., Morris, J., K. , Addor, M., Arriola, L., Budd, J., Doray, B., . . . Dolk, H. (2012). Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. *European Journal of Human Genetics, 21*(1), 27. doi:https://doi.org/10.1038/ejhg.2012.94

Losurdo, G., Principi, M., Iannone, A., Amoruso, A., Ierardi, E., Di Leo, A., & Barone, M. (2018). Extra-intestinal manifestations of non-celiac gluten sensitivity: An expanding paradigm. *World Journal of Gastroenterology, 24*(14), 1521-1530. doi:https://doi.org/10.3748/wjg.v24.i14.1521

Lowe, C., & Rabbitt, P. (1998). Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Cambridge Neuropsychological Test Automated Battery. International Study of Post-Operative Cognitive Dysfunction. *Neuropsychologia, 36*(9), 915. doi:https://doi.org/10.1016/s0028-3932(98)00036-0

Luciana, M., & Nelson, C. A. (2002). Assessment of Neuropsychological Function Through Use of the Cambridge Neuropsychological Testing Automated Battery: Performance in 4- to 12-Year-Old Children. *Developmental Neuropsychology, 22*(3), 595-624. doi:https://doi.org/10.1207/S15326942DN2203_3

Ludvigsson, J. F., Bai, J. C., Biagi, F., Card, T. R., Ciacci, C., Ciclitira, P. J., . . . British Society of Gastroenterology. (2014). Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut, 63*(8), 1210-1228. doi:https://doi.org/10.1136/gutjnl-2013-306578

Ludvigsson, J. F., Leffler, D. A., Bai, J. C., Biagi, F., Fasano, A., Green, P. H., . . . Ciacci, C. (2013). The Oslo definitions for coeliac disease and related terms. *Gut, 62*(1), 43-52. doi:https://doi.org/10.1136/gutjnl-2011-301346

Lundin, K. E. A. (2014). Non-celiac gluten sensitivity - why worry? *BMC Medicine, 12*, 86. doi:https://doi.org/10.1186/1741-7015-12-86

Lykogeorgou, M., Karkelis, S., Papadaki-Papandreou, O., & Nikita, M. (2014). Gluten free diet for children with attention deficit and hyperactivity disorder. *Archives of Disease in Childhood, 99*, A204-A205. doi:https://doi.org/10.1136/archdischild-2014-307384.554

Lynn, R., & Kanazawa, S. (2011). A longitudinal study of sex differences in intelligence at ages 7, 11 and 16 years. *Personality and Individual Differences, 51*(3), 321-324. doi:https://doi.org/10.1016/j.paid.2011.02.028

Marild, K., Stephansson, O., Grahnquist, L., Cnattingius, S., Soderman, G., & Ludvigsson, J. F. (2013). Down syndrome is associated with elevated risk of celiac disease: A nationwide case-control study. *Journal of Pediatrics, 163*(1), 237-242. doi:https://doi.org/10.1016/j.jpeds.2012.12.087

Matos Gonçalves, M., Pinho, M. S., & Simões, M. R. (2018). Construct and concurrent validity of the Cambridge neuropsychological automated tests in Portuguese older adults without neuropsychiatric diagnoses and with Alzheimer's disease dementia. *Aging, Neuropsychology, and Cognition, 25*(2), 290-317. doi:https://doi.org/10.1080/13825585.2017.1294651

Mazzone, L., Reale, L., Spina, M., Guarnera, M., Lionetti, E., Martorana, S., & Mazzone, D. (2011). Compliant gluten-free children with celiac disease: an evaluation of psychological distress. *BMC Pediatrics, 11*(1), 46. doi:https://doi.org/10.1186/1471-2431-11-46

McCall, R. B., & Carriger, M. S. (1993). A meta-analysis of infant habituation and recognition memory performance as predictors of later IQ. *Child Development, 64*(1), 57-79. doi:https://doi.org/10.2307/1131437

Molina-Infante, J., & Carroccio, A. (2017). Suspected Nonceliac Gluten Sensitivity Confirmed in Few Patients After Gluten Challenge in Double-Blind, Placebo-Controlled Trials. *Perspectives in Clinical Gastroenterology and Hepatology, 15*(3), 339-348. doi:https://doi.org/10.1016/j.cgh.2016.08.007

Muentener, P., Herrig, E., & Schulz, L. (2018). The Efficiency of Infants' Exploratory Play Is Related to Longer-Term Cognitive Development. *Frontiers in Psychology, 9*(635). doi:https://doi.org/10.3389/fpsyg.2018.00635

Munkholm, K., Vinberg, M., Pedersen, B. K., Poulsen, H. E., Ekstrøm, C. T., & Kessing, L. V. (2019). A multisystem composite biomarker as a preliminary diagnostic test in bipolar disorder. *Acta Psychiatr Scand, 139*(3), 227-236. doi:https://doi.org/10.1111/acps.12983

Myléus, A., Petersen, S., Carlsson, A., Hammarroth, S., Högberg, L., & Ivarsson, A. (2014). Health-related quality of life is not impaired in children with undetected as well as diagnosed celiac disease: a large population based cross-sectional study. *BMC public health, 14*(1), 425. doi:https://doi.org/10.1186/1471-2458-14-425

National Institutes of Health. (2017, January 31). What conditions or disorders are commonly associated with Down syndrome? Retrieved from https://www.nichd.nih.gov/health/topics/down/conditioninfo/associated

Navarro, F., Pearson, D. A., Fatheree, N., Mansour, R., Hashmi, S. S., & Rhoads, J. M. (2015). Are 'leaky gut' and behavior associated with gluten and dairy containing diet in children with autism spectrum disorders? *Nutritional Neuroscience, 18*(4), 177-185. doi:https://doi.org/10.1179/1476830514Y.0000000110

Norwegian Institute of Public Health (FHI). (2020). Risk groups and their relatives - advice and information. Retrieved from https://www.fhi.no/en/op/novel-coronavirus-facts-advice/facts-and-general-advice/risk-groups---advice-and-information/

Nygaard, E., Reichelt, K. L., & Fagan, J. F. (2001). The relation between the psychological functioning of children with Down syndrome and their urine peptide levels and levels of serum antibodies to food proteins. *Down Syndrome: Research & Practice, 6*(3), 139-145. doi:https://doi.org/10.3104/reports.107

Ory, D. T., & Mokhtarian, P. L. (2009). The impact of non-normality, sample size and estimation technique on goodness-of-fit measures in structural equation modeling: evidence from ten empirical models of travel behavior. *Quality & Quantity, 44*(3), 427-445. doi:https://doi.org/10.1007/s11135-008-9215-6

Papavassiliou, P., Charalsawadi, C., Rafferty, K., & Jackson-Cook, C. (2015). Mosaicism for Trisomy 21: A Review. *American Journal of Medical Genetics Part A, 167*. doi:https://doi.org/10.1002/ajmg.a.36861

Pavlovic, M., Berenji, K., & Bukurov, M. (2017). Screening of celiac disease in Down syndrome - Old and new dilemmas. *World Journal of Clinical Cases, 5*(7), 264-269. doi:https://doi.org/10.12998/wjcc.v5.i7.264

Penelo, E., de la Osa, N., Navarro, J. B., Domenech, J. M., & Ezpeleta, L. (2017). The Brief Problem Monitor-Parent form (BPM-P), a short version of the Child Behavior Checklist: Psychometric properties in Spanish 6- to 8-year-old children. *Psychological Assessment, 29*(11), 1309-1320. doi:https://doi.org/10.1037/pas0000428

Pennesi, C. M., & Klein, L. C. (2012). Effectiveness of the gluten-free, casein-free diet for children diagnosed with autism spectrum disorder: Based on parental report. *Nutritional Neuroscience, 15*(2), 85-91. doi:https://doi.org/10.1179/1476830512Y.0000000003

Pennisi, M., Bramanti, A., Cantone, M., Pennisi, G., Bella, R., & Lanza, G. (2017). Neurophysiology of the "celiac brain": Disentangling gut-brain connections. *Frontiers in Neuroscience, 11*, 498. doi:https://doi.org/10.3389/fnins.2017.00498

Peters, S. L., Biesiekierski, J. R., Yelland, G. W., Muir, J. G., & Gibson, P. R. (2012). Gluten causes depression in subjects with non-coeliac gluten sensitivity (NCGS). *Journal of Gastroenterology and Hepatology, 27*, 147-147.

Peters, S. L., Biesiekierski, J. R., Yelland, G. W., Muir, J. G., & Gibson, P. R. (2014). Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity - an exploratory clinical study. *Alimentary Pharmacology & Therapeutics, 39*(10), 1104-1112. doi:https://doi.org/10.1111/apt.12730

Pinto-Sanchez, M. I., & Verdu, E. F. (2018). Non-celiac gluten or wheat sensitivity: It's complicated! *Neurogastroenterology & Motility, 30*(8), e13392. doi:https://doi.org/10.1111/nmo.13392

Piotrowski, J. T., Litman, J. A., & Valkenburg, P. (2014). Measuring Epistemic Curiosity in Young Children. *Infant and Child Development, 23*(5), 542-553. doi:https://doi.org/10.1002/icd.1847

Piper, B. J., Gray, H. M., Raber, J., & Birkett, M. A. (2014). Reliability and validity of Brief Problem Monitor, an abbreviated form of the Child Behavior Checklist. *Psychiatry and Clinical Neurosciences, 68*(10), 759-767. doi:https://doi.org/10.1111/pcn.12188

Preacher, K. J., & Kelley, K. (2011). Effect size measures for mediation models: Quantitative strategies for communicating indirect effects. *Psychological Methods, 16*(2), 93-115. doi:https://doi.org/10.1037/a0022658

Proud, E., Morris, M. E., Bilney, B., Miller, K. J., Nijkrake, M. J., Munneke, M., & McGinley, J. L. (2020). Hand dexterity assessment in Parkinson's disease: construct validity of the 9-Hole peg test for the more affected hand. *Disability and Rehabilitation*, 1-5. doi:https://doi.org/10.1080/09638288.2020.1754474

R. Core Team. (2019). R: A Language and Environment for Statistical Computing. In.

Rajmil, L., López, A. R., López-Aguilà, S., & Alonso, J. (2013). Parent–child agreement on health-related quality of life (HRQOL): a longitudinal study. *Health and Quality of Life Outcomes, 11*(1), 101. doi:https://doi.org/10.1186/1477-7525-11-101

Ravel, A., Mircher, C., Rebillat, A. S., Cieuta-Walti, C., & Megarbane, A. (2020). Feeding problems and gastrointestinal diseases in Down syndrome. *Archives de Pédiatrie, 27*(1), 53-60. doi:https://doi.org/10.1016/j.arcped.2019.11.008

Ravens-Sieberer, U., Erhart, M., Rajmil, L., Herdman, M., Auquier, P., Bruil, J., . . . European, K. G. (2010). Reliability, construct and criterion validity of the KIDSCREEN-10 score: a short measure for children and adolescents' well-being and health-related quality of life. *Quality of Life Research, 19*(10), 1487-1500. doi:https://doi.org/10.1007/s11136-010-9706-5

Razali, N. M., & Yap, B. (2011). Power Comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling Tests. *Journal of Statistical Modeling and Analytics, 2*.

Regionsenter for habiliteringstjenesten for barn og unge. (2017). Retningslinje for oppfølging av barn og unge med Down syndrom. Retrieved from https://oslo-universitetssykehus.no/seksjon/regionsenter-for-habiliteringstjenesten-for-barn-og-unge-rhabu/Documents/Retningslinje%20Down%20Syndrom%20versjon%20030217.pdf

Revelle, W. (2020). psych: Procedures for Psychological, Psychometric, and Personality Research. In.

Reynolds, M. R., Floyd, R. G., & Niileksela, C. R. (2013). How well is psychometric g indexed by global composites? Evidence from three popular intelligence tests. *Psychological Assessment, 25*(4), 1314-1321. doi:https://doi.org/10.1037/a0034102

Richter, J. (2015). Preliminary evidence for good psychometric properties of the Norwegian version of the Brief Problems Monitor (BPM). *Nordic Journal of Psychiatry, 69*(3), 174-178. doi:https://doi.org/10.3109/08039488.2014.951070

Robitzsch, A., & Grund, S. (2020). miceadds: Some Additional Multiple Imputation Functions, Especially for 'mice'. In.

Rohrer-Baumgartner, N., Zeiner, P., Egeland, J., Gustavson, K., Skogan, A. H., Reichborn-Kjennerud, T., & Aase, H. (2014). Does IQ influence associations between ADHD symptoms and other cognitive functions in young preschoolers? *Behavioral and Brain Functions, 10*, 16. doi:https://doi.org/10.1186/1744-9081-10-16

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software, 48*(2), 1–36-31–36. Retrieved from http://www.jstatsoft.org/v48/i02/

Rothmann, I., Jr. (2011). Kappa-squared: Mediation Effect Size. Retrieved from http://stats.myresearchsurvey.com/kappasquared/

Schwertman, N. C., Owens, M. A., & Adnan, R. (2004). A simple more general boxplot method for identifying outliers. *Computational Statistics & Data Analysis, 47*(1), 165-174. doi:https://doi.org/10.1016/j.csda.2003.10.012

Selig, J. P., & Preacher, K. J. (2008). Monte Carlo method for assessing mediation: An interactive tool for creating confidence intervals for indirect effects. Retrieved from http://quantpsy.org/.

Sellers, A. H., Burns, W. J., & Guyrke, J. (2002). Differences in Young Children's IQs on the Wechsler Preschool and Primary Scale of Intelligence-Revised as a Function of Stratification Variables. *Applied Neuropsychology, 9*(2), 65-73. doi:https://doi.org/10.1207/S15324826AN0902_1

Shahbazkhani, B., Sadeghi, A., Malekzadeh, R., Khatavi, F., Etemadi, M., Kalantri, E., . . . Rostami, K. (2015). Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial. *Nutrients, 7*(6), 4542-4554. doi:https://doi.org/10.3390/nu7064542

Singh, P., Arora, A., Strand, T. A., Leffler, D. A., Catassi, C., Green, P. H., . . . Makharia, G. K. (2018). Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology, 16*(6), 823-836.e822. doi:https://doi.org/10.1016/j.cgh.2017.06.037

Skodje, G. I., Sarna, V. K., Minelle, I. H., Rolfsen, K. L., Muir, J. G., Gibson, P. R., . . . Lundin, K. E. A. (2018). Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity. *Gastroenterology, 154*(3), 529-539.e522. doi:https://doi.org/10.1053/j.gastro.2017.10.040

Smith, D. F., & Gerdes, L. U. (2012). Meta-analysis on anxiety and depression in adult celiac disease. *Acta Psychiatrica Scandinavia, 125*(3), 189-193. doi:https://doi.org/10.1111/j.1600-0447.2011.01795.x

Smith, L. B., Lynch, K. F., Kurppa, K., Koletzko, S., Krischer, J., Liu, E., . . . Agardh, D. (2017). Psychological Manifestations of Celiac Disease Autoimmunity in Young Children. *Pediatrics, 139*(3). doi:https://doi.org/10.1542/peds.2016-2848

Smith, P. J., Need, A. C., Cirulli, E. T., Chiba-Falek, O., & Attix, D. K. (2013). A comparison of the Cambridge Automated Neuropsychological Test Battery (CANTAB) with "traditional" neuropsychological testing instruments. *Journal of Clinical and Experimental Neuropsychology, 35*(3), 319-328. doi:https://doi.org/10.1080/13803395.2013.771618

Smith, Y. A., Hong, E., & Presson, C. (2000). Normative and Validation Studies of the Nine-Hole Peg Test with Children. *Perceptual and Motor Skills, 90*(3), 823-843. doi:https://doi.org/10.2466/pms.2000.90.3.823

Solsvik, T. (2020). Norway detects its first case of coronavirus. *Reuters*. Retrieved from https://www.reuters.com/article/us-china-health-norway/norway-detects-its-first-case-of-coronavirus-idUSKCN20K31G

Spielberger, C. D., & Starr, L. M. (1994). *Curiosity and exploratory behavior*. Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.

Statistisk sentralbyrå. (2020). Befolkningens utdanningsnivå. Retrieved from https://www.ssb.no/utdanning/statistikker/utniv

Stokes, J., Pogge, D., Wecksell, B., & Zaccario, M. (2011). Parent–Child Discrepancies in Report of Psychopathology: The Contributions of Response Bias and Parenting Stress. *Journal of Personality Assessment, 93*(5), 527-536. doi:https://doi.org/10.1080/00223891.2011.594131

Sullivan, G. M., & Feinn, R. (2012). Using Effect Size-or Why the P Value Is Not Enough. *Journal of Graduate Medical Education, 4*(3), 279-282. doi:https://doi.org/10.4300/JGME-D-12-00156.1

Syväoja, H. J., Tammelin, T. H., Ahonen, T., Räsänen, P., Tolvanen, A., Kankaanpää, A., & Kantomaa, M. T. (2015). Internal consistency and stability of the CANTAB neuropsychological test battery in children. *Psychological Assessment, 27*(2), 698-709. doi:https://doi.org/10.1037/a0038485

Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. *International Journal of Medical Education, 2*, 53-55. doi:https://doi.org/10.5116/ijme.4dfb.8dfd

Torgersen, J., Flaatten, H., Engelsen, B. A., & Gramstad, A. (2012). Clinical Validation of Cambridge Neuropsychological Test Automated Battery in a Norwegian Epilepsy Population. *Journal of Behavioral and Brain Science, 02*(01), 108-116. doi:https://doi.org/10.4236/jbbs.2012.21013

Uhde, M., Ajamian, M., Caio, G., De Giorgio, R., Indart, A., Green, P. H., . . . Alaedini, A. (2016). Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut, 65*(12), 1930-1937. doi:https://doi.org/10.1136/gutjnl-2016-311964

University of Oslo. (2020a). Services for sensitive data (TSD). Retrieved from https://www.uio.no/english/services/it/research/sensitive-data/index.html

University of Oslo. (2020b). UiO's buildings are closed until Easter. Retrieved from https://www.uio.no/english/about/hse/corona/news/uio-s-buildings-are-closed-until-easter.html

van Buuren, S. (2018). *Flexible Imputation of Missing Data, Second Edition*: Taylor & Francis Ltd.

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software, 45*(3), 1-67. Retrieved from https://www.jstatsoft.org/v45/i03/

van der Fels, I. M. J., te Wierike, S. C. M., Hartman, E., Elferink-Gemser, M. T., Smith, J., & Visscher, C. (2015). The relationship between motor skills and cognitive skills in 4–16 year old typically developing children: A systematic review. *Journal of Science and Medicine in Sport, 18*(6), 697-703. doi:https://doi.org/10.1016/j.jsams.2014.09.007

van Ginkel, J. R. (2020). Standardized Regression Coefficients and Newly Proposed Estimators for R2 in Multiply Imputed Data. *Psychometrika, 85*(1), 185-205. doi:https://doi.org/10.1007/s11336-020-09696-4

Venables, W. N., & Ripley, B. D. (2002). *Modern Applied Statistics with S*: Springer.

Volta, U., Bardella, M. T., Calabro, A., Troncone, R., Corazza, G. R., & Study Group for Non-Celiac Gluten, S. (2014). An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Medicine, 12*, 85. doi:https://doi.org/10.1186/1741-7015-12-85

Volta, U., Caio, G., Karunaratne, T. B., Alaedini, A., & De Giorgio, R. (2017). Non-coeliac gluten/wheat sensitivity: advances in knowledge and relevant questions. *Expert Review of Gastroenterology & Hepatology, 11*(1), 9-18. doi:https://doi.org/10.1080/17474124.2017.1260003

Volta, U., & De Giorgio, R. (2012). New understanding of gluten sensitivity. *Nature Reviews Gastroenterology & Hepatology, 9*(5), 295-299. doi:https://doi.org/10.1038/nrgastro.2012.15

Vundinti, B., & Ghosh, K. (2011). Incidence of down syndrome: Hypotheses and reality. *Indian Journal of Human Genetics, 17*(3), 117-119. doi:https://doi.org/10.4103/0971-6866.92080

Wickham, H., François, R., Henry, L., & Müller, K. (2020). dplyr: A Grammar of Data Manipulation. In.

Williams, R. (2020). Heteroskedasticity. Retrieved from https://www3.nd.edu/~rwilliam/stats2/l25.pdf

Wishart, J. (2001). Motivation and learning styles in young children with Down syndrome. *Down Syndrome Research and Practice, 7*(2), 47-51. doi:https://doi.org/10.3104/reports.113

Wishart, J. G. (1993). The development of learning difficulties in children with Down's syndrome. *Journal of Intellectual Disability Research, 37*(4), 389-403. doi:https://doi.org/10.1111/j.1365-2788.1993.tb00882.x

Withoff, S., Li, Y., Jonkers, I., & Wijmenga, C. (2016). Understanding Celiac Disease by Genomics. *Trends in Genetics, 32*(5), 295-308. doi:https://doi.org/10.1016/j.tig.2016.02.003

Witt, S., Bloemeke, J., Bullinger, M., Dingemann, J., Blom, M., & Quitmann, J. (2019). Agreement between mothers', fathers', and children's' ratings on health-related quality of life in children born with esophageal atresia – a German cross-sectional study. *BMC Pediatrics, 19*. doi:https://doi.org/10.1186/s12887-019-1701-6

Wolf, E. J., Harrington, K. M., Clark, S. L., & Miller, M. W. (2013). Sample Size Requirements for Structural Equation Models: An Evaluation of Power, Bias, and Solution Propriety. *Educational and Psychological Measurement, 76*(6), 913-934. doi:https://doi.org/10.1177/0013164413495237

Yelland, G. W. (2017). Gluten-induced cognitive impairment ("brain fog") in coeliac disease. *Journal of Gastroenterology and Hepatology, 32 Suppl 1*, 90-93. doi:https://doi.org/10.1111/jgh.13706

Appendix

Appendix A: Abbreviations

9-HPT	Nine-Hole Peg Test
ADHD	Attention deficit hyperactive disorder
Anti-DGP IgG	IgG antibody to deamidated gliadin peptide
Anti-tTG IgA	IgA antibody to transglutaminase 2
BPM	Brief Problem Monitor
CANTAB	Cambridge Neuropsychological Test Automated Battery
CD	Celiac disease
CFA	Confirmatory factor analysis
CM-score	Composite cognitive-motor score
DGP	Deamidated gluten peptides
DS	Down syndrome
GSRS	Gastrointestinal Symptom Rating Scale
HRQoL	Health related quality of life
IBS	Irritable Bowel Syndrome
I/D-YC	I/D-Young Children
IQR	Interquartile range
MOT	Motor screening task
NCGS	Non-celiac gluten sensitivity
UiO	University of Oslo
OUH	Oslo University Hospital
PAL	Paired Associated Learning
PSI-4-SF	Parenting Stress Index Fourth Edition Short Form
RTI	Reaction Time Index
SB5	Stanford Binet Intelligence Scale, 5th Edition
SB5 ABIQ	Stanford Binet 5 Abbreviated IQ
sCD14	Soluble CD14
SSP	Spatial span
TG2	Transglutaminase 2
WAIS-III	Wechsler Adult Intelligence Scale Third Edition
WISC-III	Wechsler Intelligence Scale for Children

Appendix B: Recruitment Materials

B1 Generic application for help recruiting

B2 Generic application to borrow facilities for testing

B3 Invitation to join the study with consent form

Søknad om hjelp til rekruttering av forsøkspersoner til forskning vedrørende sammenhengen mellom glutensensitivitet og psykologisk funksjon hos barn med Down syndrom.

Vi har for tiden et forskningsprosjekt hvor vi ser på sammenhengen mellom biologiske mål på glutensensitivitet og psykologisk fungering samt livskvalitet hos barn med Downs syndrom uten cøliaki. I den anledning trenger vi hjelp til å rekruttere forsøkspersoner.

Vi vil i studien benytte blodprøver og nevrokognitive testresultater av barna, i tillegg til spørreskjema overfor foreldrene.

Vi trenger 70 barn med Down syndrom i alderen fra og med 5 år, til og med 11 år, hvor barnene ikke kan være diagnostisert med cøliaki.

Bakgrunn og hensikt med studien:

Hensikten med studien er å få mer kunnskap om glutensensitivitet hos barn med Down syndrom, og om det er en sammenheng mellom slik sensitivitet og barnas fungering. Med glutensensitivitet mener vi symptomer som kan ligne cøliaki, men uten at barnet oppfyller kriteriene for cøliaki. Cøliaki er en glutenutløst sykdom, hvor tynntarmens slimhinne blir betent, tarmtottene redusert, og evnen til å absorbere næringsstoffer fra kosten reduseres. Barn med Down syndrom har oftere cøliaki eller glutensensitivitet enn personer uten Down syndrom. Det er per i dag ukjent om cøliaki eller glutensensitivitet har noen konsekvenser for barnas psykologiske fungering. Med psykologisk fungering menes her for eksempel evnenivå, psykisk helse, atferd, og ulike former for ferdigheter. Noen svært få studier internasjonalt indikerer at det kan være en sammenheng mellom cøliaki eller glutensensitivitet og psykologisk fungering. Det trengs imidlertid vesentlig mer forskning for å stadfeste om, og eventuelt hvordan type, sammenheng det er, og om det bør ha noen konsekvenser for anbefalte tiltak for barn med Down syndrom.

Det er vedlagt en utvidet beskrivelse av prosjektet

Prosjektleder for prosjektet:
Egil Nygaard, førsteamanuensis i psykologi ved Universitetet i Oslo.
Epost: egilny@psykologi.uio.no, tlf. 412 91 922.

Ansvarlige for den praktiske gjennomføringen er:
Stud. Psych. Mikkel Glimsdal, Psykologisk institutt, Universitet i Oslo.
Epost: mikkelgl@uio.no, tlf. 996 90 699

Stud. Psych. Daniel Bryne, Psykologisk institutt, Universitet i Oslo.
Epost: daniebry@uio.no, tlf. 413 76 268

Vi ville sette stor pris på om dere kunne hjelpe oss i forbindelse med å rekruttere barn med Down syndrom i den aktuelle aldersgruppen. Hvis dere ønsker ytterligere informasjon vennligst kontakt enten Egil, Mikkel eller Daniel.

Søknad om bruk av testplass for forskningsprosjektet glutensensitivitet og utvikling hos barn med Down syndrom

I henhold til dagens samtale med (NAVN) sender jeg herved søknad om hjelp til å skaffe et rom til testing av barn med Downs syndrom. I forbindelse med et samarbeidsprosjekt mellom Oslo universitetssykehus og Psykologisk Institutt ved UIO har vi behov for et sted i (STED) der vi kan teste barnene i området som blir med på studien. Hver testing kan ta opptil 1 og en halv time.

Det er noe usikkert når testingen skal foretas. Det avhenger delvis av når det passer foreldrene, når det passer dere og når jeg har mulighet å komme til (STED). Vi har planer om å gjennomføre all testing i perioden blir fra 1 september 2019 til 30 juni 2020.

Det er få krav til testrommet unntatt at det ikke bør være for mye forstyrrelser. Vi trenger stol og bord som passer til barn mellom fem og elleve år, stoler til foreldre og testleder, og ideelt sett en stikkontakt til å kunne lade nettbrett.

Hvis vi kan snakke på telefon vedrørende hva dere har mulighet til og hva jeg trenger ville det vært fint.

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

GLUTENSENSITIVITET OG UTVIKLING HOS BARN MED DOWN SYNDROM

FORELDER TIL DELTAGER

Dette er et spørsmål til deg og ditt barn om å delta i en forskningsprosjekt for å undersøke om det er noen sammenheng mellom tegn på glutensensitivitet og psykologisk fungering hos barn med Down syndrom. Vi inviterer **alle barn med Down syndrom som har fylt 5 år, men som ikke har fylt 12 år, som bor på Østlandet** til å bli med i studien. Studien foretas av Universitetet i Oslo (UiO) i samarbeid Oslo Universitetssykehus, Rikshospitalet.

BAKGRUNNEN OG HENSIKTEN MED STUDIEN

Hensikten med studien er å få mer kunnskap om glutensensitivitet hos barn med Down syndrom, og om det er en sammenheng mellom slik sensitivitet og barnas fungering. Med glutensensitivitet mener vi symptomer som kan ligne cøliaki, men uten at barnet oppfyller kriteriene for cøliaki. Cøliaki er en glutenutløst sykdom, hvor tynntarmens slimhinne blir betent, tarmtottene redusert, og evnen til å absorbere næringsstoffer fra kosten reduseres. Barn med Down syndrom har oftere cøliaki eller glutensensitivitet enn personer uten Down syndrom. Det er per i dag ukjent om cøliaki eller glutensensitivitet har noen konsekvenser for barnas psykologiske fungering. Med psykologisk fungering menes her for eksempel evnenivå, psykisk helse, atferd, og ulike former for ferdigheter. Noen svært få studier internasjonalt indikerer at det kan være en sammenheng mellom cøliaki eller glutensensitivitet og psykologisk fungering. Det trengs imidlertid vesentlig mer forskning for å stadfeste om, og eventuelt hvordan type, sammenheng det er, og om det bør ha noen konsekvenser for anbefalte tiltak for barn med Down syndrom.

HVA INNEBÆRER PROSJEKTET?

Studien innebærer at barnet blir undersøkt i ca. en time med psykologiske tester. Dere foreldre vil også bli bedt om å fylle ut spørreskjemaer i ca. like lang tid. Dere vil i tillegg få med dere henvisning til blodprøvetaking. Den psykologiske undersøkelsen blir foretatt av ansatt ved Psykologisk Institutt ved UiO, enten på Universitetet i Oslo, på et sted i nærheten av dere bor, eller hjemme hos dere. Blodprøven tas der barnet vanligvis blir tatt blodprøver av.

I prosjektet vil vi innhente og registrere opplysninger om barnet og deg. Dette er informasjon fra tre kilder: psykologiske tester, informasjon dere oppgir på spørreskjema, og analysesvar på blodprøvene. De psykologiske testene vil gi informasjon om barnets kognitive ferdigheter. Spørreskjemaet vil inneholde spørsmål om barnets funksjonsnivå; barnets psykiske helse og atferd; barnets ferdigheter innen kommunikasjon, dagliglivet, sosialt og motorikk; matinntak, tegn på mageplager, avføringsvaner og vanlige bieffekter av glutenintoleranse hos barnet; i tillegg til informasjon om hvordan det er å være foreldre til barnet og sosio-demografisk informasjon. Blodprøvene vil undersøke biologiske markører på glutensensitivitet.

Ikke alle barn vet at det har Down syndrom. Det er fint hvis dere sier ifra til oss hvis dere ikke ønsker at vi skal fortelle barna at det har Down syndrom, f.eks. via informasjonsskriv til barna. Vi tilpasser informasjonen vi gir barna til deres ønsker.

MULIGE FORDELER OG ULEMPER

Studien vil ikke ha noen direkte konsekvens for den behandlingen barnet mottar. Hvis undersøkelsene indikerer forhold som bør følges opp eller undersøkes videre vil vi være behjelpelig med henvisninger til nødvendige undersøkelser. En pediatrisk gastro-enterolog ved Rikshospitalet vil vurdere alle analysesvar fra blodprøvene. Undersøkelsene vil kunne gi indikasjoner på for eksempel cøliaki. Ved indikasjoner på cøliaki fra blodprøvene og/eller symptomer vil barnet bli henvist av gastro-enterologen til videre oppfølging. Den psykologiske undersøkelsen av barnet (kognitiv testing av barnet og informasjon fra dere foreldre) er ikke en klinisk undersøkelse av barnets hjelpebehov. Hvis det allikevel kommer fram informasjon som kan være nyttig for dere å vite om, vil vi gi dere denne informasjonen. Ved forespørsel fra dere foreldre, kan dere få skriftlig og muntlig tilbakemelding på undersøkelsene, inkludert om barnets generelle kognitive ferdigheter (IQ).

Studien benytter standardiserte undersøkelser som er vanlig for denne aldersgruppen. Det forventes ikke noen ulemper eller ubehag for barnet fra den psykologiske undersøkelser, utover tidsbruken. Spørreskjemaet til dere foreldre inneholder spørsmål om barnet som kan vekke negative følelser hos noen foreldre.

Noen barn får vondt av blodprøver. Dere får derfor med dere henvisning slik at blodprøvene kan tas der barnet er vant til dette. Dere får med dere Emla plaster som lokalbedøvelse. Blodprøvene kan tas samtidig som eventuelle andre blodprøver barnet skal ta.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for barnets videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte prosjektleder Egil Nygaard, tlf 41291922, epost egilny@psykologi.uio.no.

HVA SKJER MED INFORMASJONEN OM DEG OG BARNET?

Informasjonen som registreres om deg og barnet skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og barnet ditt og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine og barnas opplysninger gjennom en navneliste. Det er kun prosjektleder Egil Nygaard og autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg eller barnet.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg og barnet vil bli anonymisert eller slettet 10 år etter at prosjektet er ferdig, det vil si i 2031. En oppbevaring i 10 år gir blant annet mulighet for senere oppfølgingsstudie, se eget punkt under. Det vil ikke være mulig å identifisere enkeltdeltagere i resultatene av studien når disse publiseres. Prosjektmedarbeiderne har taushetsplikt.

DELING AV DATA OG OVERFØRING TIL UTLANDET

Ved å delta i prosjektet, samtykker du også til at blodprøvene sendes til våre samarbeidspartnere i New York, USA som ledd i forskningssamarbeid og publisering. Dette kan være land med lover som ikke tilfredsstiller europeisk personvernlovgivning. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte. Blodprøvene sendes uten identifiserbar informasjon, for eksempel uten at de får informasjon om barnets navn eller bopel. Koden som knytter deg til dine personidentifiserende opplysninger vil ikke bli utlevert.

HVA SKJER MED BLODPRØVER SOM BLIR TATT AV BARNA?

Blodprøvene som tas av barnet skal oppbevares i en generell forskningsbiobank. Biobanken er lokalisert på Oslo Universitetssykehus, Rikshospitalet, heter «Tarmsykdommer», og administreres av en av samarbeidspartnerne i prosjektet, Knut Lundin. Det er mulig at blodprøvene vil bli brukt i senere studier i samme biobank. De som på daværende tidspunkt er myndige eller foreldre for umyndige vil i så fall forespørres på nytt om prosjektdeltagelse.

Det er mulig at blodprøvene vil bli analysert hos en av prosjektets internasjonale samarbeidspartnere ved Columbia University Medical Center i New York. Samarbeidspartnerne vil ikke få informasjon om hvem blodprøven er fra, for eksempel navn på barnet.

FORSIKRING

Prosjektet organiseres ihht Lov om medisinsk og helsefaglig forskning. Universitetet i Oslo er selvassurandør ved eventuell erstatningssaker.

OPPFØLGINGSPROSJEKT

Denne studier er begrenset til undersøkelsene nevnt over. Det er imidlertid mulig at vi vil foreta senere oppfølgingsstudie, og du vil bli spurt om du godkjenner at vi kontakter dere senere ved oppstart av et eventuelt oppfølgingsstudie.

ØKONOMI

Det er ingen kommersielle interesser knyttet til prosjektet. Studien er finansiert av Psykologisk Institutt ved Universitet i Oslo.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (saksnr. 2018/1122).

Etter ny personopplysningslov har behandlingsansvarlig og prosjektleder Egil Nygaard et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og artikkel 9 nr. 2 og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER OG INFORMASJON OM UTFALLET AV STUDIEN

Om du vil ha mer informasjon om prosjektet kan du besøke vår nettside på https://www.sv.uio.no/psi/forskning/prosjekter/kognisjon-og-psykisk-helse-hos-barn-med-downs-syndrom/index.html.

Dersom du har spørsmål til prosjektet kan du ta kontakt med prosjektleder Egil Nygaard, egilny@psykologi.uio.no, tlf. 412 91 922, eller forskningsassistentene; Mikkel Glimsdal, mikkelgl@uio.no, tlf. 996 90 699; Daniel Bryne, daniebry@uio.no, tlf. 413 76 268.

For påmelding ta kontakt med en av forskningsassistentene.

Personvernombud ved institusjonen er Maren Magnus Voll, personvernombud@uio.no.

Etter hvert som resultatene av studien publiseres, kan kopi av rapporter og artikler fås ved henvendelse til prosjektleder, Egil Nygaard. Publiserte resultater vil også legges ut fortløpende på prosjektleder sin nettside http://www.sv.uio.no/psi/personer/vit/egilny/

TA GJERNE KONTAKT HVIS DET ER NOE DERE LURER PÅ!

Med vennlig hilsen

Egil Nygaard	Knut Lundin	Christine Olbjørn	Kari-Anne Næss	Carina Hinrichs
UiO	UiO/Rikshospitalet	UiO/Rikshospitalet	UiO	Rikshospitalet

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE OG MITT BARNS PERSONOPPLYSNINGER OG BARNETS BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET (DELTAKER ER DEN FORELDER SOM VIL FYLLE UT SPØRRESKJEMAER)

Deltakers e-postadresse

Deltakers telefonnummer

Deltakers navn med trykte bokstaver

Sted og dato

Deltakers signatur

SAMTYKKE PÅ VEGNE AV BARNET

Ved prosjekter som inkluderer barn og ungdom under 16 år, skal i utgangspunktet begge foresatte undertegne.

Som foresatte til _____(Fullt navn) samtykker vi til at hun/han kan delta i prosjektet.

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Appendix C: Assessment materials

C1 Test instructions 9-HPT

C2 Test instructions CANTAB

C3 Routing form SB5

C4 Assessments procedure

C5 Infection control protocol

Instruksjoner 9-hole peg test

Prosedyre:

1. Test dominant hånd først
2. Posisjoner brettet horisontalt med den runde boksen på samme side som hånden som testes
3. Les følgende instruksjoner mens du demonstrerer:

«La meg vise deg hva du skal gjøre. Plukk opp pluggene en om gangen, og putt dem i hullene til alle de ni hullene er fylt. Bruk bare hånden som bare skal testes, bruk den andre til å støtte brettet. Pluggene kan legges i hullene i hvilken som helst rekkefølge. Fjern deretter pluggene, en om gangen. Det er viktig at du prøver å gjøre det så fort som mulig»

4. Når demonstrasjonen er ferdig, si:

«Først kan du ta en prøverunde med hver hånd. Start med [dominant hånd], mens du støtter brettet med den andre hånden. Er du klar? Start!»

5. Når deltageren er ferdig med første prøverunde, snu boksen og si

«Godt jobba! Nå ta en prøverunde til med den andre hånden. Er du klar? Klar, ferdig, gå!»

6. Når begge prøverundene er ferdig, si

«Nå kommer den faktiske testen, først med [dominant hånd]. Først skal jeg gjenta reglene en siste gang. Plukk opp pluggene en om gangen, og legg dem i hullene til alle de ni hullene er fylt. Bruk bare hånden som bare skal testes. Fjern deretter pluggene, en om gangen. Pluggene kan legges i hullene i hvilken som helst rekkefølge. Det er viktig at du prøver å gjøre det så fort som mulig. Er du klar? Klar, ferdig, gå!»

7. Snu boksen, og gjenta testen på samme måte for den ikke dominante hånden.

Motor screening task (MOT)

Før oppgaven starter si:	"Her er padden som vi vil bruke. Jeg kommer til å vise deg hvordan den skal brukes. Er du klar?"
	Øvelsesrunde 1: demonstator
Først si…	«Poenget er å røre midten av kryssene.» *[Trykk deretter på kryssene som vises på skjermen.]*
Demonstrer et nøyaktig trykk og en unøyaktig trykk Si…	«Hvis du trykker riktig vil det komme en melodi og krysset vil forsvinne.» *[demonstrer korrekt trykking]* «Hvis du ikke trykker riktig vil krysset bli værende på skjermen og du vil ikke høre melodien.» *[demonstrer feil trykking]*
Mens det tredje X(krysset) fortsatt er på skjermen si…	«Du burde bruke tuppen av pekefingeren på den hånden du skriver med for at det skal fungere slik det skal. Hvis du trykker riktig på krysset vil det forsvinne. Etter at du har trykket på krysset tar du hånden bort og venter på neste kryss.»
	Øvelsesrunde 2: **Deltagers tur**
Før du starter si…	«Nå er det din tur til å prøve. Husk å ta på krysset med tuppen av pekefingeren din.»
	Trykk på ▶ for å starte
*Om **nødvendig** kan du si:*	• Trykk litt hardere • Bruk tuppen av pekefingeren • Se nå etter neste kryss • Du trenger ikke å trykke så hardt
	Testrunder
På starten av hver testfase si…	"Nå kan du gjøre det samme igjen, men litt lengre denne gangen. Klar, ferdig, gå."
	Trykk på ▶ for å starte

Reaction time index

Knapp på skjermen Si…	"Ser du den grå knappen? " *[Vent til den grå knappen blir lys, deretter trykk på den]*
	Øvelsesrunde 1: Demonstrator
Demonstrer og si…	"…Og der kom det fem sirkler. *[Tell sirkler]* La meg vise deg hva du skal gjøre." "Først så holder jeg ned den grå knappen" *[Demonstrator holder ned knappen med pekefinger til sirkelen blinker gult]* "Når en av de fem sirklene blinker så slipper jeg knappen og trykker på den sirkelen så fort jeg kan" *[Ta på sirkelen med samme pekefinger]* "Så går jeg tilbake til å holde ned knappen" *[Hold ned knappen]* «Se hvordan jeg **bare** slipper knappen når **en av** sirklene har blinket gult.» *[Trykker på sirkel som blinker]*
	Øvelsesrunde 2: **Deltagers tur**
Si…	"Nå kan du prøve. Hvilken hånd tegner du med? Bruk pekefingeren på den hånden til å gjøre denne oppgaven" [Peker på egen pekefinger]
Si…	"Nå start å øve ved å holde ned knappen. Så ser du ser de gule sirkelen blinke, trykk på den så fort du kan "
Si…	"Godt jobbet, fortsett"
Om nødvendig kan du si	"Trykk ned knappen" "Prøv å ikke slipp knappen før etter at du har sett den blinke" "Bruk samme hånd til å presse knappen og sirkelen" "Pass på at du ikke tar på skjermen andre steder enn i sirkelen"
	Testrunder
Testfasen starter når sirklene flyr ut. Stop deltageren, og si…	«Godt jobba, nå er du ferdig med å øve deg. Nå skal du gjøre det samme igjen, men denne gangen litt lengre. Prøv å gjøre det så fort og nøyaktig som mulig.»
Når knappen blir lysere, si… Om nødvendig, si…	«Nå kan du starte.» «Slipp og trykk knappen igjen»

Spatial span (SSP)

Firkant på skjermen Si…	"Se på skjermen" *[Pek på skjermen]* «Der er det noen hvite firkanter. Firkantene vil bytte farge, en etter en. Du må huske rekkefølgen firkantene bytter farge i. Jeg skal nå vise deg hvordan det fungerer. To firkanter vil bytte farge. La oss se på firkantene og huske rekkefølgen de bytter farge i."
	Øvelsesrunde 1: Demonstrator
	Trykk på ▶ for å starte
Se de to firkantene bytte farge, hør tonen, **så** si	"Den lyden betyr at rekken er ferdig. Poenget er å ta på firkantene i **samme rekkefølge** som de byttet farge. Så denne var først." *[Demonstratoren trykker på firkanten]* "Og det var den andre" *[Demonstratoren trykker på firkanten]*
	Øvelsesrunde 2: **Deltagers tur**
Før testen starter si	"Nå er det din tur. To firkanter vil bytte farge, en etter en. Etter tonen, trykk på firkantene som byttet farge i samme rekkefølgen som de byttet farge. La oss se"
	Trykk på ▶ for å starte
Etter tonen si	"Hvilken firkant byttet farge først?" *[Deltageren trykker på firkanten]* "Og hvem var den andre firkanten som byttet farge?" *[Deltageren trykker på firkanten]*
Hvis korrekt si	"Bra gjort"
Hvis feil, forklar igjen	"To firkanter vil bytte farge, en etter en. Etter lyden, trykk på firkantene som byttet farge, i samme rekkefølgen som de byttet farge. La oss se"
	Øvelsesrunde 3: Deltager
Forklar før testen starter	"Som før, to firkanter bytter farge. Prøv å husk rekkefølgen de bytter farge i"
	Trykk på ▶ for å starte
Etter tonen si…	"Hvilken firkant byttet farge først?" *[Deltageren trykker på firkanten]* "Og hvem var den andre firkanten som byttet farge?"
	Testrunder
På starten av hver test si	"Nå skal vi gjøre det samme igjen. Denne gangen vil [tall i nedre venstre hjørne] bytte farge."
	Trykk på ▶ for å starte

Paired assosiation learning (PAL)

Bokser på skjermen Si..	«Som du kan se så er det 6 bokser på skjermen» *[pek på boksene]* «Boksene vil åpne seg en etter en. Boksene åpnes i ulik rekkefølge hver runde. Noen bokser vil være tomme, mens andre vil ha mønstre inni seg. Du må huske hvor mønstrene er. Om du gjør en feil vil boksene åpne seg igjen og du kan prøve en gang til. Nå vil mønstrene vises en etter en i midten av skjermen.»
	Øvelsesrunde 1: demonstrator
Si…	«Nå se på boksene åpne seg mens jeg viser deg.»
	Trykk på  for å starte
Når en **tom boks** åpnes si:	«Det er ingenting i den»
Når en **boks med mønster** åpnes si:	«Der var det et mønster, prøv å husk hvilken boks det er i.»
Etter at det første mønsteret vises i midten si:	«Der er det første mønstret. Jeg vil nå trykke på den boksen jeg så det mønstret dukke opp i.» *[ta på boksen]*
Når det andre mønstre dukker opp i midten si:	Og der er det andre mønstret. Jeg vil nå trykke på den boksen jeg så det mønstret dukke opp i. *[ta på boksen]*
	Øvelsesrunde 2: **Deltagers tur**
Si…	«Nå er det din tur. Igjen vil det være seks bokser på skjermen, to av dem vil ha mønstre inni seg. Prøv å husk hvor du ser mønstrene.»
	Trykk på  for å starte
Når en **tom boks** åpnes si:	«Det er ingenting i den»
Når en **boks med mønster** åpnes si:	«Der var det et mønster, prøv å husk hvilken boks det er i.»
Etter at det første mønsteret vises i midten si:	«Der er det første mønstret. Trykk på den boksen du så det mønstret dukke opp i.» *[ta på boksen]*
Når det andre mønstre dukker opp i midten si:	«Og der er det andre mønstret. Trykk på den boksen du så det mønstret dukke opp i.» *[ta på boksen]*
Om det gjøres **feil** forklar igjen:	«Siden du ikke trykket på riktige bokser kommer du nå til å se begge mønstrene igjen og ha få en ny sjanse til å vise hvilke bokser de dukker opp i. «

ID:_____

Alder:_____

dag måned år

Dato_____/_____/_____

Routing-Nonverbal(NV) Domain

Startpunkt Alder 2 til 4

Sett sirkel rundt svar

						Score	
1.		b	**C**	d		0	1
2.		b	c	**D**		0	1
3.	a	**B**	c	d	e	0	1
4.	a	b	**C**	d	e	0	1

Startpunkt Alder 5 til 6

Poeng for å starte her: 4

						Score	
5.	a	**B**	c	d	e	0	1
6.	a	b	c	d	**E**	0	1
7.	a	b	c	d	**E**	0	1
8.	a	b	c	d	**E**	0	1
9.	a	**B**	c	d	e	0	1
10.	**A**	b	c	d	e	0	1
11.	a	b	c	**D**	e	0	1
12.	a	b	c	d	**E**	0	1
13.	a	b	**C**	d	e	0	1

Startpunkt Alder 7 til 12

Poeng for å starte her: 13

						Score	
14.	a	b	c	**D**	e	0	1
15.	a	b	c	d	**E**	0	1
16.	a	**B**	c	d	e	0	1
	A	b	c	c	e	.	.
17.	**A**	b	c	d	e	0	1
	a	b	c	d	**E**	.	.

Startpunkt Alder 13+

Poeng for å starte her: 17

						Score	
18.	a	b	c	**D**	e	0	1
19.	a	**B**	c	**d**	e	0	1
20.	a	b	**C**	d	e	0	1
21.	a	b	**C**	d	e	0	1
22.	**A**	b	c	d	e	0	1
23.	a	b	c	d	**E**	0	1
24.	**A**	b	c	d	e	0	1
25.	a	b	c	d	**E**	0	1
26.	**A**	b	c	d	e	0	1
27.	a	b	c	**D**	e	0	1
28.	a	b	c	**D**	e	0	1
29.	a	b	c	d	**E**	0	1
30.	a	**B**	c	d	e	0	1
31.	a	b	c	d	**E**	0	1
32.	a	b	**C**	d	e	0	1
33.	a	**B**	c	d	e	0	1
34.	a	b	**C**	d	e	0	1
35.	**A**	b	c	d	e	0	1
36.	a	b	c	**D**	e	0	1

Start poeng [ ] + Opnådde poeng [ ] = Total poeng [ ]

Routing-Verbal(V) Domain

Startpunkt Alder 2

Riktig svar

		Score	
1.	munn	0	1
2.	fingre	0	1
3.	nese	0	1

Startpunkt Alder 3

Poeng for å starte her: 3

4.	munn	0	1
5.	hår	0	1

Startpunkt Alder 4

Poeng for å starte her: 5

6.	ball	0	1
7.	katt	0	1
8.	and	0	1
9.	fugl	0	1

Startpunkt Alder 5 til 9

Poeng for å starte her: 9

10.	drikke	0	1
11.	klippe	0	1
12.	løpe, jogge, spurte	0	1
13.	knyte	0	1
14.	skrive	0	1

Startpunkt Alder 10 til 17

Poeng for å starte her: 14

		Score		
15.	kopp _____	0	1	2
16.	eple _____	0	1	2
17.	kjole _____	0	1	2
18.	hund _____	0	1	2
19.	hatt _____	0	1	2
20.	pappegøye _____	0	1	2

Startpunkt Alder 18+

Poeng for å starte her: 26

21.	søledam _____	0	1	2
22.	fabrikk _____	0	1	2

23. tillate _____ 0 1 2

24. låne _____ 0 1 2

25. øyevipp _____ 0 1 2

26. nysgjerrighet _____ 0 1 2

27. ferdighet _____ 0 1 2

28. skjelving _____ 0 1 2

29. plausibel _____ 0 1 2

30. tirade _____ 0 1 2

31. hvile _____ 0 1 2

32. inkrustasjon _____ 0 1 2

33. paria _____ 0 1 2

34. akromatisk _____ 0 1 2

35. overfladisk _____ 0 1 2

36. penultimate _____ 0 1 2

37. interstices _____ 0 1 2

38. halcyon _____ 0 1 2

39. friable _____ 0 1 2

40. homunculus _____ 0 1 2

41. antinomy _____ 0 1 2

42. casulstry _____ 0 1 2

43. pococurante _____ 0 1 2

44. nictitate _____ 0 1 2

9-hole pegboard

H. Dom. ☐ V. Dom. ☐ **Tid:**

Høyre - Test	
Venstre - Test	
Høyre	
Venstre	

Start poeng ☐ + Opnådde poeng ☐

= Total poeng ☐

Vokabular totalpoeng	**Rute til bok 3**
0-17	Level 2 (side 12)
18-27	Level 3 (side 13)
28-47	Level 4 (side 14)
48-74	Level 5 (side 15)

Forberedelser	
Gi Deltaker-ID og Kontakt-ID, fylt inn i kodenøkkel	
Avtalt tid og booket testrom	
Sørger for at følgende er tilgjengelig og desinfiser hvor nødvendig:	
• Routingark	
• Klistremerketabell	
• Samtykkeskjema	
• Instruksjoner	
• Rekvisisjonsark + konvolutt	
• Premier	
• iPader, fult ladet	
• Stanford Binet 5-bok + manipulasjonsobjekter	
• Gul lapp med deltager-ID	
Desinfiser flater, stoler og dørhåndtak	
Testsituasjon	
Rekvisisjonsskjemaer + konvolutt gitt til foresatt	
Nytt samtykkeskjema signert	
Desinfiser utstyr, flater og dørhåndtak	

Smittevernsprotokoll
Glutensensitivitet og utvikling hos barn med down syndrom

Psykologisk Institutt, Universitetet i Oslo, våren 2020.

Alle lab-aktiviteter må følge den nåværende *Veileder for smittevern ved Universitetet i Oslo:*
https://www.uio.no/om/hms/korona/retningslinjer/veileder-smittevern.html

Ansatte: Alle ansatte skal ha gjennomført UiOs e-læringskurt i smittevern.

Preventive tiltak

- Personale eller deltagere med feber eller symptomer på akutt luftveisinfeksjon burde ikke være til stede på laben. Personale eller deltagere som utvikler relevante symptomer når de er til stede testrommet bør forlate lokalet umiddelbart.
- Personale og deltagere bør være fri for relevante symptomer i minst syv dager før en er på testrommet.
- Personale skal vaske hendene mellom kontakt med hver deltager.
- Deltagere skal gis mulighet til å vaske eller desinfisere hendene før og etter testingen.
- Dørhåndtak og andre kontaktflater skal rengjøres flere ganger daglig.
- Labutstyr skal rengjøres mellom hver deltager.
- Mat og drikke skal ikke tilbys deltagere.

Før testdag

Når timen planlegges:

- Informer deltageren om preventive tiltak.
- Spør forelder om de eller barnet:
    - Har luftveissymptomer (sår hals, tungpustethet, hoste eller feber)?
    - Har magesmerter, kvalme, oppkast eller diaré?
    - Vært i utlandet siste 10 dager?
    - Har du vært i kontakt med noen som har testet positivt for covid-19?
- Hvis ja på noen av spørsmålene over, utsett avtalen.

Påminnelse om avtale, preventive tiltak, risikofaktorer på e-post 1-3 dager før testdag. Instruer deltager om å møte på utsiden av Harald Schjeldrups Hus, Forskningsveien 3A og be dem sende SMS når de ankommer.

Testdag

Før testingen:

- Testledere må møte i god tid før møte med deltager.
- Testleder skal unngå bruk av ringer, klokke og lignende på hender og håndledd som kan medføre dårligere håndhygiene.
- Testlederen tørker av alle overflater med desinfeksjonsmiddel:
    - Stoler og bord.
    - Dørhåndtak
    - Alt utstyr som brukes i forbindelse med testingen:
        - Manipulasjonsobjekter Stanford binet-5
        - iPader

        - 9-hole peg-test
- Pass på at det er tilgjengelig munnbind, tørkepapir og desinfeksjonsmiddel på testrommet.

Oppmøte:

- Møt deltageren utenfor Harald Schjelderups Hus.
- Påminn deltageren om preventive tiltak.
- Opprettholde 1m avstand såfremt det er mulig, og unngå å håndhilse
- Instruer deltagerne om å ta på så få objekter som mulig
- Åpne dørene for deltagerne (bruk døråpner om mulig).
- Hvis deltagerne hvor de kan vaske hendene.

Under testingen

- Prøv å begrens tiden nærme deltageren.
- Dersom en deltager eller testleder utvikler symptomer på akutt luftveisinfeksjon under testingen skal personen få på seg munnbind og testingen avsluttes.

Etter møte gjennomføres samme desinfiseringsprosedyre:

- Følg deltageren ut og åpne alle dører for dem.
- Testlederen tørker av alle overflater med desinfeksjonsmiddel:
    - Stoler og bord.
    - Dørhåndtak.
    - Alt utstyr som brukes i forbindelse med testingen.
        - Manipulasjonsobjekter Stanford binet-5
        - iPader
        - 9-hole peg-test
    - Annet utstyr som testleder, deltager eller foresatte har berørt.
    - Dersom testleder låser seg inn i det arkivskapet, skal skapdør og lås tørkes av i etterkant.

Daniel Bryne
Epost: daniebry@uio.no Telefonnr: 413 76 268

Mikkel Glimsdal
Epost: mikkegl@uio.no Telefonnr: 996 90 699

Appendix D: Questionnaires

D1 Introduction

D2 BPM

D3 PSI-4-SF

D4 KIDSCREEN-10

D5 I/D-YC

D6 The Childs Diet

D7 GSRS

D8 Sleep

D9 Somatic disorders

Glutensensitivitet og utvikling hos barn med Down syndrom

Spørreskjemaer

Kjære forelder

Her finner du en rekke spørreskjemaer, som vi håper at du vil svare på! Denne spørreundersøkelsen er satt sammen av flere ulike velbrukte spørreundersøkelser og noen skjemaer som er spesielt utviklet for dette prosjektet. Dette gjør at svarsalternativene vil endre seg gjennom spørreskjemaet, derfor er det viktig at svarsalternativene leses nøye.

Det varierer hvor lang tid ulike personer bruker på å fylle ut skjemaene. Vi tror du bør sette av cirka en time. Vi anbefaler at du er alene når du svarer, skjemaene inneholder spørsmål som kan være sensitive. Det er viktig at du svarer på så mange spørsmål som mulig. Dersom det skulle være spørsmål du synes det er vanskelig å svare på kan du eventuelt hoppe over disse.

Har du spørsmål til skjemaene kan du ta direkte kontakt med førsteamanuensis og prosjektleder Egil Nygaard: egil.nygaard@psykologi.uio.no, 41291922.

Tusen takk for at du tar deg tid!

Med vennlig hilsen

Egil Nygaard, på vegne av prosjektmedarbeiderne
Førsteamanuensis
Spesialist i klinisk psykologi
Psykologisk Institutt
Universitetet i Oslo

Hva er barnets deltagernummer? *

Spør en forskningsassistent for deltagernummer dersom du mangler det

……

Sosiodemografi:

Barnets fødselsdato: ……

Dagens dato: ……..

Barnets kjønn:

☐ Gutt

☐ Jente

Barnets vekt (kg): …….

Barnets høyde (cm): ……

Hvor er barnet født:

☐ Norge

☐ Annet (hvis annet spesifiser her) ……

Din relasjon til barnet:

☐ Mor

☐ Far

☐ Annet (hvis annet spesifiser her) ……..

Omsorgsituasjonen til barnet:

☐ Biologiske foreldre som bor sammen

☐ Biologiske foreldre som ikke bor sammen, begge har omsorg for barnet

☐ Kun en av biologiske foreldre har omsorg for barnet

- ☐ Biologiske forelder med omsorgen for barnet bor sammen med annen voksen
- ☐ Biologiske forelder med alene omsorgen for barnet bor ikke sammen med annen voksen

☐ Annet (hvis annet spesifiser her) ……

Mors høyeste fullførte utdannelse:

☐ Grunnskole

☐ Videregående skole

☐ Fagskole

☐ Universitets- eller høgskole, lavere grad (inntil 4 år)

☐ Universitets- eller høgskole, høyere grad (mer enn 4 år)

☐ Vet ikke

Fars høyeste fullførte utdannelse:

☐ Grunnskole

☐ Videregående skole

☐ Fagskole

☐ Universitets- eller høgskole, lavere grad (inntil 4 år)

☐ Universitets- eller høgskole, høyere grad (mer enn 4 år)

☐ Vet ikke

Barnets atferd (ASEBA, BPM-P)

Nedenfor er en liste med utsagn som beskriver barn og ungdom. For hvert utsagn som beskriver barnet/ungdommen nå eller de siste 6 **Månedene**, vennligst velg **2** hvis beskrivelsen **stemmer veldig bra**, **1** hvis beskrivelsen **stemmer delvis** og **0** hvis beskrivelsen **ikke stemmer**.

Vennligst svar så godt du kan på alle spørsmålene selv om noen ikke passer for barnet.

0 = Stemmer ikke (så vidt du vet) 1 = Stemmer delvis 2 = Stemmer veldig bra

Kommentarer

0 1 2 1. Oppfører seg som yngre enn sin alder ----------

0 1 2 2. Krangler mye ----------

0 1 2 3. Fullfører ikke oppgaver han/hun begynner på

---

0 1 2 4. Kan ikke konsentrere seg, være oppmerksom lenge om gangen

---

0 1 2 5. Kan ikke sitte stille, er urolig eller hyperaktiv

---

0 1 2 6. Ødelegger familiemedlemmers eller andres ting

---

0 1 2 7. Ulydig hjemme ----------

0 1 2 8. Ulydig i barnehagen/på skolen ----------

0 1 2 9. Føler seg mindreverdig eller underlegen ----------

0 1 2 10. Er impulsiv eller handler uten å tenke ----------

0 1 2 11. For redd eller engstelig ----------

0 1 2 12. Har for sterk skyldfølelse ----------

0 1 2 13. Blir lett flau eller forlegen ----------

0 1 2 14. Uoppmerksom, blir lett distrahert ----------

0 1 2 15. Sta, mutt eller irritabel ----------

0 1 2 16. Får raseriutbrudd eller heftig sinne ----------

0 1 2 17. Truer andre ----------

0 1 2 18. Ulykkelig, trist eller deprimert ----------

0 1 2 19. Bekymrer seg ----------

Foreldres stress (PSI, 4th edition, short form)

Vennligst les hvert utsagn under nøye. For hvert utsagn, vennligst fokuser på barnet med Down syndrom og sett sirkel rund svaralternativet som best representerer din mening.

Svaralternativer:
SE = Svært enig
E = Enig
IS = Ikke sikker
U = Uenig
SU = Svært uenig

Mens du kanskje ikke finner et svar som svarer perfekt til dine følelser, vennligst velg svaret som kommer nærmest til å beskrive hvordan du føler deg. Din første reaksjon til hvert spørsmål bør være ditt svar. Svar et alternativ på hvert utsagn og svar på alle utsagnene.

1.	Jeg føler ofte at jeg ikke takler ting særlig bra	SE	E	IS	U	SU
2.	Jeg finner at jeg gir mer av livet mitt til å tilfredsstille behovene til mine barn enn jeg noen gang hadde forventet.	SE	E	IS	U	SU
3.	Jeg føler meg fanget av mitt ansvar som forelder.	SE	E	IS	U	SU
4.	Siden jeg fikk dette barnet har jeg ikke vært i stand til å gjøre nye og annerledes ting.	SE	E	IS	U	SU
5.	Siden jeg fikk et barn føler jeg at jeg nesten aldri får gjøre ting som jeg liker.	SE	E	IS	U	SU
6.	Jeg er misfornøyd med de siste klærne som jeg kjøpte til meg selv.	SE	E	IS	U	SU
7.	Det er nokså mange ting med livet mitt som bekymrer meg.	SE	E	IS	U	SU
8.	Å få barn har ført til flere problemer med min ektefelle/omsorgsgivende partner enn jeg hadde forventet.	SE	E	IS	U	SU
9.	Jeg føler meg ensom og uten venner	SE	E	IS	U	SU
10.	Når jeg går på fest/selskap forventer jeg vanligvis ikke å hygge meg	SE	E	IS	U	SU

11.	Jeg er ikke så interessert i andre mennesker som før.	SE	E	IS	U	SU
12.	Jeg nyter ikke ting like mye som før.	SE	E	IS	U	SU
13.	Det er ikke ofte at barnet mitt gjør ting for meg som får meg til å føle meg bra.	SE	E	IS	U	SU
14.	Når jeg gjør noe for barnet mitt, føler jeg at det setter lite pris på min innsatts.	SE	E	IS	U	SU
15.	Barnet mitt smiler mye mindre til meg enn jeg hadde forventet.	SE	E	IS	U	SU
16.	Noen ganger føler jeg at barnet mitt ikke liker meg og ikke har lyst til å være nær meg.	SE	E	IS	U	SU
17.	Barnet mitt er veldig emosjonelt og blir lett opprørt.	SE	E	IS	U	SU
18.	Barnet mitt ser ikke ut til å lære like raskt som barn flest.	SE	E	IS	U	SU
19.	Barnet mitt ser ikke ut til å smile like mye som barn flest.	SE	E	IS	U	SU
20.	Barnet mitt er ikke i stand til å gjøre så mye som jeg forventet.	SE	E	IS	U	SU
21.	Det tar lang tid og er veldig vanskelig for barnet mitt å bli vant til nye ting.	SE	E	IS	U	SU
22.	Jeg føler at jeg er: (velg et av alternativene under) 1. En meget god forelder 2. Bedre enn en gjennomsnittsforelder 3. En gjennomsnittlig forelder 4. En som har noen problemer med å være forelder 5. Ikke særlig god til å være forelder	1	2	3	4	5
23.	Jeg hadde forventet å ha sterkere, varmere følelser for barnet mitt enn jeg har, og dette bekymrer meg.	SE	E	IS	U	SU
24.	Iblant gjør barnet mitt ting som plager meg bare for å være slem,	SE	E	IS	U	SU

25.	Det virker som barnet mitt gråter og skaper seg oftere enn andre barn flest.	SE	E	IS	U	SU
26.	Barnet mitt våkner vanligvis opp i dårlig humør.	SE	E	IS	U	SU
27.	Jeg føler at barnet mitt er veldig humørsykt og blir lett opprørt.	SE	E	IS	U	SU
28.	Sammenlignet med barn flest har barnet mitt store problemer med å bli vant til forandringer i tidsplaner eller i huset.	SE	E	IS	U	SU
29.	Barnet mitt reagerer sterkt når det skjer noe som han/hun ikke liker.	SE	E	IS	U	SU
30.	Når barnet mitt leker er det sjeldent at han/hun fniser eller ler.	SE	E	IS	U	SU
31.	Det ble mye vanskeligere enn jeg forventet å etablere en rutine for leggetid eller måltider for barnet mitt.	SE	E	IS	U	SU
32.	Jeg har erfart at å få barnet mitt til å gjøre noe eller å holde opp å gjøre noe er: (Velg et av alternativene under) 1. mye vanskeligere enn jeg hadde forventet 2. noe vanskeligere enn jeg hadde forventet 3. omtrent like vanskelig som jeg hadde forventet 4. noe lettere enn jeg hadde forventet 5. mye lettere enn jeg hadde forventet	1	2	3	4	5
33.	Tenk nøye over og tell hvor mange ting som barnet ditt gjør som plager deg. For eksempel somler bort tiden, nekter å høre etter, er hyperaktiv, gråter, avbryter andre, slåss, jamrer, osv. (Velg et av alternativene under) 1. 1-3 2. 4-5 3. 6-7 4. 8-9 5. 10+	1	2	3	4	5

34.	Det er noen ting barnet mitt gjør som virkelig plager meg mye.	SE	E	IS	U	SU
35.	Atferden til barnet mitt er ett større problem enn jeg hadde forventet.	SE	E	IS	U	SU
36.	Barnet mitt krever mer av meg enn barn flest.	SE	E	IS	U	SU

Barnets helse (KIDSCREEN 10)

Når du tenker på den siste uka….

Når du tenker på den siste uka……					
1. Har barnet ditt følt seg frisk og sprek?	Ikke I det hele tatt	Litt	Ganske	Veldig	I høy grad
2. Har barnet ditt følt seg full av energi?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
3. Har barnet ditt følt seg trist?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
4. Har barnet ditt følt seg ensom?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
5. Har barnet ditt hatt nok tid for seg selv?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
6. Har barnet ditt kunne gjøre de tingene han/hun ønsker i fritiden sin?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
7. Har barnet ditt følt at foreldrene behandler ham/henne rettferdig?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
8. Har barnet ditt hatt det gøy sammen med vennene sine?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
9. Har barnet ditt klart seg bra på skolen?	Ikke i det hele tatt	Litt	Ganske	Veldig	I høy grad
10. Har barnet ditt klart å følge med på skolen?	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid

Til vanlig, hvordan vil barnet ditt karakterisere helsen sin?

- utmerket
- veldig bra
- bra
- ganske bra
- dårlig

Barnets nysgjerrighet (Piotrowski et al., 2014)

Vennligst anslå hvor ofte barnet du observerer ser ut til å vise karakteristikkene eller atferden beskrevet i hver av utsagnene nedenfor. Baser dine vurderinger av hvert utsagn på din ærlige vurdering av barnets intellektuelle utforskning og nysgjerrighet sammenlignet med andre barn på den alderen.

Svaralternativer:
1 = Nesten aldri
2 = Noen ganger
3 = Ofte
4 = Nesten alltid

		Nesten aldri	Noen ganger	Ofte	Nesten alltid
1.	Barnet mitt har det moro når det lærer om nye temaer.	1	2	3	4
2.	Barnet mitt tiltrekkes av nye ting i miljøet.	1	2	3	4
3.	Barnet mitt liker å snakke om temaer som er nye for han/henne.	1	2	3	4
4.	Barnet mitt viser tydelig glede når han/hun oppdager noe nytt.	1	2	3	4
5.	Barnet mitt stiller mange spørsmål når han/hun holder på å lære noe nytt.	1	2	3	4
6.	Når barnet mitt møter for et vanskelig problem, fokuserer han/hun all oppmerksomheten sin på hvordan løse det.	1	2	3	4
7.	Barnet mitt anstrenger seg betydelig for å forstå det som er forvirrende eller uklart.	1	2	3	4
8.	Barnet mitt er plaget når det er noe han/hun ikke forstår, og anstrenger seg hardt for å forstå det.	1	2	3	4
9.	Barnet mitt vil jobbe lenge for å løse et problem fordi han/hun ønsker å vite svaret.	1	2	3	4
10.	Barnet mitt undersøker ting nøye ved å snu på det eller se på det fra alle sider.	1	2	3	4

Barnets kosthold

Spørsmål 1: Ble barnet fullammet fra fødsel?

☐ Ja

☐ Nei

Spørsmål 2: Dersom barnet fikk morsmelk lenger, hvor gammelt var barnet da det sluttet å få morsmelk?

☐☐ Måneder

Spørsmål 3: Hvor gammelt var barnet da fast føde (annen mat enn morsmelk/ kosttilskudd) ble gitt for første gang?

☐☐ Måneder

Spørsmål 4: Hvor gammelt var barnet da glutenholdig grøt (hvete-, spelt-, rug eller byggrøt) ble gitt for første gang?

☐☐ Måneder

Spørsmål 5: Hvilke matvarer gir dere IKKE til barnet?

☐ Glutenholdig korn/mel (hvete, spelt, rug, bygg)

☐ Vanlig kumelk /yoghurt/ost

☐ Appelsin/appelsinjuice/annen sitrusfrukt

☐ Fisk/skalldyr

☐ Nøtter/nøtteprodukter (peanøttsmør o.l.)

☐ Belgfrukter (erter, bønner o.l.)

☐ Egg

☐ Soya

☐ Salt

☐ Matvarer med tilsetningsstoffer

☐ Mat som ikke er økologisk dyrket

☐ Det er ingen matvarer vi IKKE gir til barnet

☐ Annet

Hvis annet, spesifiser

_____

Spørsmål 6: Barna som er med i denne studien er fra 5-11 år. Hva de spiser og drikker vil avhenge av alder. Har barnet problemer i forhold til mat/spising som ikke er naturlige i forhold til barnets alder?

☐ Nei, har ikke noen problemer

☐ Ja, dårlig matlyst/småspist

☐ Ja, liker få matvarer

☐ Ja, vanskelig med tilvenning til familiens kosthold

☐ Ja, allergi/intoleranse mot matvarer

Oppgi hvilke:

_____

☐ Ja, andre problemer med spising

Oppgi hvilke (f.eks svelgeproblemer, brekker seg lett)

_____

_____

Spørsmål 7: Har barnet vært sondeernært?

☐ Ja

☐ Nei

☐ Vet ikke

Hvor gammelt var barnet da det fikk sondeernæring (i måner)?

_____

*Dette elementet vises kun dersom alternativet «Ja» er valgt i spørsmålet «7. Har barnet vært sondeernært?

Hvor lenge fikk barnet sondeernæring (i dager)?

_____

*Dette elementet vises kun dersom alternativet «Ja» er valgt i spørsmålet «7. Har barnet vært sondeernært?

Spørsmål 8: Hvor ofte tar barnet kosttilskudd?

☐ Hver dag

☐ 4-6 ganger pr. uke

☐ 1-3 ganger pr. uke

☐ Sjeldnere enn 1 gang pr uke

☐ Aldri

Hvilke(n) type(r) benyttes (angi produktnavn og mengde)?

_____

_____

(Eksempel Nycoplus multi flytende, Sanasol, Nycoplus multi vitamin og mineraltbl for barn, kalsium 250 mg, kalsium 500 mg, NeoFer (jerntilskudd), omega-3 tilskudd, vitamin C, Møllers tran med sitronsmak, vitamin D)

Spørsmål 9: Tar barnet helsekostprodukter (f.eks probiotika, alger el.) nå (beskriv hvilke produkter og dosering)?

☐ **Ja**

☐ **Nei**

Hvis ja, hvilke(n) type(r) benyttes (angi produktnavn og mengde)?

_____

Spørsmål 10: Hvor ofte spiser barnet vanlig, glutenholdig brød?

☐ Hver dag

☐ 4-6 ganger pr. uke

☐ 1-3 ganger pr. uke

☐ Sjeldnere enn 1 gang pr uke

☐ Aldri

Spørsmål 11: Hvor ofte spiser barnet glutenholdig mat til middag (f.eks.pizza, pasta)**?**

☐ Hver dag

☐ 4-6 ganger pr. uke

☐ 1-3 ganger pr. uke

☐ Sjeldnere enn 1 gang pr uke

☐ Aldri

Spørsmål 12: Hvor ofte spiser barnet glutenholdige boller, kaker, skolebrød eller lignende?

☐ Hver dag

☐ 4-6 ganger pr. uke

☐ 1-3 ganger pr. uke

☐ Sjeldnere enn 1 gang pr uke

☐ Aldri

Spørsmål 13: Hvor ofte drikker barnet melk? (gjelder alle typer melk)

☐ Hver dag

☐ 4-6 ganger pr. uke

☐ 1-3 ganger pr. uke

☐ Sjeldnere enn 1 gang pr uke

☐ Aldri

Oppgi eventuelt her hvis det er kun spesielle typer melk, f.eks. laktosefri melk:

_____

Spørsmål 14: Hvor ofte spiser barnet melkesjokolade?

☐ Hver dag

☐ 4-6 ganger pr. uke

☐ 1-3 ganger pr. uke

☐ Sjeldnere enn 1 gang pr uke

☐ Aldri

Spørsmål 15: Hvor ofte kjøper du mat fra seksjonen for glutenfrie produkter når du handler?

☐ Hver gang jeg handler

☐ Halvparten av gangene jeg handler

☐ Hver tredje eller fjerde gang jeg handler

☐ En sjelden gang iblant

☐ Aldri

Spørsmål 16: Har barnet fulgt vekstkurven sin gjennom oppveksten?

☐ Ja

☐ Nei

Hvis ikke, spesifiser under:

_____

THE GASTROINTESTINAL SYMPTOM RATING SCALE

(GSRS)

Les dette først:

Undersøkelsen inneholder spørsmål om hvordan barnet ditt har det, og hvordan barnet ditt har hatt det DEN SISTE UKEN. Kryss av for det alternativ som best passer for barnet ditt og hans/hennes situasjon.

1. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av SMERTER ELLER UBEHAGFRA DEN ØVRE DEL AV MAGEN?

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

2. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av HALSBRANN? (Med halsbrann menes en sviende eller brennende følelse av ubehag bak brystbeinet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

3. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av SURE OPPSTØT? (Med sure oppstøt menes plutselige oppstøt av surt mageinnhold.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

4. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av SUG I MAGEN? (Med sug i magen menes her en følelse i magen av behov for å spise mellom måltidene.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

5. Har du lagt merke til at barnet ditt i løpet av den siste uken følt deg UVEL? (Med å føle seg uvel menes ubehagsfølelse som kan gå over i kvalme og brekninger/oppkast.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

6. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av RUMLING I MAGEN? (Med rumling menes vibrasjoner eller "buldring" i magen.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

7. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av OPPBLÅSTHET? (Med oppblåsthet menes utspiling, ofte forbundet med en følelse av luft i magen.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

8. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av RAPING? (Med raping menes behov for "utlufting", ofte forbundet med lindring av følelse av oppblåsthet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

9. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av LUFTAVGANG? (Med luftavgang menes her behov for å "slippe seg", ofte forbundet med lindring av følelse av oppblåsthet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

10. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av FORSTOPPELSE? (Med forstoppelse menes minsket avføringshyppighet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

11. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av DIARÉ? (Med diaré menes økt avføringshyppighet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

12. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av LØS AVFØRING? (Hvis barnet ditt har hatt vekslende hard og løs avføring, gjelder dette spørsmålet bare i hvilken utstrekning barnet ditt har følt seg plaget av at avføringen har vært løs.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

13. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av HARD AVFØRING? (Hvis barnet ditt har hatt vekslende hard og løs avføring, gjelder dette spørsmålet bare i hvilken utstrekning barnet ditt har følt seg plaget av at avføringen har vært hard.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

14. Har du lagt merke til at barnet ditt i løpet av den siste uken vært plaget av TVINGENDE AVFØRINGSBEHOV? (Med tvingende avføringsbehov menes raskt oppståtte behov for å gå på toalettet,ofte forbundet med en følelse av mangelfull kontroll.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

15. Har barnet ditt i løpet av den siste uken i forbindelse med AVFØRING HATT EN FØLELSE AV UFULLSTENDIG TØMMING AV TARMEN? (Med ufullstendig tømming av tarmen menes at det trass i anstrengelser i forbindelse med avføring gjenstår en følelse av ufullstendig tømming.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

Søvn

Spørsmål 1: Omtrent hvor mange timer sover barnet vanligvis per natt på hverdager?

- ☐ 8 timer eller mindre
- ☐ 9 timer
- ☐ 10 timer
- ☐ 11 timer
- ☐ 12 timer eller mer

Spørsmål 2: Hvor ofte hender det at barnet våkner om natten?

- ☐ 3 eller flere ganger per natt
- ☐ 1-2 ganger per natt
- ☐ Noen ganger per uke
- ☐ Sjelden, aldri

Spørsmål 3: Hvor ofte snorker barnet?

- ☐ Aldri
- ☐ Mindre enn 1 natt i uken
- ☐ Ca 1 natt i uken
- ☐ Flere netter i uken
- ☐ Nesten hver natt

Kroppslige sykdommer

Har eller har barnet hatt noen vesentlige kroppslige sykdommer?

		Nei	Ja, nåværende	Ja, tidligere	Beskriv (inklusive alvorlighetsgrad og når)
1.	Hørselsproblemer				
2.	Synsproblemer				
3.	Motoriske problemer				
4.	Nevrologiske problemer				
5.	Hjerteproblemer				
6.	Cøliaki				
7.	Andre allergier				
8.	Andre somatiske problemer?				

Medisinbruk

Bruker barnet medisiner:

☐ Nei

☐ Ja

Hvis ja, spesifiser under:

Syredempende: _____

Allergi/astma medisin: _____

Epilepsi medisin: _____

Stoffskifte-medisin: _____

Andre medisiner _____

Tusen takk for innsatsen ☺

Appendix E: Blood samples

E1 Requisition general blood tests

E2 Requisition celiac diagnostics

E3 Supplementary note with clarifying information concerning blood tests

FÜRST
MEDISINSK LABORATORIUM

Fordøyelsessykdommer

Postboks 158, Alnabru
N-0614 Oslo
Telefon: 22 90 95 00
post@furst.no

Versjon 211

Prøve ID

Rekvirent ID

Underskrift

(legekontor, adresse, dato)

☐ Allmennmedisin ☒ Annen spesialitet ☐ Poliklinikk ☐ Annet

Ref.nr. for pasientkobling

Fødselsdato | Personnr. | Kjønn (K/M) Kvinne K Mann M

Pasientnavn

Adresse

Postnr. | Poststed

Kopi av svarbrev ønskes sendt til
Foreldre. Fastlege?

Kliniske opplysninger
Down syndrom.
Mistanke om gluten-følsomhet.

Betales av
☒ HELFO:
☐ Bedriftshelsetjeneste:
☐ Institusjon:
☐ Annet:

Prøvetakingsdato d d m m å å
Tidspunkt (kl.) t t m m

Fylles ut av prøvetaker

Cøliaki

Cøliaki *(2 mL serum)*

☒ 470 Diagnostikk av cøliaki

Diagnostikk av cøliaki er basert på analyser med IgA og IgG antistoffer. Ved å kombinere analyse av anti-tTG IgA med analyse av anti-deamidert gliadin IgG, vil diagnostikk av cøliaki være mulig, også ved IgA-mangel.

Viktige opplysninger:
- ☐ Oppfølging av cøliaki-pasienter
- ☐ Oppfølging av cøliaki-pasienter med IgA-mangel
- ☐ Pasienten har cøliaki i nær familie
- ☐ Pasienten har stått på glutenfri kost før de diagnostiske prøver tas

HLA-DQ2/DQ8 *(3 mL EDTA-blod)*

☒ 823 HLA-DQ2/DQ8
Rekvireres på spesiell indikasjon

Mer enn 99% av alle cøliakipasienter har vevstype DQ2 og/eller DQ8, en vevstype som finnes hos ca. 30% av befolkningen. En positiv vevstype-test vil følgelig ikke være diagnostisk. På den annen side vil en negativ test utelukke cøliaki med så stor grad av sikkerhet at pasienten kan spares for videre utredning.

Laktoseintoleranse

Laktasemangel, gentest *(3 mL EDTA-blod)*

☐ 253 Gentest *(primær laktasemangel), se bakside for mer informasjon*

Magesår

Helicobacter pylori antistoff *(0,5 mL serum)*

☐ 707 Anti-H.pylori IgG

Dette er en primærtest, brukes ikke til oppfølging etter behandling.

Inflammatorisk tarmsykdom *(Ulcerøs kolitt og Crohns sykdom)*

☐ 484 Calprotectin i feces *(minimum halvfullt rør)*

Vennligst kryss av
- ☐ testen er ledd i utredning
- ☐ testen er ledd i oppfølging av behandling

Mage- tarm- blødning

☐ 075 Blod i feces, *se bakside for pasientinformasjon*

For lab

For lab
- ☐ EKG
- ☐ URIN
- ☐ FEC
- ☐ 222
- ☐ 271
- ☐ GRAVI
- ☐ <16ÅR
- ☐ 987
- ☐ 945
- ☐ 946
- EDTA PL.
- CIT
- HEP.BL
- K. BL.
- GEL
- EDTA
- ☐ INNL
- ☐ TILS
- ☐ HJ
- ☐ FU
- ☐ DR
- ☐ MAJ
- ☐ SFJ
- ☐ SS
- ☐ OSE
- ☐ BERG
- ☐ LS
- ☐ VER

Sign

Ved forespørsel gis opplysninger om hvilke metoder som er akkreditert Generell informasjon om prøvetaking og analyser, se www.furst.no

10.2014

Timebestilling Oslo 22 90 96 00. Rekvisisjonen må medbringes.

INFORMASJON OM ANALYSER OG MATERIALE

Cøliaki
Det analyseres på antistoffer som er spesifikke for cøliaki. Det er mest aktuelt å analysere på IgA-antistoffer. IgG-analyser er nyttige hos pasienter med IgA-mangel.
Antistoff-nivået går ned ved glutenfri kost. Glutenfri kost før de diagnostiske prøver tas kan gi falskt negative resultater. Det må opplyses om det finnes cøliaki i nær familie, og om pasienten har stått på glutenfri kost.

HLA-DQ2/DQ8 for cøliakidiagnostikk
På spesiell indikasjon anbefaler Fürst cøliakiassosiert vevstyping. Analysen er uegnet for screening. Analyse av HLA-DQ2/DQ8 bør brukes som supplement til etablert cøliakidiagnostikk. Analysen kan være nyttig i vanskelige tilfeller eller i bedømmelse av familierisiko. Negativ test utelukker cøliaki med så stor grad av sikkerhet at pasienten i en del tilfeller kan spares for videre utredning.

Laktoseintoleranse
Gentest er førstevalg ved mistanke om medfødt, primær laktasemangel (laktoseintoleranse) og krever kun en enkel blodprøve (EDTA-blod). Gentesten utføres ikke hos barn under 3 år. Primær laktasemangel utvikles vanligvis ikke før 3-årsalder, og eventuelle abdominalplager før dette må da antas å ha annen årsak. Selv om primær laktasemangel påvises, er det vanlig at pasienten tolererer litt melkeprodukter (tilsvarende ca 2 dL melk i døgnet). Av hensyn til ernæring og vekst bør barn med primær laktasemangel trolig likevel få i seg litt melkeprodukter, selv om de inneholder laktose.

Laktosebelastning kan være aktuelt ved sekundær laktasemangel, men da vil behandling av primærsykdommen stå i fokus. Fürst Medisinsk Laboratorium utfører ikke lenger laktosebelastning, men kan utføre måling av glukose i blodprøver som tas før og etter laktosebelastning. For mer informasjon, se www.furst.no.

Magesår
Antistoff mot Helicobacter pylori er en primærtest og kan ikke brukes til oppfølging etter behandling. Diagnostisk bruk av testen forutsetter at pasienten ikke har gjennomgått antibiotikabehandling rettet mot helicobacter. Antistoff kan foreligge i flere år etter vellykket behandling.

Inflammatorisk tarmsykdom (Ulcerøs kolitt og Crohns sykdom)
Ved diagnostikk og oppfølging av inflammatorisk tarmsykdom bestemmes mengden av calprotectin i feces. Feces overføres til en prøvebeholder uten tilsetning, minimum halvfullt rør. Prøven kan sendes straks eller fryses ned for senere leveranse.

Mage- og tarm- blødning
Blod i feces analyseres ved mistanke om blødninger fra mage- /tarmkanal. I 4 døgn før prøven tas og i prøvetiden må pasienten unngå rødt kjøtt, blodmat, fisk med mørkt kjøtt (laks, tunfisk, makrell og sardiner), blomkål, pepperrot, rå tomater, reddiker, melon, bananer og soyabønner. Unngå alkohol i prøvetiden. Innta ikke: acetylsalisylsyre (Dispril, Aspirin, Globoid), jernpreparater og C-vitamintabletter. Det anbefales minimum 3 feces-prøver fra ulike dager. Spesialkonvolutt (Hemo-Fec test slide) fås på legekontoret. Les bruksanvisning på konvolutten.

Kommentar til resultater
Fürst gir kliniske kommentarer til analyseresultat. Gode opplysninger om problemstillingen er nødvendig for at det skal kunne gis relevant klinisk kommentar.

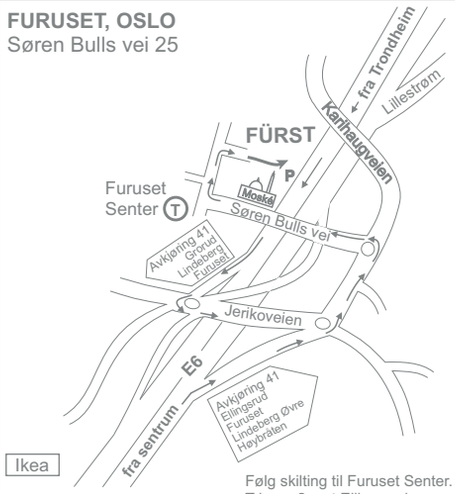
PRØVETAKINGSSTASJONER

Noe ventetid må påregnes om morgenen og ved lunsjtider for pasienter som velger drop-in.

I sommerperioden og i høytider kan enkelte prøvetakingsstasjoner ha endrede åpningstider eller være stengt.

Det må kunne vises gyldig legitimasjon ved prøvetaking hos Fürst.

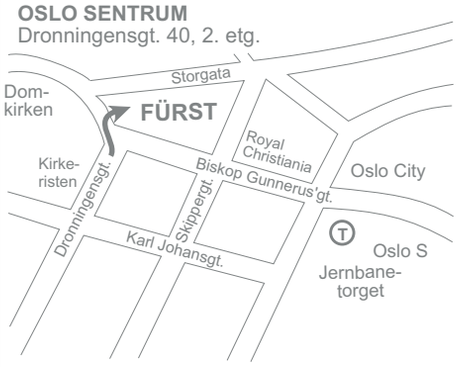
FURUSET, OSLO
Søren Bulls vei 25



Følg skilting til Furuset Senter.
T-bane 2 mot Ellingsrud.

Hovedlaboratoriet ligger ved Furuset senter og T-banestasjon med prøvetakingsenhet i underetasjen. Mulighet for parkering.
Lett adkomst for pasienter i rullestol.
Åpent mandag - fredag 7.30 - 15.00, onsdager kveldsåpent til 20.00.

OSLO SENTRUM
Dronningensgt. 40, 2. etg.



Inngang ved NAF-huset. Parkeringsmulighet i nærliggende parkeringshus, eksempelvis i Oslo City.
Åpent mandag - fredag 7.30 - 15.00.

MAJORSTUEN, OSLO
Kirkevn. 64B, 3. etg. (inng. Bogstadvn.)

Egner seg for pasienter som vil benytte vestgående T-baner, buss eller trikk.
Åpent mandag - fredag 7.30 - 15.00, tirsdager kveldsåpent til 20.00.

SANDEFJORD
Dronningensgate 3, 3. etg., (Gleditschgården)

Adkomst for pasienter i rullestol.
Åpent mandag - fredag 7.30 - 15.00.

Merking av rør

Etikettene plasseres loddrett utenpå fabrikantens etikett!

FURST
MEDISINSK LABORATORIUM

NORSK AKKREDITERING TEST 038

Timebestilling: 22 90 96 00 (se baksiden)
Søren Bulls vei 25
N-1051 Oslo
Telefon 22 90 95 00
post@furst.no

T 022

ProveID

Rekvirent ID:

Underskrift

(legekontor, adresse, dato)

☐ Allmennmedisin ☒ Annen spesialitet ☐ Poliklinikk ☐ Annet

Kopi av svarbrev ønskes sendt til
Foreldre. Fastlege?

Kliniske opplysninger
Down syndrom.
Mistanke om gluten-følsomhet.

Ref.nr. for pasientkobling

Fødselsnummer d d m m å å

Kjønn: (K/M) Kvinne K Mann M

Pasientnavn

Adresse

Postnr.

Poststed

Betales av
☒ Helfo
☐ Bedriftshelsetjeneste:
☐ Institusjon:
☐ Annet:

Prøvetakingsdato d d m m å å
Tidspunkt t t m m
Fylles ut av prøvetaker

FORKLARING TIL KODENE
F=fastende, 1=EDTA plasma, 4=se www.furst.no, 5=pasienten må møte

Hematologi, HbA1c *(EDTA-blod)*

- ☒ 001 Hb
- ☐ 002 Erytrocytter
- ☐ 012 Hematokrit
- ☒ 013 MCV/MCH
- ☐ 010 Retikulocytter
- ☒ 004 Leukocytter
- ☒ 009 Leukoc. m/Diff. 4
- ☐ 005 Eosinofile 4
- ☒ 011 Trombocytter
- ☐ 037 HbA1c

På spesielle indikasjoner (genanalyser)

- ☐ 164 Hemokromatose
- ☐ A80 Hemoglobinopati
- ☐ 253 Laktasemangel
- ☐ A89 HLA-B27

Hemostase *(Citrat-blod)*

- ☐ 166 INR

Klinisk kjemi, lipider, proteiner *(serum)*

- ☐ 020 Kalium
- ☐ 021 Natrium
- ☐ 022 Klorid
- ☐ 025 Kalsium
- ☐ 024 Fosfat, uorg.
- ☐ 026 Magnesium
- ☐ 043 Jern/TIBC
- ☐ 036 CK
- ☐ 238 CK-MB
- ☐ 180 Lipase
- ☐ 038 Amylase total
- ☐ 181 Amylase pankr
- ☐ 054 Triglyserider F
- ☐ 047 Kolesterol
- ☐ 049 Protein total
- ☐ 069 Albumin
- ☐ 093 Alfa 1-antitrypsin
- ☐ 105 Haptoglobin
- ☐ 050 Elektroforese
- ☐ 065 Imm.globuliner
- ☐ 041 Glukose fastende F

Brettelinje

- ☒ 119 Ferritin
- ☐ 030 Fosf. alk (ALP)
- ☐ 107 Gamma GT
- ☐ 040 Bilirubin
- ☐ 035 LD
- ☒ 033 ASAT
- ☒ 034 ALAT
- ☐ 100 HDL-kolesterol
- ☐ 300 LDL-kolesterol
- ☐ 451 Lp (a)
- ☐ 346 ApoB/ApoA1 ratio
- ☐ 453 MikroCRP
- ☒ 088 CRP
- ☐ 059 Urinsyre
- ☐ 058 Urinstoff
- ☐ 048 Kreatinin
- ☐ 247 Kreatinin eGFR
- ☐ A98 Cystatin C m. eGFR

Hormoner, tumormarkører og andre *(serum hvis ikke annet angitt)*

- ☒ 118 TSH
- ☒ 189 Fritt T4
- ☐ 186 Fritt T3
- ☐ 083 Anti-TPO
- ☐ 301 Kortisol kl 08
- ☐ 302 Kortisol kl 19 4
- ☐ 190 Prolaktin 4
- ☐ 631 FSH
- ☐ 630 LH
- ☐ 132 Østradiol
- ☐ 131 Progesteron
- ☐ 634 hCG
- ☐ 632 Testosteron
- ☐ 633 SHBG
- ☐ 232 PSA
- ☐ A50 CEA
- ☐ A51 CA125
- ☐ 157 C-peptid F
- ☐ 146 PTH 1+4
- ☐ 142 Homocystein 1+4
- ☐ 342 MMA
- ☐ 060 Vitamin B12
- ☐ 086 Folat i serum
- ☐ 111 NT proBNP

Infeksjonsserologi *(serum)*

- ☐ 716 Hepatitt A
- ☐ 727 Hep A vaksinekontroll
- ☐ 700 Hepatitt B
- ☐ 705 Hep B vaksinekontroll
- ☐ 702 Hepatitt C
- ☐ 363 Anti-CMV
- ☐ 091 Mononukleose
- ☐ 733 HIV
- ☐ 512 Anti-Syfilis
- ☐ 359 Anti-Rubella
- ☐ 361 Anti-Toxoplasma
- ☐ 310 Anti-Varicella zoster
- ☐ S02 Anti-M.pneumoniae
- ☐ 707 Anti-H.pylori

Andre *(serum)*

- ☐ 087 Reum.faktor
- ☐ 187 Anti-CCP
- ☐ 073 ANA-screen
- ☐ 272 ANCA
- ☐ 163 Total IgE
- ☐ 657 Etanol 4
- ☐ 658 CDT
- ☐ 308 TRAS
- ☐ 491 Vit A
- ☐ 489 Vit D
- ☐ 494 Vit E
- ☐ 497 Vit K

Medikamenter *(serum - medikamentfaste; se baksiden)*

- ☐ 039 Digoksin
- ☐ 097 Fenobarbital
- ☐ 098 Fenytoin
- ☐ 099 Karbamazepin
- ☐ 101 Valproat
- ☐ 023 Litium 4

☐ *Kontroll* ☐ *Doseendring* ☐ *Bivirkninger* ☐ *Terapisvikt*

Sporelementer *(heparinrør med gel)*

- ☐ 028 Sink 4
- ☐ 018 Selen
- ☐ 114 Kobber
- ☐ 112 Aluminium 4

Tungmetaller *(heparinblod)*

- ☐ 027 Bly
- ☐ 115 Kadmium
- ☐ 029 Kvikksølv

Urinanalyser

- ☐ 070 Urin stix
- ☐ 149 Protein total
- ☐ 152 Elektroforese
- ☐ 320 Kalium
- ☐ 321 Natrium
- ☐ 548 Kreatinin
- ☐ 360 Albumin (AKR)
- ☐ 328 Sink
- ☐ 414 Kobber
- ☐ 215 Kadmium
- ☐ 130 Kvikksølv

Andre undersøkelser

- ☐ 042 Glukosebelastning F+4
- ☐ 080 EKG taking 5
- ☐ 081 EKG tyding 4

For lab

- ☐ EKG
- ☐ URIN
- ☐ FEC
- ☐ 222
- ☐ 271
- ☐ GRAVI
- ☐ <16 ÅR
- ☐ 987
- ☐ 945
- ☐ 946

EDTA PL. CIT HEPBL K.BL GEL EDTA

Fylles ut av Fürst

- ☐ INNL
- ☐ TILS
- ☐ HJ
- ☐ FU
- ☐ DR
- ☐ MAJ
- ☐ SFJ
- ☐ SS
- ☐ OSE
- ☐ BERG
- ☐ LS
- ☐ VER

SIGN

For lab — Fylles ut av Fürst

Annet: 1 rør serum til Rikshospitalet

Ved forespørsel gis opplysninger om hvilke metoder som er akkreditert

Se www.furst.no for rekvisisjoner til andre fagområder, og generell informasjon om rekvirering, prøvetaking og analyser.

Wittusen & Jensen, 03.2014

Timebestilling Oslo 22 90 96 00. Rekvisisjonen må medbringes.

PASIENTINFORMASJON

FORBEREDELSE TIL PRØVETAKING
I dagene før prøvetaking bør man avstå fra hard fysisk aktivitet. Dersom en ikke har fått beskjed om faste, kan man på prøvetakingsdagen spise en lett frokost. Store og fettrike måltider bør unngås i timene før prøven tas.
Det er gunstig å møte i god tid slik at en kan sitte avslappet i 10 -15 min før prøven tas. Prøvetaking med dagens moderne utstyr er en enkel prosedyre som medfører lite ubehag. Før prøvetaking på barn kan man få kjøpt bedøvelsesplaster reseptfritt på apotek eller hos Fürst. Plasteret må settes på 1 time før prøvetaking.
For enkelte analyser gjelder spesielle forholdsregler for prøvetaking. I hele åpningstiden kan man komme uten å ha bestilt time, men noe ventetid må da påregnes.

Det må kunne vises gyldig legitimasjon ved prøvetaking hos Fürst.

Prøver som krever timebestilling, tlf: 22 90 96 00: Glukosebelastning (042), Kortisol kl. 19 (302).

Fastende prøver: Til følgende prøver må pasienten møte fastende: C-peptid (157), Glukose (041), Glukosebelastning (042).
Med faste menes at man ikke skal spise, drikke, røyke eller bruke snus fra kl. 24.00 (midnatt) før prøvetaking, 1 glass vann kan inntas. Triglyserider (054) krever faste i 12 timer.

Jern (043): Ikke ta jernpreparater 1 døgn før prøvetaking. Prøven tas helst før kl. 12.00.

Medikamentanalyser: Kryss foran følgende prøver innebærer at dagens tablett tas etter prøvetaking: Digoksin (039), Fenobarbital (097), Fenytoin (098), Karbamazepin (099) og Valproat (101). Det samme gjelder thyreoidea-preparater (Levaxin, Euthyrox og Liothyronin) og ved eventuell måling av Fritt T4 (189). Ved prøvetaking til Litium (023) kan nærmere informasjon fås av rekvirerende lege eller hos Fürst. Preparatnavn og dosering noteres i felt for kliniske opplysninger.

Urinanalyser: Ta med ca 20 mL morgenurin.
(Til prøvetaker: Husk å merke prøveröret, **ikke transporthylsen** med en strekkodeetikett fra rekvisisjonen. Etiketten skal ha sluttkarakter 8).

PRØVETAKINGSENHETER

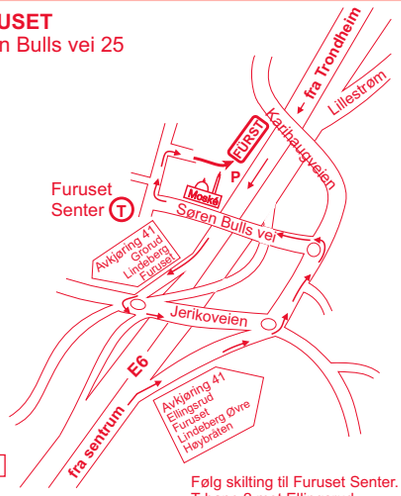
Noe ventetid må påregnes om morgenen og ved lunsjtider for pasienter som velger drop-in.

I forbindelse med høytider og sommerferie kan enkelte prøvetakingsstasjoner ha endrede åpningstider eller være stengt.

MERKING AV RØR

Etikettene plasseres loddrett utenpå fabrikantens etikett!

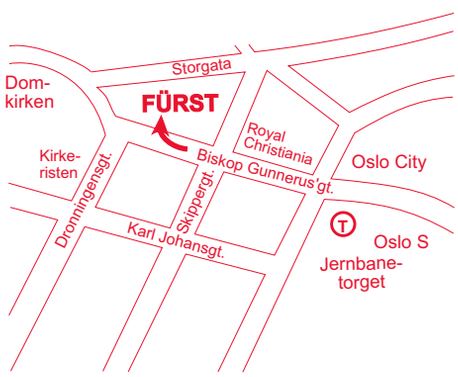
FURUSET
Søren Bulls vei 25



Følg skilting til Furuset Senter.
T-bane 2 mot Ellingsrud.

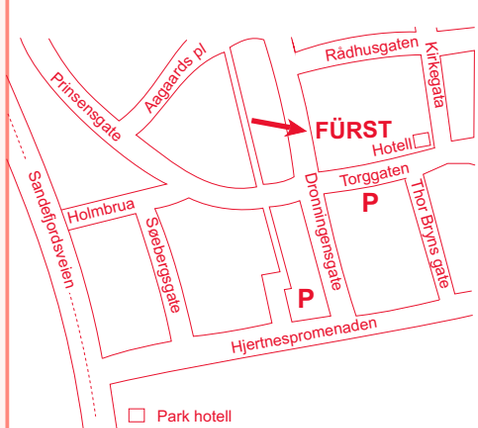
Hovedlaboratoriet ligger 3 min. gange fra Furuset senter og T-banestasjon.
Mulighet for parkering, og adkomst for pasienter i rullestol.
Åpent mandag - fredag 7.30 - 15.00, onsdager kveldsåpent til 20.00.

OSLO SENTRUM
Dronningensgt. 40, 2. etg.



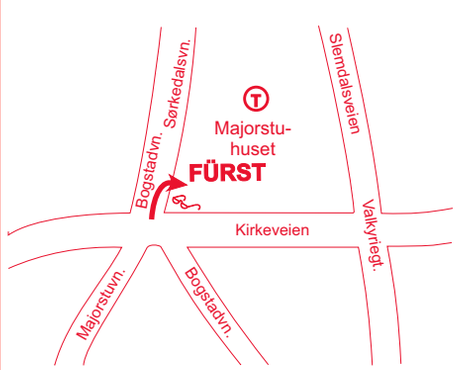
Inngang ved NAF-huset. Parkeringsmulighet i nærliggende parkeringshus, eksempelvis i Oslo City.
Åpent mandag - fredag 7.30 - 15.00.

SANDEFJORD
Dronningensgate 3, 3. etg., (Gleditschgården)



Adkomst for pasienter i rullestol.
Åpent mandag - fredag 7.30 - 15.00.

MAJORSTUEN
Kirkevn. 64B, 3. etg. (inng. Bogstadvn.)



Egner seg for pasienter som vil benytte vestgående T-baner, buss eller trikk.
Åpent mandag - fredag 7.30 - 15.00, tirsdager kveldsåpent til 20.00.

UiO : Universitetet i Oslo

Oslo universitetssykehus

ANGÅENDE REKVISJSONEN

Denne revisjonen gjelder forskningsprosjektet «Glutensensitivitet og utvikling hos barn med down syndrom» som er et samarbeid mellom Psykologisk institutt ved Universitet i Oslo og Oslo Universitetssykehus, Rikshospitalet.

I forbindelse med studien trenger vi at alle de deltakende barna tar blodprøver slik at vi kan måle identifiserte og eksperimentelle biomarkører. Noen av disse analysene skal gjøres ved Fürst, andre ved Gastrolab på Rikshospitalet. Dette betyr blodprøver må sendes to steder:

- Fürst trenger EDTA-blod og serum til å kunne utføre analysene på rekvisisjonsarket
- Gastrolab trenger et rør serum til eksperimentelle analyser, som sendes i vedlagt brun konvolutt.

Dersom dette skulle være uklart eller det skulle være noen spørsmål, er det bare å ta kontakt.

Med vennlig hilsen,

Daniel Bryne
daniebry@uio.no
413 76 268

Mikkel Glimsdal
mikkelgl@uio.no
996 90 699

Appendix F: Project outline sent to REK

Kognisjon og psykisk helse hos barn med Down syndrom med glutensensitivitet

Forskningsprotokoll

Bakgrunn og problemstilling

I denne kryss-seksjonelle studien ønsker vi å undersøke sammenhengen mellom biologiske mål på glutensensitivitet og psykologiske forhold hos barn med Down syndrom uten cøliaki. Vi ønsker å undersøke 60 barn i alderen 5 til 11 år. Vi vil i studien benytte blodprøver og nevrokognitive testresultater av barna, i tillegg til intervju og spørreskjema overfor foreldrene. Målsetningen med studien er å undersøke om det er sammenheng mellom glutensensitivitet og psykologisk fungering hos barna. Vi vil ha spesielt fokus på kognitiv fungering i tillegg til atferdsmessige tegn på engstelighet, tristhet og sinne hos barna.

Cøliaki er en glutenutløst sykdom, som diagnostiseres ved at man påviser typiske morfologiske forandringer i vevsprøver fra tynntarmslimhinnen. De fleste pasienter med cøliaki har også typisk serologiske tegn med IgA antistoffer mot enzymet vevstransglutaminase eller IgG antistoffer mot deamidert gliadin peptid (Ludvigsson et al., 2014). Hos barn kan man i en del tilfeller stille diagnosen på basis av slike antistoffer alene (Husby et al., 2012). Den anbefalte behandlingen for cøliaki er gluten fri diett.

Flere studier har de siste årene fokusert på de som har cøliaki-lignende symptomer når de spiser glutenholdig mat, men som ikke oppfyller kriteriene for cøliakidiagnosen (Brottveit et al., 2013; Lundin, 2014; Skodje et al., 2018). Slike problemer kalles ofte «glutenallergi», «ikke cøliakisk gluten sensitivitet» eller lignende. Det er uenighet om hvordan man skal definere glutensensitivitet, og det er usikkert om det er selve gluten eller andre deler av kornet som gir symptomer (Biesiekierski et al., 2013; Skodje et al., 2018). Dette kan tyde på at tilstanden «ikke-cøliakisk glutensensitivitet» egentlig er en variant av «irritabelt tarm syndrom – irritable bowel syndrome (IBS)». Selv om enkelte nyere studier har funnet ulike biologiske markører som til en viss grad kan skille mellom cøliaki og personer uten cøliaki med lignende symptomer (Uhde et al., 2016), så er det uavklart hvilke biologiske markører som utgjør de beste kriteriene for glutensensitivitet. Uten en slik avklaring er det vanskelig å vurdere hvem som skal få hvilken type behandling.

De siste årene har et begrenset antall studier undersøkt mulige sammenhenger mellom psykologisk fungering og cøliaki. En studie har vist forbedrede kognitive skår hos 11 nylig diagnostiserte voksne pasienter med cøliaki som begynte på glutenfri diett (Lichtwark et al., 2014; Yelland, 2017). Det er også funnet dårligere kognitiv funksjon hos 18 eldre personer med cøliaki til tross for lengre glutenfri diett i forhold til eldre personer uten cøliaki (Casella et al., 2012). En spørreundersøkelse viste at 401 voksne personer med cøliaki og 173 med irritabel tarm syndrom hadde større risiko for perifere nevrologiske problemer enn en kontrollgruppe (Shen et al., 2012). En nylig publisert litteraturgjennomgang konkluderer med at det er sammenheng mellom cøliaki og subkliniske nevroanatomiske funn (Pennisi et al., 2017).

Noen få studier har undersøkt sammenhengen mellom psykologisk fungering og glutensensitivitet hos personer uten cøliaki. Peters, Biesiekierski, Yelland, Gibson, and Muir (2012) fant i en dobbelblind studie at 3-dagers gluteninntak ga økt nedstemthet hos 22 personer uten cøliaki men med irritert tarm syndrom. En randomisert studie av 45 barn med oppmerksomhets- og

hyperaktivitetsvansker (ADHD) fant en forskjell om barna gikk på glutenfri diett eller ikke i 6 måneder (Lykogeorgou, Karkelis, Papadaki-Papandreou, & Nikita, 2014). Det er også funnet at ataksi er relatert til glutensensitivitet (Hadjivassiliou et al., 2003). Det er nå økende fokus på om inflammatoriske konsekvenser av glutensensitivitet kan medføre nedsatte kognitive evner og dårligere livskvalitet (Daulatzai, 2015).

På grunn av få studier, med begrenset antall deltagere og andre metodiske begrensninger er det uavklart hvilke sammenhenger det er mellom psykologisk funksjon og cøliaki eller glutensensitivitet. Det er også usikkert om en eventuell sammenheng er begrunnet i en direkte negativ konsekvens av gluten eller om sammenhengen er mer indirekte. Proteiner fra gluten kan passere blod-hjernebarrieren, og det er mulig at protein fra gluten påvirker hjernen direkte (Pennisi et al., 2017). Det er også mulig at en eventuell sammenheng mellom glutensensitivitet og psykologisk funksjon er begrunnet i at de somatiske symptomene påvirker generelt funksjonsnivå hos personen, f.eks. at senket energinivå, fysisk ubehag og mangelfullt opptak av nødvendige næringsstoffer fra tarmen kan medføre dårligere kognitiv fungering og psykiske plager. Hvis det er en årsakssammenheng mellom glutensensitivitet eller cøliaki og psykologisk fungering, vil det være sannsynlig at en slik sammenheng starter relativt raskt etter at barnet begynner på en glutenholdig diett. Dette vil da kunne påvirke barnet negativt i viktige utviklingsfaser av livet.

Barn med Down syndrom har en kraftig forhøyet risiko for cøliaki (ca 6-7%) (Du, Shan, Cao, Feng, & Cheng, 2018) i forhold til andre personer (ca 1%) (Leonard, Sapone, Catassi, & Fasano, 2017). For eksempel fant en stor svensk registerstudie seksdoblet risiko for cøliaki hos personer med Down syndrom (Marild et al., 2013). Dette har medført at mange barn med Down syndrom blir screenet for cøliaki og, hvis bekreftet, behandlet for dette med glutenfri diett (Regionsenter for habiliteringstjenesten for barn og unge (RHABU), 2017). De som behandles vil dermed være beskyttet fra eventuelle negative konsekvenser av gluten. Barn med Down syndrom har imidlertid også en svært forhøyet risiko for glutensensitivitet. For eksempel fant en studie av 77 barn med Down syndrom at 64% hadde mageplager, 43% hadde forstoppelse (Gomes et al., 2016), blodprøver indikerte mulig cøliaki hos 27%, og biopsi bekreftet cøliaki hos 13% av barna.

Vi gjorde en av de tidligste studiene av sammenheng mellom mulige biologiske mål på glutensensitivitet og psykologisk fungering, og den første som undersøkte en slik eventuell sammenheng hos barn med Down syndrom (Nygaard, Reichelt, & Fagan, 2001). Vi studerte 55 barn med Down syndrom og fant vesentlige negative korrelasjoner (r = -,13 til -,51) mellom mulige biologiske markører på glutensensitivitet (IgA og IgG aktivitet mot gliadin og gluten) og psykologisk fungering (kognitiv og motorisk funksjon). Det vil si at jo mer antistoffer barna hadde mot gluten eller gliadin, jo dårligere psykologisk fungering hadde barna. Denne studien bør repliseres før man eventuelt går videre med intervensjonsstudier. En grunn er den begrensede størrelsen på studien. En annen årsak er at antistoffer mot gliadin er et sett av flere, og ikke nødvendigvis de beste, mulige biologiske markører på glutensensitivitet (Uhde et al., 2016). I henhold til senere studier er det andre psykologiske faktorer som kan være relatert til glutensensitivitet i tillegg til kognisjon og motorisk utvikling (se over). Det er nå et økende antall studier som undersøker cøliaki, glutensensitivitet og matinntak hos personer med Down syndrom, blant annet en nystartet longitudinell studie i England (fades-study@bristol.ac.uk). Det er imidlertid så langt vi vet ingen andre som har undersøkt, eller holder på å undersøke, sammenhengen mellom glutensensitivitet og psykologisk fungering hos personer med Down syndrom.

Da barn med Down syndrom er kraftig overrepresentert med plager relatert til glutensensitivitet og har vesentlig dårligere psykisk fungering enn befolkningen ellers, at glutensensitivitet kan ha

negative konsekvenser for psykisk fungering, og det er usikkert hvordan best måle glutensensitivitet, ønsker vi å undersøke disse forholdene nærmere.

Hypotesene i dette prosjektet, som er basert på rasjonale og tidligere funn beskrevet over, er:

1) Barn med Down syndrom vil ha en forhøyet risiko for glutensensitivitet, i forhold til normalbefolkningen, både målt ved biologiske markører og kliniske foreldre-rapporterte symptomer.
2) Det vil være en negativ sammenheng mellom glutensensitivitet og psykologisk fungering. Med psykologisk fungering menes her: kognitiv fungering og atferdsmessige tegn på engstelighet, tristhet og sinne.

Vi håper at studien vil bidra til mer kunnskap om biologiske markører for glutensensitivitet samt mulige psykiske konsekvenser av glutensensitivitet. Dette er viktig kunnskap, både for å kunne identifisere personer med glutensensitivitet og for å underbygge behovet for videre studier av mulige konsekvenser av slike plager. Slik kunnskap er spesielt viktig for barn med Down syndrom som har en overhyppighet av både glutensensitivitet og dårligere psykologisk fungering enn personer uten Down syndrom.

Metoder

Deltagere, rekruttering og styrkeberegning

Vi vil rekruttere foreldre og barn med Down syndrom via brukerorganisasjoner (Norsk Nettverk for Down Syndrom (NNDS), Ups and Downs, Norsk forbund for utviklingshemmede), habiliteringstjenester og pedagogisk psykologisk rådgivningskontorer (PPT) på sør og øst landet (Helse sør-øst). Kontakten vil basere seg på at foreldrene kontakter oss etter å ha fått informasjon om studien via disse organisasjonene. Foreldrene kan kontakte oss via telefon, post eller epost.

Etter at kontakt er oppnådd, informerer vi foreldrene via telefon om prosjektet og sender dem informasjonsskriv og samtykkeskjemaer. Vi vil påpeke at deltagelsen er frivillig og at de kan trekke sitt barn fra studien når som helst. Vi vil passe på å ikke legge press på deltagerne for å få dem til å stille opp. Vi gjør så avtale per telefon om tid. Samtykkeskjemaene kan leveres enten ved oppmøte til barnas undersøkelse eller på forhånd.

Inklusjonskriteria vil være:

- Down syndrom, både trisomi 21 og translokasjon, men uten kjent mosaikk
- Bor i geografisk rekrutteringsområde (Helse Sør-Øst nedslagsfelt, eller nær Stavanger, Bergen eller Trondheim)
- Barnet fylt 5 år, men ikke fylt 11 år
- Informert samtykke fra foreldre

Eksklusjonskriteria vil være:

- Tidligere cøliaki diagnose.
- Andre tilstander som etter ansvarlig klinikers mening gjør det uheldig å delta i undersøkelsen.

Den eneste sammenlignbare tidligere studien vi kan basere en styrkeberegning på (Nygaard et al., 2001) fant en gjennomsnittlig korrelasjon på 0,38 mellom 4 biologiske markører (IgA og IgG mot gluten og gliadin) og 2 psykologiske mål (generelle mentale evner og umiddelbar nyhetspreferanse).

Dette indikerer at vi trenger 52 deltagere for å være tilstrekkelig trygge på å unngå type I ($\alpha = 0,05$) og type II ($\beta = 0,20$) feil.

Det fødes ca. 70 barn med Down syndrom per år i Norge (Folkehelseinstituttet, 2015), det vil si at det er ca. 420 barn med Down syndrom i aldersgruppen 5 til 11 år i Norge. Ut fra tidligere erfaring vet vi at det er en høy andel av foreldre til barn med Down syndrom i Norge som er positive til at barna deres deltar i forskningsprosjekter (Naess, Nygaard, Ostad, Dolva, & Lyster, 2017; Nygaard et al., 2001), og vi forventer at 50% ønsker å være med i studien. På grunn av økonomiske begrensninger vil rekruttering skje i Øst- og Sør-Norge, det vil si i et geografisk område med ca. halvparten av Norges befolkning. På grunn av Covid-19 tiltakene vil sannsynligvis færre potensielle deltagere være med og derfor økes området til barn nær andre store byer i Norge; Stavanger, Bergen og Trondheim. Det vil si at vi potensielt kan få med ca. 100 barn i studien. Av økonomiske hensyn stopper rekrutteringen ved 70 deltagere. Dette vil da være tilstrekkelig til å ivareta behovet for høyere antall deltagere ved underanalyser og ved eventuell delvis manglende informasjon eller frafall.

Design og statistikk

Studien har et kryss-seksjonelt design med en gruppe med barn med Down syndrom. Statistiske metoder vil hovedsakelig være non-parametriske partielle korrelasjoner mellom biologiske markører på glutensensitivitet og psykologisk fungering. Analysene vil kontrollere for sosio-demografisk informasjon (kjønn, alder og foreldrenes utdannelse).

Målemetoder

Prosedyre

Avhengig av foreldrenes preferanse, så vil alle undersøkelser av barnet skje ved Universitetet i Oslo (UiO) eller i egnede lokaler i det geografiske området barnet bor. Vi vil for eksempel ha samarbeid med lokale Habiliteringstjenester og i noen tilfeller bruke deres lokaler for undersøkelse av barna. All testing av barna vil skje av en egnet person ansatt ved Psykologisk institutt ved UiO. Denne personen vil være en master eller profesjonsstudent i psykologi som vil være spesielt opplært i testing av barn. Vi vil bruke vel-etablerte og standardiserte nevropsykologiske tester og testprosedyrer som inngår i vanlige kliniske undersøkelser av små barn og i dokumenterte eksperimentelle prosedyrer. Testene vil ikke medføre ubehag for barna. Total undersøkelsestid vil være under en time, og det tas pauser når barna har behov for det. Foreldrene vil være tilstede under testing i de fleste tilfeller (der forelder eller barn ønsker det) på grunn av barnas unge alder.

Blodprøver av barna skjer ved at foreldrene får med seg henvisning fra testadministrator, familien får gjort blodprøver lokalt der barnet er vant til å bli medisinsk undersøkt, og blodprøvene sendes til vårt laboratorium på Oslo Universitetssykehus, Rikshospitalet. Noen barn får vondt når det tas blodprøver, og familien får derfor tilbud om Emla plaster som lokalbedøvelse ved blodprøvetakingen. Vi ønsker at barna skal ta blodprøver der barna er vant til at det skjer. Da barn med Down syndrom oftere tar blodprøver enn andre barn, vil dette være et viktig element for å minske mulige negative sider ved å skulle ta blodprøven. Det trengs kun 2 prøveglass til de planlagte blodprøveanalysene, det vil si minimal ekstra mengde utover det som tas ved barnas normale blodprøvetakinger.

Testadministrator vil ikke vite resultater fra blodprøvene på testtidspunktet. Dette er hovedsakelig for å sikre reliable testresultater. Det vil også medføre at man ikke tar blodprøver av andre barn enn der man har fått informasjon om psykologisk fungering. Det har imidlertid den ulempen at

eventuelle barn med tidligere uoppdaget cøliaki vil bli psykologisk undersøkt. Disse barna vil bli ekskludert fra hovedanalysene i studien.

Test av barna

Følgende test vil foretas for å vurdere barnas psykologiske fungering:

Leiter International Performance Scale – 3rd Edition. Dette er en nonverbal test av kognitive ferdigheter hos personer fra 3 til 75 år (Roid, Miller, Pomplun, & Koch, 2013). Det vil bli benyttet 4 deltester (figur-grunn, formkomplettering, klassifikasjon/analogier og sekvensiell orden) som samlet gir et reliabelt mål på generelle nonverbale kognitive ferdigheter (IQ). Testene forventes å ta totalt ca 30-45 minutter.

Spatial span (Cambridge Cognition) vil bli brukt for å måle barnas visuelle arbeidshukommelse. Denne visuelle nonverbale testen tar ca 5 minutter.

Flanker Inhibitory Control and Attention oppgave (NIH Toolbox) vil bli benyttet for å måle barnas barnas evner til å hanskes med mange impulser. Testen foretas på et nettbrett og tar ca 3 minutter.

Spørreskjema til foreldre

Foreldre (den som kommer med barnet til undersøkelsen) vil bli bedt om å fylle ut følgende spørreskjema for vurdering av barnas psykologiske fungering:

1. Brief Problem Monitor (BPM) som er en kortversjon (19 spørsmål) av det mest brukte spørreskjemaet for vurdering av internaliserende og eksternaliserende atferd hos barn i den vestlige verden (ASEBA, 2018), det vil si foreldrerapporterte tegn på engstelighet, tristhet og sinne hos barn. Den er oversatt til norsk.
2. Parenting Stress Index, 4th Edition vil bli brukt for å kartlegge stress i relasjonen mellom foreldre og barn (Abidin, 2012). Det vil bli brukt en kortversjon med 36 spørsmål.
3. DISABKIDS (DCGM-12) eller KIDSCREEN (11 spm) vil bli brukt for å kartlegge barnets helserelaterte livskvalitet (Froisland et al., 2012). Det vil brukes en kortversjon med 12 (evt. 11) spørsmål. Begge instrumentene er tidligere oversatt og validert i Norge. DISABKIDS er svært lik den mye brukte KIDSCREEN, men er bedre tilpasset mindre barn med funksjonshemninger. Det tar noe tid å skaffe godkjennelse av bruk av DISABKIDS, og vi har derfor foreløpig inkludert KIDSCREEN i spørreskjemaoversikten.
4. Barnets nysgjerrighet vil kartlegges med 10 spørsmål som er tidligere validert for barn i tilsvarende alder (Piotrowski, Litman, & Valkenburg, 2014).
5. Spørreskjema om barnets kosthold er basert på et tidligere skjema som er brukt i en studie av barn med kumelksallergi, men skjemaet er tilpasset denne studiens fokus på glutenintoleranse. Skjemaet har 15 spørsmål.
6. Spørreskjema om mageplager, avføringsvaner og vanlige bieffekter av glutenintoleranse hos barnet er laget for studien, med 35 spørsmål.

Foreldrene vil også bli bedt om sosio-demografisk informasjon. De vil også bli spurt om barnet har alvorlige somatiske problemer eller somatiske funksjonsnedsettelser innen motorikk, hørsel og syn, og barnets medisinbruk.

Biologiske markører

Det vil bli foretatt blodprøver av barna hvor følgende mulige markører på glutenintoleranse eller cøliaki vil bli analysert:

Vevstyping: HLA-DQ2.5, HLA-DQ8, HLA-DQ2.2 med tanke på cøliaki. Gjentas ikke hvis analysen allerede er gjort.

Antistoffer: Standard analyser vil være IgA mot transglutaminase 2 (TG2) og IgG mot deamidert gliadin peptid. Eksperimentelle analyser (utføres på alle) er immunglobulin subklasser, IgA og IgG mot gluten og gliadin, IgG og IgM mot flagellin, intestinal fatty acid binding protein (I-FABP), lipopolysaccharide-binding protein (LBP), oppløselig CD14 (sCD14)

«Vanlige blodprøver»: Hemoglobin, MCV, ferritin, hvite med diff, trombocytter, CRP , TSH og fritt T4, ASAT, ALAT.

Personvern og etikk

Foreldrene vil motta informasjonsskriv via eksisterende kontaktpersoner, og må selv ta initiativ til å melde barna på studien. Informasjonsskrivet vil inneholde informasjon om personvern. Det skal leveres signert informasjonsskriv fra forelder før barnet blir med i studien.

Informasjonen som registreres er svar fra foreldre på spørreskjema, barnets kognitive testresultat og analyseresultater fra blodprøvene (se beskrivelse over). Universitetet i Oslo ved administrerende direktør er databehandlingsansvarlig. Alle som får innsyn har taushetsplikt. Bare personer autorisert av prosjektleder vil få tilgang til data, og de vil få det bare for den perioden de har behov for det slik at det sikres oversikt over hvem som har tilgang. Dataene vil lagres elektronisk på et område spesielt tilrettelagt for oppbevaring og behandling av sensitive data (TSD) ved Universitetet i Oslo (https://www.uio.no/tjenester/it/forskning/sensitiv/). Systemet er sertifisert for lagring av sensitiv helseinformasjon. All prosessering og analyse av dataene vil skje innenfor TSD sitt høy-sikkerhets system. Kodeliste og direkte identifiserbar informasjon (navn og kontaktinformasjon) vil oppbevares separat fra den innsamlede informasjonen. Kun av-identifisert informasjon vil bli benyttet i forskningen. Alle resultater presenteres på gruppebasis, slik at ingen deltagere skal kunne gjenkjennes.

Resultater fra analysene av blodprøvene vil bli lagret i deltagernes pasientjournaler på Oslo Universitetssykehus, Rikshospitalet. Analysene foretas på Rikshospitalet, og blodprøvene oppbevares i allerede godkjent forskningsbiobank (forskningsbiobanken «Tarmsykdommer», ref.nr. 2012/341) ved Oslo Universitetssykehus Rikshospitalet. Denne forskningsbiobanken er tidligere godkjent for voksne, og det vil søkes om utvidelse for også å oppbevare blodprøver fra barn. Resultater fra blodprøvene overføres manuelt til TSD av ansatt person i prosjektet, og all papirinformasjon som benyttes i denne forbindelse makuleres med en gang informasjonen er elektronisk lagret i TSD.

Vi vil bruke nettskjema for innsamling av informasjonen fra foreldrene, enten mens de er med barnet til undersøkelse eller hjemmefra. Dataene (svar på elektronisk spørreskjema) sendes kryptert inn i TSD. Løsningen er godkjent for innsamling av helsedata og annen svært sensitiv informasjon (https://www.uio.no/tjenester/it/applikasjoner/nettskjema/). Noen av testene av barna vil være databaserte. Slik testinformasjon vil kun lagres lokalt på nettbrett inntil de kan overføres via sikre linjer til den sentrale databasen i TSD.

Forskningsgruppen har samarbeid med Armin Alaedini ved Columbia University Medical Center i New York, og vi vil innhente samtykke fra foreldrene at man foretar analyser av blodprøver i utlandet. Informasjonsskrivet vil opplyse om dette. Det vil ikke bli sendt annen personidentifiserende informasjon utover selve blodprøvene til disse samarbeidspartnerne. Eksisterende forskningsbiobank «Tarmsykdommer» har godkjennelse for slike analyser utenlands.

Barn med Down syndrom har en overhyppighet av glutensensitivitet (Gomes et al., 2016). Ved å benytte denne gruppen i studien retter man fokus på en gruppe personer som dermed vil ha stort potensial for å få nytte av studien. Ved å bruke en gruppe med høy andel av glutensensitivitet vil man minske andelen av barn som må undersøkes for å finne tilstrekkelig antall til å kunne konkludere om de sammenhenger som studeres. Dermed minimeres blant annet mulighetene for falske positive blodprøver og antall barn som må ta biopsi.

Tilbakemelding til foreldre

Foreldrene vil, ved forespørsel, få skriftlig og muntlig tilbakemelding fra de undersøkelsene de ønsker tilbakemelding på. De vil også få tilbakemelding hvis de blodprøvene indikerer behov for videre undersøkelser eller tiltak. Christine Olbjørn vil som pediatrisk gastro-enterolog i prosjektet ta stilling til alle prøvesvar og henvise barnet videre ved behov for ytterligere utredning. Hvis de psykologiske undersøkelsene indikerer alvorlige vansker eller avvik som barnet ikke får tilstrekkelig hjelp med, vil vi bidra med råd om hvordan man kan få hjelp. Vi vil i slike tilfeller kunne skrive en rapport som de kan ta med seg videre i hjelpesystemet, f.eks. til barnets fastlege for videre henvisninger. Vi vil gi informasjon i informasjonsskrivet om rutiner for tilbakemelding og oppfølging.

I en tidligere studie vi foretok av tilsvarende barn (Nygaard et al., 2001), fant vi 2 barn som hadde uoppdaget cøliaki. Diagnostikk av mulig cøliaki vil følge vanlige retningslinjer. Ved indikasjon på cøliaki fra blodprøvene og/eller symptomer/mistanke om cøliaki vil barnet bli henvist av Olbjørn til det lokale helsevesen slik at barnet blir utredet med blodprøver og/eller vevsprøver (biopsi) av tynntarmsslimhinnen for å bekrefte eller avkrefte mulig diagnose (Størdal, Olbjørn, Vikskjold, & K., 2016). Dersom barnet får diagnostisert cøliaki vil det anbefales gluten fri diett, som per i dag er standard behandlingsform for denne lidelsen.

Fremdriftsplan

Det planlegges oppstart av prosjektet i oktober 2018. Rekruttering og undersøkelse av barna planlegges å være ferdig i desember 2019. Analyser og publisering av resultater skjer fra januar 2019 og frem til planlagt prosjektslutt i oktober 2021.

Dataene, og kodeliste med kontaktinformasjon, ønskes oppbevart fram til 2031 for å muliggjøre senere oppfølgingsstudier. Det er per i dag ingen kunnskap om mulige langtidseffekter av glutensensitivitet. Foreldrene vil bli informert om hvor lenge informasjonen oppbevares og bes om å samtykke i at vi kan ta kontakt ved eventuelle oppfølgingsstudier.

Gjennomførbarhet

Prosjektleder har tidligere gjort en lignende studie av barn med Down syndrom i samme aldersgruppe (Nygaard, 2002; Nygaard et al., 2001; Nygaard, Smith, & Torgersen, 2002). Han har lang erfaring med kognitive testing av barn, både i klinisk og forskningsmessig sammenheng. Han har også erfaring med planlegging, organisering, rekruttering, gjennomføring, analysering og publisering i mange ulike studier. Prosjektgruppen inneholder også svært høy kunnskap og erfaring med somatisk studier innen temaene cøliaki og glutensensitivitet (se under). Alle tester, spørreskjemaer og blodprøveanalyser er velprøvde og gir god gjennomførbarhet. Vi har et rekrutteringsgrunnlag som er mer enn tilstrekkelig til å sikre en statistisk styrke, og selv om man får noe frafall eller lavere andel som deltar enn ved tidligere studier av tilsvarende barn (Naess et al., 2017; Nygaard et al., 2001) vil man ha tilstrekkelig med deltagere til å oppfylle vanlige krav til statistisk styrke. Vi mener derfor at prosjektet har realistisk og høy gjennomførbarhet.

Kompetanse

Prosjektleder, Egil Nygaard, førsteamanuensis i psykologi ved Universitetet i Oslo, har gjort lignende studie før, har mye erfaring fra utredning av barns psykologiske fungering, og har lang forskningsmessig erfaring med tverrfaglige studier. Knut Lundin er professor ved institutt for klinisk medisin, UiO, og overlege på Seksjon for Gastromedisin ved Oslo Universitetssykehus, Rikshospitalet. Han er en av Norges fremste forskere om cøliaki og glutensensitivitet. Barnelege Christine Olbjørn er barne-gastroenterolog, har for tiden permisjon fra overlegestilling på Barne og ungdomsklinikken på Akershus universitetssykehus og er klinisk stipendiat ved Det medisinske fakultet i Oslo. Hun er i ferd med å sluttføre en PhD på inflammatorisk tarmsykdom hos barn. Hun vil medvirke til gjennomgang av prøveresultater og vil sørge for at barn med unormale prøveresultater og/eller symptomer får nødvendig medisinsk utreding og evt. behandling. Carina Hinrichs ved Gastromedisinsk avdeling på Rikshospitalet vil foreta analysene av blodprøvene. Kari-Anne Næss er professor på Institutt for spesialpedagogikk og er sannsynligvis forskeren med mest erfaring fra forskningsprosjekter om barn med Down syndrom i Norge. Prosjektet vil ansette en prosjektmedarbeider som er på slutten av psykologiutdannelsen sin. Medarbeideren vil læres opp og veiledes av blant annet prosjektleder.

Referanser

Abidin, R. R. (2012). *Parenting stress index (4th ed.)*: Lutz.

ASEBA. (2018). Brief Problem Monitor. Retrieved from http://www.aseba.org/bpm.html

Biesiekierski, J. R., Peters, S. L., Newnham, E. D., Rosella, O., Muir, J. G., & Gibson, P. R. (2013). No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology, 145*(2), 320-328 e321-323. doi:10.1053/j.gastro.2013.04.051

Brottveit, M., Beitnes, A. C., Tollefsen, S., Bratlie, J. E., Jahnsen, F. L., Johansen, F. E., . . . Lundin, K. E. (2013). Mucosal cytokine response after short-term gluten challenge in celiac disease and non-celiac gluten sensitivity. *American Journal of Gastroenterology, 108*(5), 842-850. doi:10.1038/ajg.2013.91

Casella, S., Zanini, B., Lanzarotto, F., Ricci, C., Marengoni, A., Romanelli, G., & Lanzini, A. (2012). Cognitive performance is impaired in coeliac patients on gluten free diet: a case-control study in patients older than 65 years of age. *Digestive & Liver Disease, 44*(9), 729-735. doi:10.1016/j.dld.2012.03.008

Daulatzai, M. A. (2015). Non-celiac gluten sensitivity triggers gut dysbiosis, neuroinflammation, gut-brain axis dysfunction, and vulnerability for dementia. *CNS & Neurological Disorders Drug Targets, 14*(1), 110-131.

Du, Y., Shan, L. F., Cao, Z. Z., Feng, J. C., & Cheng, Y. (2018). Prevalence of celiac disease in patients with Down syndrome: a meta-analysis. *Oncotarget, 9*(4), 5387-5396. doi:10.18632/oncotarget.23624

Folkehelseinstituttet. (2015, 4th December 2015). Fakta om Down syndrom. Retrieved from https://www.fhi.no/fp/gravide-og-fodende-kvinners-helse/fakta-om-down-syndrom/

Froisland, D. H., Markestad, T., Wentzel-Larsen, T., Skrivarhaug, T., Dahl-Jorgensen, K., & Graue, M. (2012). Reliability and validity of the Norwegian child and parent versions of the DISABKIDS Chronic Generic Module (DCGM-37) and Diabetes-Specific Module (DSM-10). *Health and Quality of Life Outcomes, 10*. doi:10.1186/1477-7525-10-19

Gomes, R. C., Maia, J. C., Arrais, R. F., Jatoba, C. A. N., Rocha, M. A. C., Brito, M. E. F., . . . Maranhao, H. D. (2016). The celiac iceberg: from the clinical spectrum to serology and histopathology in children and adolescents with type 1 diabetes mellitus and Down syndrome. *Scandinavian Journal of Gastroenterology, 51*(2), 178-185. doi:10.3109/00365521.2015.1079645

Hadjivassiliou, M., Grunewald, R., Sharrack, B., Sanders, D., Lobo, A., Williamson, C., . . . Davies-Jones, A. (2003). Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain, 126*(Pt 3), 685-691.

Husby, S., Koletzko, S., Korponay-Szabo, I. R., Mearin, M. L., Phillips, A., Shamir, R., . . . Nutrition. (2012). European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *Journal of Pediatric Gastroenterology & Nutrition, 54*(1), 136-160. doi:10.1097/MPG.0b013e31821a23d0

Leonard, M. M., Sapone, A., Catassi, C., & Fasano, A. (2017). Celiac disease and nonceliac gluten sensitivity: A review. *JAMA, 318*(7), 647-656. doi:10.1001/jama.2017.9730

Lichtwark, I. T., Newnham, E. D., Robinson, S. R., Shepherd, S. J., Hosking, P., Gibson, P. R., & Yelland, G. W. (2014). Cognitive impairment in coeliac disease improves on a gluten-free diet and correlates with histological and serological indices of disease severity. *Alimentary Pharmacology & Therapeutics, 40*(2), 160-170. doi:10.1111/apt.12809

Ludvigsson, J. F., Bai, J. C., Biagi, F., Card, T. R., Ciacci, C., Ciclitira, P. J., . . . British Society of, G. (2014). Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut, 63*(8), 1210-1228. doi:10.1136/gutjnl-2013-306578

Lundin, K. E. A. (2014). Non-celiac gluten sensitivity - why worry? *BMC Medicine, 12*, 86. doi:10.1186/1741-7015-12-86

Lykogeorgou, M., Karkelis, S., Papadaki-Papandreou, O., & Nikita, M. (2014). Gluten free diet for children with attention deficit and hyperactivity disorder. *Archives of Disease in Childhood, 99*, A204-A205. doi:10.1136/archdischild-2014-307384.554

Marild, K., Stephansson, O., Grahnquist, L., Cnattingius, S., Soderman, G., & Ludvigsson, J. F. (2013). Down syndrome is associated with elevated risk of celiac disease: A nationwide case-control study. *Journal of Pediatrics, 163*(1), 237-242. doi:10.1016/j.jpeds.2012.12.087

Naess, K. B., Nygaard, E., Ostad, J., Dolva, A. S., & Lyster, S. H. (2017). The profile of social functioning in children with Down syndrome. *Disability and Rehabilitation, 39*(13), 1320-1331. doi:10.1080/09638288.2016.1194901

Nygaard, E. (2002). "The relation between the psychological functioning of children with Down syndrome and their urine peptide levels and levels of serum antibodies to food proteins": Erratum. *Down Syndrome: Research & Practice, 8*(1), 37.

Nygaard, E., Reichelt, K. L., & Fagan, J. F. (2001). The relation between the psychological functioning of children with Down syndrome and their urine peptide levels and levels of serum antibodies to food proteins.[erratum appears in Downs Syndr Res Pract 2002 Mar;8(1):37]. *Down Syndrome: Research & Practice, 6*(3), 139-145.

Nygaard, E., Smith, L., & Torgersen, A. M. (2002). Temperament in children with Down syndrome and in prematurely born children. *Scandinavian Journal of Psychology, 43*(1), 61-71.

Pennisi, M., Bramanti, A., Cantone, M., Pennisi, G., Bella, R., & Lanza, G. (2017). Neurophysiology of the "celiac brain": Disentangling gut-brain connections. *Frontiers in Neuroscience, 11*, 498. doi:10.3389/fnins.2017.00498

Peters, S., Biesiekierski, J. R., Yelland, G., Gibson, P., & Muir, J. (2012). Gluten causes depression in subjects with non-coeliac gluten sensitivity (NCGS). *Journal of Gastroenterology and Hepatology, 27*, 147-147.

Piotrowski, J. T., Litman, J. A., & Valkenburg, P. (2014). Measuring epistemic curiosity in young children. *Infant and Child Development, 23*(5), 542-553. doi:10.1002/icd.1847

Regionsenter for habiliteringstjenesten for barn og unge (RHABU). (2017). Retningslinje for oppfølging av barn og unge med Down syndrom. Retrieved from https://oslo-universitetssykehus.no/seksjon/regionsenter-for-habiliteringstjenesten-for-barn-og-unge-rhabu/Documents/Retningslinje%20Down%20Syndrom%20versjon%20030217.pdf

Roid, G. H., Miller, L. J., Pomplun, M., & Koch, C. (2013). *Leiter International Performance Scale - 3rd Edition*: Hogrefe Psykologiförlaget AB.

Shen, T. C., Lebwohl, B., Verma, H., Kumta, N., Tennyson, C., Lewis, S., . . . Green, P. H. (2012). Peripheral neuropathic symptoms in celiac disease and inflammatory bowel disease. *Journal of Clinical Neuromuscul Disease, 13*(3), 137-145. doi:10.1097/CND.0b013e31821c55a1

Skodje, G. I., Sarna, V. K., Minelle, I. H., Rolfsen, K. L., Muir, J. G., Gibson, P. R., . . . Lundin, K. E. A. (2018). Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology, 154*, 529-539. doi:10.1053/j.gastro.2017.10.040

Størdal, K., Olbjørn, C., Vikskjold, F. B., & K., H. H. (2016). Cøliaki hos barn - Veileder for diagnostikk og oppfølging. Retrieved from http://www.helsebiblioteket.no/retningslinjer/coliaki-hos-barn/innledning

Uhde, M., Ajamian, M., Caio, G., De Giorgio, R., Indart, A., Green, P. H., . . . Alaedini, A. (2016). Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut, 65*(12), 1930-1937. doi:10.1136/gutjnl-2016-311964

Yelland, G. W. (2017). Gluten-induced cognitive impairment ("brain fog") in coeliac disease. *Journal of Gastroenterology and Hepatology, 32 Suppl 1*, 90-93. doi:10.1111/jgh.13706

Appendix G: Statistical Scripts

G1 Syntax SPSS: Data preparation

G2 Syntax SPSS: Descriptive statistics

G3 Script R: Multiple imputation

G4 Script R: Statistical analysis

G5 Script R: Regression diagnostics

G1 Syntax SPSS: Data preparation

```
* Encoding: UTF-8.

* Importing SB5 and 9-HPT data as xlsx-files and saving them as sav-files.
GET DATA
  /TYPE=XLSX
  /FILE='N:\durable\Statistics\Raw data\Testdata 1.xlsx'
  /SHEET=name 'Sheet1'
  /CELLRANGE=FULL
  /READNAMES=ON
  /DATATYPEMIN PERCENTAGE=95.0
  /HIDDEN IGNORE=YES.
EXECUTE.
SAVE OUTFILE='N:\durable\Statistics\SPSS data\testdata1.sav'.

GET DATA
  /TYPE=XLSX
  /FILE='N:\durable\Statistics\Raw data\Testdata 2.xlsx'
  /SHEET=name 'Sheet1'
  /CELLRANGE=FULL
  /READNAMES=ON
  /DATATYPEMIN PERCENTAGE=95.0
  /HIDDEN IGNORE=YES.
EXECUTE.
SAVE OUTFILE='N:\durable\Statistics\SPSS data\testdata2.sav'.

* Importing CANTAB data as xlsx-files and saving them as sav-files, influding
codebook-file to get correct labels.
GET DATA
  /TYPE=XLSX
  /FILE='N:\durable\Statistics\Raw data\CANTAB.xlsx'
  /SHEET=name 'Sheet1'
  /CELLRANGE=FULL
  /READNAMES=ON
  /DATATYPEMIN PERCENTAGE=95.0
  /HIDDEN IGNORE=YES.
EXECUTE.
INCLUDE FILE='N:\durable\Statistics\Codebooks\codebook CANTAB.sps'.

RENAME VARIABLES (SubjectID = ID).

ALTER TYPE RowNumber (F2).
DO IF (RowNumber EQ 3).
 COMPUTE ID ="G004".
END IF.
EXECUTE.

SORT CASES BY ID (A).

SAVE OUTFILE='N:\durable\Statistics\SPSS data\cantab.sav'.

* Importing biodata as xlsx-files and saving them as sav-files.
GET DATA
  /TYPE=XLSX
  /FILE='N:\durable\Statistics\Raw data\Biological data 1.xlsx'
  /SHEET=name 'Sheet1'
```

```
  /CELLRANGE=FULL
  /READNAMES=ON
  /DATATYPEMIN PERCENTAGE=95.0
  /HIDDEN IGNORE=YES.
EXECUTE.
SAVE OUTFILE='N:\durable\Statistics\SPSS data\biodata1.sav'.

GET DATA
  /TYPE=XLSX
  /FILE='N:\durable\Statistics\Raw data\Biological data 2.xlsx'
  /SHEET=name 'Sheet1'
  /CELLRANGE=FULL
  /READNAMES=ON
  /DATATYPEMIN PERCENTAGE=95.0
  /HIDDEN IGNORE=YES.
EXECUTE.
SAVE OUTFILE='N:\durable\Statistics\SPSS data\biodata2.sav'.

* Importing nettskjema data as xlsx-files and saving them as sav-file.
Renaming ID-variable for consistency. Including codebook-file to get correct
label.
GET DATA
  /TYPE=XLSX
  /FILE='N:\durable\Statistics\Raw data\nettskjema.xlsx'
  /SHEET=name 'Sheet1'
  /CELLRANGE=FULL
  /READNAMES=ON
  /DATATYPEMIN PERCENTAGE=95.0
  /HIDDEN IGNORE=YES.
EXECUTE.
INCLUDE FILE='N:\durable\Statistics\Codebooks\codebook nettskjema.sps'.

* Fixing wrong id's.
*Renaming nettskjema id variable.
RENAME VARIABLES (@_id = NettskjemaID).
RENAME VARIABLES (id = ID).
ALTER TYPE ID(a4).
ALTER TYPE NettskjemaID (F7).

*Deleting test case.
SELECT IF NOT (NettskjemaID EQ 6250635).
EXECUTE.

*Correcting miswritten subject nr 8664062,873777,88305841,8942928.
DO IF (NettskjemaID EQ 8664062).
 COMPUTE id ="G004".
ELSE IF (NettskjemaID EQ 8737771).
 COMPUTE id = 'G007'.
ELSE IF (NettskjemaID EQ 8830584).
 COMPUTE id = 'G014'.
ELSE IF (NettskjemaID EQ 8942928).
 COMPUTE id = 'G023'.
END IF.
EXECUTE.

SORT CASES BY ID (A).
```

```
SAVE OUTFILE='N:\durable\Statistics\SPSS data\nettskjema.sav'.

 * Matching punched testdata to test for punching errors.
DATASET DECLARE TestdataErrors.
DATASET DECLARE TestdataCorrect.
*DATASET CLOSE DataSet2.

GET FILE='N:\durable\Statistics\SPSS data\testdata1.sav'.
DATASET NAME DataSet2.
DATASET ACTIVATE DataSet2.
SORT CASES BY ID .

GET FILE='N:\durable\Statistics\SPSS data\testdata2.sav'.
DATASET NAME DataSet4.
DATASET ACTIVATE DataSet4 WINDOW=ASIS.
SORT CASES BY ID .

COMPARE DATASETS
  /COMPDATASET = DataSet2
  /VARIABLES  matrix_sum matrix_scaled verbal_sum verbal_scaled ab_sum ABIQ
dominant_handrl test_right test_left
  /CASEID  ID
  /SAVE FLAGMISMATCHES=YES VARNAME=CasesCompare MATCHDATASET=YES
MATCHNAME=TestdataCorrect
    MISMATCHDATASET=YES MISMATCHNAME=TestdataErrors
  /OUTPUT VARPROPERTIES=NONE CASETABLE=YES TABLELIMIT=100.

DATASET CLOSE DataSet2.

SAVE OUTFILE='N:\durable\Statistics\SPSS data\TestdataErrors.sav'
  /COMPRESSED.
DATASET CLOSE DataSet4.
DATASET CLOSE TestdataCorrect.
DATASET CLOSE TestdataErrors.

* Matching punched data from blood samples to test for punching errors..
DATASET DECLARE BiodataError.

GET FILE='N:\durable\Statistics\SPSS data\biodata1.sav'.
DATASET NAME DataSet2.
DATASET ACTIVATE DataSet2.
SORT CASES BY ID .

GET FILE='N:\durable\Statistics\SPSS data\biodata2.sav'.
DATASET NAME DataSet1.
DATASET ACTIVATE DataSet1 WINDOW=ASIS.
SORT CASES BY ID .

COMPARE DATASETS
  /COMPDATASET = DataSet2
  /VARIABLES HLA_DQ75 HLA_DQ25 HLA_DQ2 HLA_DQ8 IgA_TG2 IgG_DGP IgA_gluten
IgG_gluten IgG_flagellin IgM_flagellin I_FABP LBP Scd14 Hemoglobin MCH MCV
  Trombocytter Leukocytter Neutrofile_g Lymfocytter Monocytter Eosinofile_g
Basofile_g Ferritin ASAT ALAT CRP TSH Free_T4
  /CASEID ID
  /SAVE FLAGMISMATCHES=YES VARNAME=CasesCompare MATCHDATASET=YES
MATCHNAME=BiodataError
```

```
    MISMATCHDATASET=NO
  /OUTPUT VARPROPERTIES=NONE CASETABLE=YES TABLELIMIT=100.

DATASET CLOSE DataSet1.
DATASET CLOSE DataSet2.
DATASET CLOSE BiodataError.

 * Merging datafiles to get all the data in one file.
GET
  FILE='N:\durable\Statistics\SPSS data\nettskjema.sav'.
DATASET NAME Analysefil.

GET FILE='N:\durable\Statistics\SPSS data\testdata1.sav'.
DATASET NAME Testdata.
DATASET ACTIVATE Testdata.
SORT CASES BY ID.
DATASET ACTIVATE Analysefil.
SORT CASES BY ID.
MATCH FILES /FILE=*
  /FILE='Testdata'
  /BY ID.
EXECUTE.
DATASET CLOSE Testdata.

GET FILE='N:\durable\Statistics\SPSS data\cantab.sav'.
DATASET NAME CANTAB.
DATASET ACTIVATE Analysefil.
SORT CASES BY ID.
DATASET ACTIVATE CANTAB.
SORT CASES BY ID.
DATASET ACTIVATE Analysefil.
MATCH FILES /FILE=*
  /FILE='CANTAB'
  /BY ID.
EXECUTE.
DATASET CLOSE CANTAB.

GET FILE='N:\durable\Statistics\SPSS data\biodata1.sav'.
DATASET NAME Biodata.
DATASET ACTIVATE Analysefil.
SORT CASES BY ID.
DATASET ACTIVATE Biodata.
SORT CASES BY ID.
DATASET ACTIVATE Analysefil.
MATCH FILES /FILE=*
  /FILE='Biodata'
  /BY ID.
EXECUTE.
DATASET CLOSE Biodata.

SAVE OUTFILE='N:\durable\Statistics\SPSS data\Analysefil.sav'.

*Deleting case G008 and G019 due to the amount of missing data.
SELECT IF NOT (ID EQ 'G008').
SELECT IF NOT (ID EQ 'G019').

*Deleting case G005 og G011 due to previously diagnosed celiac disease.
```

```
SELECT IF NOT (ID EQ 'G005').
SELECT IF NOT (ID EQ 'G011').
EXECUTE.

*Calculate dominant hand.
DO IF (dominant_handrl EQ 'r').
 COMPUTE dominant_handrl = '0'.
ELSE.
 COMPUTE dominant_handrl = '1'.
END IF.
EXECUTE.

ALTER TYPE dominant_handrl (F1).
VALUE LABELS dominant_handrl 0 = Right 1 = Left.
Execute.

DO IF (dominant_handrl EQ 0).
  COMPUTE time_dominant = test_right.
  COMPUTE time_nondominant = test_left.
ELSE.
  COMPUTE time_dominant = test_left.
  COMPUTE time_nondominant = test_right.
END IF.
EXECUTE.

*Fixing gender values.
ALTER TYPE sos3 (F1).
RECODE sos3 (1=0) (2=1).
EXECUTE.
VARIABLE LABELS sos3 'Gender'.
VALUE LABELS sos3
  0 'Gutt'
  1 'Jente'.

*Alter type height, weight.
ALTER TYPE sos4 (F3.1).
ALTER TYPE sos5 (F3.1).

* Date and Time Wizard: Age.
Alter type sos1 (Edate10).
Alter type sos2 (Edate10).
COMPUTE  Age=DATEDIF(sos2, sos1, "days").
VARIABLE LABELS  Age "Age at test date".
VARIABLE LEVEL  Age (SCALE).
FORMATS  Age (F5.0).
VARIABLE WIDTH  Age(5).
EXECUTE.

* Descriptive statistics for article ( Frequency Percent, Mean, and Standard
diviation).
COMPUTE Age_years=Age / 365.
EXECUTE.

COMPUTE Parent_education_sum=sos9 + sos10.
EXECUTE.

*Fixing variable levels.
```

```
VARIABLE LEVEL sos9 sos10 bpm1 bpm2 bpm3 bpm4 bpm5 bpm6 bpm7 bpm8 bpm9 bpm10
bpm11 bpm12 bpm13 bpm14 bpm15 bpm16 bpm17 bpm18 bpm19 psi1 (ORDINAL)
 / psi2 psi3 psi4 psi5 psi6 psi7 psi8 psi9 psi10 psi11 psi12 psi13 psi14 psi15
psi16 psi17 psi18 psi19 psi20 psi21 psi22 psi23 psi24 psi25 psi26 psi27 psi28
psi29 psi30 psi31 psi32 psi33 psi34 psi35 psi36 kid1 (ORDINAL)
 / kid2 kid3 kid4 kid5 kid6 kid7 kid8 kid9 kid10 kid11 cur1 cur2 cur3 cur4
cur5 cur6 cur7 cur8 cur9 cur10 gsrs1 gsrs2 gsrs3 gsrs4 gsrs5 gsrs6 gsrs7 gsrs8
gsrs9 gsrs10 gsrs11 gsrs12 gsrs13 gsrs14 gsrs15 (ORDINAL)
 / diet8 diet10 diet11 diet12 diet13 diet14 diet15 (ORDINAL)
 / slp1 diet2 diet3 diet4 diet7_1 diet7_2  matrix_sum matrix_scaled verbal_sum
verbal_scaled ab_sum ABIQ test_right test_left MOTML MOTSDL MOTTC MOTTE
PALFAMS PALMETS  PALNPR PALTA (SCALE)
 / PALTA2 PALTA4 PALTA6 PALTA8 PALTE PALTE2 PALTE4 PALTE6 PALTE8 PALTEA2
PALTEA28 PALTEA4 PALTEA6 PALTEA8 RTIFESI RTIFESNR RTIFESPR RTIFMDMT RTIFMDRT
RTIFMMT (SCALE)
 / RTIFMRT RTIFMTSD RTIFRTSD RTIFTES SSPFMNE SSPFSL SSPFSR SSPFTE SSPFTUE
(SCALE).

 * Describing minimum and maximum values to check for punching errors.
DESCRIPTIVES VARIABLES=sos1 sos2 sos3 sos4 sos5 sos6 sos7 sos8 sos9 sos10 bpm1
bpm2 bpm3 bpm4 bpm5 bpm6 bpm7 bpm8 bpm9 bpm10 bpm11 bpm12 bpm13 bpm14 bpm15
bpm16 bpm17 bpm18 bpm19 psi1
psi2 psi3 psi4 psi5 psi6 psi7 psi8 psi9 psi10 psi11 psi12 psi13 psi14 psi15
psi16 psi17 psi18 psi19 psi20 psi21 psi22 psi23 psi24 psi25 psi26 psi27 psi28
psi29 psi30 psi31 psi32 psi33 psi34 psi35 psi36 kid1 kid2 kid3 kid4
kid5 kid6 kid7 kid8 kid9 kid10 kid11 cur1 cur2 cur3 cur4 cur5 cur6 cur7 cur8
cur9 cur10 gsrs1 gsrs2 gsrs3 gsrs4 gsrs5 gsrs6 gsrs7 gsrs8 gsrs9 gsrs10 gsrs11
gsrs12 gsrs13 gsrs14 gsrs15 diet10 diet11 diet12 diet13 diet14 diet15
slp1 slp2 slp3 matrix_sum matrix_scaled verbal_sum verbal_scaled ab_sum ABIQ
dominant_handrl test_right test_left HLA_DQ75 HLA_DQ25 HLA_DQ2 HLA_DQ8 IgA_TG2
IgG_DGP IgA_gluten IgG_gluten IgG_flagellin IgM_flagellin I_FABP LBP
Scd14 Hemoglobin MCH MCV Trombocytter Leukocytter Neutrofile_g Lymfocytter
Monocytter Eosinofile_g Basofile_g Ferritin ASAT ALAT CRP TSH Free_T4
  /STATISTICS=MIN MAX.

* Reversing variables to get consistent scoring for KIDSCREEN, sleep, PSI.
RECODE slp1 (1=5) (4=2) (2=4) (5=1).
RECODE slp2 (1=4) (2=3) (3=2) (4=1).
RECODE kid3 (1=5) (2=4) (4=2) (5=1).
RECODE kid4 (1=5) (2=4) (4=2) (5=1).
RECODE kid11 (1=5) (2=4) (4=2) (5=1).
RECODE diet15 (1=5) (2=4) (4=2) (5=1).
RECODE psi22 (1=5) (4=2) (2=4) (5=1).
RECODE psi33 (1=5) (4=2) (2=4) (5=1).

EXECUTE.

* Adding labels for SB5 and 9-HPT data, computed variables.
VARIABLE LABELS
  matrix_sum 'SB5 Sum matrix subtest'
  matrix_scaled 'SB5 Scaled score matrix subtest'
  verbal_sum 'SB5 Sum verbal subtest'
  verbal_scaled 'SB5 Scaled score verbal subtest'
  ab_sum 'SB5 Sum of scaled scores'
  ABIQ 'SB5 Abbriated IQ'
  dominant_handrl 'Dominant hand'
  test_right '9-HPT Right hand test run'
```

```
  test_left '9-HPT Left hand test run'
  time_dominant '9-HPT Dominant hand'
  time_nondominant '9-HPT Non-dominant hand'.
EXECUTE.

 * Checking for missing data (if someone asked "do not know" on questions on
the parents level of education) .
MISSING VALUES sos9,sos10 (6).

*Removing outliers RTIFMDMT PALTEA24.
DO IF (PALTEA28 EQ 24).
COMPUTE PALTEA28 = 41.
ELSE IF (RTIFMDMT EQ 3414).
COMPUTE RTIFMDMT = 677.
END IF.
EXECUTE.

*SAVE.
SAVE OUTFILE='N:\durable\Statistics\R\Dataset R.sav'.

OUTPUT SAVE OUTFILE='N:\durable\Statistics\Output\Preliminary.spv'.
```

G2 Syntax SPSS: Descriptive statistics

```
* Encoding: UTF-8.

GET FILE='N:\durable\Statistics\R\Dataset R.sav'.

DESCRIPTIVES VARIABLES=slp1 slp2 slp3
  /SAVE.

COMPUTE bpm_total=sum(bpm1 + bpm2 + bpm3 + bpm4 + bpm5 + bpm6 + bpm7 + bpm8 +
bpm9 + bpm10 + bpm11 + bpm12 + bpm13 + bpm14 + bpm15 + bpm16 + bpm17 + bpm18 +
bpm19)/19.
COMPUTE kidscreen_total=mean(kid1 to kid11).
COMPUTE psi_total=mean(psi1 to psi36).
COMPUTE gsrs=mean(gsrs1 to gsrs15).
COMPUTE curiosity=mean(cur1 to cur10).
COMPUTE sleep=mean(Zslp1 to Zslp3).
COMPUTE lactose=mean(diet13 + diet14).
COMPUTE gluten=mean(diet10 + diet11 + diet12 + diet15).
COMPUTE MeanEducation=MEAN(sos9 + sos10).
COMPUTE Parent_education_sum=sos9 + sos10.
EXECUTE.

*Outliers min max average.
EXAMINE VARIABLES=ABIQ
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=PALFAMS
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=PALTEA28
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=RTIFMDMT
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
```

```
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=RTIFMDRT
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=RTIFESPR
  /PLOT BOXPLOT STEMLEAF HISTOGRAM
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=SSPFSR
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=verbal_sum
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=matrix_sum
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=time_dominant
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.
```

```
EXAMINE VARIABLES=psi_total
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=kidscreen_total
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=gsrs
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=bpm_total
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=sleep
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=curiosity
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=lactose
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
```

```
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=gluten
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.


EXAMINE VARIABLES= IgG_DGP
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES= IgA_TG2
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=  IgA_gluten
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=IgG_gluten
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=IgG_flagellin
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
```

```
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.


EXAMINE VARIABLES=IgM_flagellin
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=Scd14
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES= I_FABP
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.


EXAMINE VARIABLES=LBP
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.



FREQUENCIES VARIABLES= ABIQ time_dominant
    kidscreen_total psi_total sleep curiosity lactose gluten gsrs HLA_DQ2_5
HLA_DQ8
    HLA_DQ2_2 IgA_TG2 IgG_DGP IgA_gluten IgG_gluten IgG_flagellin
IgM_flagellin I_FABP LBP Scd14
    Hemoglobin MCV Ferritin Leukocyte_diff CRP TSH Free_T4 ASAT ALAT
  /FORMAT=NOTABLE
  /STATISTICS=STDDEV VARIANCE RANGE MINIMUM MAXIMUM MEAN MEDIAN MODE
  /ORDER=ANALYSIS.

FREQUENCIES VARIABLES=sos3
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN MEDIAN MODE
  /ORDER=ANALYSIS.
```

```
FREQUENCIES VARIABLES=sos9
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN MEDIAN MODE
  /ORDER=ANALYSIS.

FREQUENCIES VARIABLES= sos10
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN MEDIAN MODE
  /ORDER=ANALYSIS.

FREQUENCIES VARIABLES= Parent_education_sum
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN MEDIAN MODE
  /ORDER=ANALYSIS.

FREQUENCIES VARIABLES=Age
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN MEDIAN MODE
  /ORDER=ANALYSIS.

*Analyze Patterns of Missing Values.of values used for imputation.
MULTIPLE IMPUTATION  sos1 sos2 sos3 sos4 sos5 sos6 sos7 sos8 sos9 sos10 bpm1
bpm2 bpm3 bpm4 bpm5
    bpm6 bpm7 bpm8 bpm9 bpm10 bpm11 bpm12 bpm13 bpm14 bpm15 bpm16 bpm17 bpm18
bpm19 psi1 psi2 psi3 psi4
    psi5 psi6 psi7 psi8 psi9 psi10 psi11 psi12 psi13 psi14 psi15 psi16 psi17
psi18 psi19 psi20 psi21
    psi22 psi23 psi24 psi25 psi26 psi27 psi28 psi29 psi30 psi31 psi32 psi33
psi34 psi35 psi36 kid1 kid2
    kid3 kid4 kid5 kid6 kid7 kid8 kid9 kid10 kid11 cur1 cur2 cur3 cur4 cur5
cur6 cur7 cur8 cur9 cur10
    diet1 diet3 diet2 diet4 diet7 diet8 diet9 diet10 diet11 diet12 diet13
diet14 diet15 diet16 gsrs1
    gsrs2 gsrs3 gsrs4 gsrs5 gsrs6 gsrs7 gsrs8 gsrs9 gsrs10 gsrs11 gsrs12
gsrs13 gsrs14 gsrs15 slp1 slp2
    slp3 som1 som2 som3 som4 som5 som6 som7 som8 som9 matrix_sum  verbal_sum
time_dominant  time_nondominant
    PALFAMS PALTEA28 RTIFMDMT RTIFMDRT SSPFSR IgA_gluten IgG_gluten
   /IMPUTE METHOD=NONE
   /MISSINGSUMMARIES  OVERALL VARIABLES (MAXVARS=200 MINPCTMISSING=0.01)
PATTERNS.

* Analyze Patterns of Missing Values.of values used in analysis.
MULTIPLE IMPUTATION  bpm1 bpm2 bpm3 bpm4 bpm5 bpm6 bpm7 bpm8 bpm9 bpm10 bpm11
bpm12 bpm13 bpm14 bpm15 bpm16 bpm17 bpm18 bpm19 psi1 psi2 psi3 psi4
    psi5 psi6 psi7 psi8 psi9 psi10 psi11 psi12 psi13 psi14 psi15 psi16 psi17
psi18 psi19 psi20 psi21
    psi22 psi23 psi24 psi25 psi26 psi27 psi28 psi29 psi30 psi31 psi32 psi33
psi34 psi35 psi36 kid1 kid2
    kid3 kid4 kid5 kid6 kid7 kid8 kid9 kid10 kid11 cur1 cur2 cur3 cur4 cur5
cur6 cur7 cur8 cur9 cur10
    gsrs1 gsrs2 gsrs3 gsrs4 gsrs5 gsrs6 gsrs7 gsrs8 gsrs9 gsrs10 gsrs11 gsrs12
gsrs13 gsrs14 gsrs15 matrix_sum  verbal_sum  time_dominant
    PALFAMS PALTEA28 RTIFMDMT RTIFMDRT SSPFSR IgA_gluten IgG_gluten
   /IMPUTE METHOD=NONE
   /MISSINGSUMMARIES  OVERALL VARIABLES (MAXVARS=200 MINPCTMISSING=0.01)
PATTERNS.
```

```
*Littles MCAR test.
MVA VARIABLES=  sos1 sos2 sos3 sos4 sos5 sos6 sos7 sos8 sos9 sos10 bpm1 bpm2
bpm3 bpm4 bpm5
    bpm6 bpm7 bpm8 bpm9 bpm10 bpm11 bpm12 bpm13 bpm14 bpm15 bpm16 bpm17 bpm18
bpm19 psi1 psi2 psi3 psi4
    psi5 psi6 psi7 psi8 psi9 psi10 psi11 psi12 psi13 psi14 psi15 psi16 psi17
psi18 psi19 psi20 psi21
    psi22 psi23 psi24 psi25 psi26 psi27 psi28 psi29 psi30 psi31 psi32 psi33
psi34 psi35 psi36 kid1 kid2
    kid3 kid4 kid5 kid6 kid7 kid8 kid9 kid10 kid11 cur1 cur2 cur3 cur4 cur5
cur6 cur7 cur8 cur9 cur10
    diet1 diet3 diet2 diet4 diet7 diet8 diet9 diet10 diet11 diet12 diet13
diet14 diet15 diet16 gsrs1
    gsrs2 gsrs3 gsrs4 gsrs5 gsrs6 gsrs7 gsrs8 gsrs9 gsrs10 gsrs11 gsrs12
gsrs13 gsrs14 gsrs15 slp1 slp2
    slp3 som1 som2 som3 som4 som5 som6 som7 som8 som9 matrix_sum  verbal_sum
     dominant_handrl test_right test_left time_dominant
    time_nondominant PALFAMS PALTEA28 RTIFMDMT RTIFMDRT SSPFSR IgA_gluten
IgG_gluten
  /EM(TOLERANCE=0.001 CONVERGENCE=0.0001 ITERATIONS=50).



*SAVE.
SAVE OUTFILE='N:\durable\Statistics\SPSS data\Dataset Descriptives.sav'.
OUTPUT SAVE OUTFILE='N:\durable\Statistics\Output\Descriptives.spv'.
```

G3 Script R: Multiple imputation

```
setwd("N:/durable/Statistics/r")
library(haven)
library(mice)
library(miceadds)
library(lavaan)
library(tidyverse)

set.seed(5382)

datafile <- "Dataset R.sav"
data <- read_sav(datafile)
data <- as_tibble(data)

var_count <- length(data)
obs_count <- length(data[["sos1"]])

missing_vector <- vector(mode = "list", obs_count)
for(i in 1:obs_count){
  missing_vector[[i]] <- NA
}

data$bpm <- missing_vector
data$psi <- missing_vector
data$cur <- missing_vector
data$kidscreen <- missing_vector
data$sleep <- missing_vector
data$gluten <- missing_vector
data$gsrs <- missing_vector
data$meaneducation <- missing_vector
data$ZRTI_mean <- missing_vector
data$ZPAL_mean <- missing_vector
data$gscore <- missing_vector
data$bscore <- missing_vector
data$Zslp1 <- missing_vector
data$Zslp2 <- missing_vector
data$Zslp3 <- missing_vector
data$ZPALFAMS <- missing_vector
data$ZPALTEA28 <- missing_vector
data$ZRTIFMDMT <- missing_vector
data$ZRTIFMDRT <- missing_vector
data$ZSSPFSR <- missing_vector
data$Zverbal <- missing_vector
data$Zmatrix <- missing_vector
data$Z9HPT <- missing_vector
data$ZIgA_gluten <- missing_vector
data$ZIgG_gluten <- missing_vector

imputable <- dplyr::select(data, Age, Age_years, Parent_education_sum, sos1,
sos2, sos3, sos4, sos5, sos6, sos7, sos8, sos9, sos10, bpm1, bpm2, bpm3,
                    bpm4, bpm5, bpm6, bpm7, bpm8, bpm9, bpm10, bpm11, bpm12,
bpm13, bpm14, bpm15, bpm16, bpm17,
                    bpm18, bpm19, psi1, psi2, psi3, psi4, psi5, psi6, psi7,
psi8, psi9, psi10, psi11, psi12,
                    psi13, psi14, psi15, psi16, psi17, psi18, psi19, psi20,
psi21, psi22, psi23, psi24, psi25,
```

```
                    psi26, psi27, psi28, psi29, psi30, psi31, psi32, psi33,
psi34, psi35, psi36, kid1, kid2,
                    kid3, kid4, kid5, kid6, kid7, kid8, kid9, kid10, kid11,
cur1, cur2, cur3, cur4, cur5,
                    cur6, cur7, cur8, cur9, cur10, diet1, diet3, diet2, diet4,
diet7, diet8, diet9, diet10,
                    diet11, diet12, diet13, diet14, diet15, diet16, gsrs1,
gsrs2, gsrs3, gsrs4, gsrs5, gsrs6, gsrs7,
                    gsrs8, gsrs9, gsrs10, gsrs11, gsrs12, gsrs13, gsrs14,
gsrs15, slp1, slp2, slp3, som1, som2,
                    som3, som4, som5, som6, som7, som8, som9, matrix_sum,
verbal_sum,
                    ab_sum, ABIQ, dominant_handrl, test_right, test_left,
time_dominant, time_nondominant,
                    PALFAMS, PALTEA28, RTIFMDMT, RTIFMDRT, SSPFSR, IgA_gluten,
IgG_gluten,
                    bpm, psi, cur, kidscreen, sleep, gluten, gsrs,
meaneducation, ZRTI_mean, ZPAL_mean, gscore, bscore,
                    Zslp1,Zslp2,Zslp3, ZPALFAMS, ZPALTEA28, ZRTIFMDMT,
ZRTIFMDRT, ZSSPFSR, Zverbal, Zmatrix, Z9HPT, ZIgA_gluten, ZIgG_gluten)


factored_data <- imputable
var_count <- length(factored_data)

view(sapply(factored_data,class))
for(i in 1:var_count){            ##TODO: Find which which values were the
problem and check if some should be excluded

  factored_data[i] <- as.numeric(unlist(factored_data[i]))
 # for(j in i){
  #  j <- as.numeric(j)
  #print(is.numeric(factored_data[i]))
#  }
}
#view(sapply(factored_data,class))

print(colnames(data))
print(factored_data)

factored_data$sos3 <- factor(factored_data$sos3)
factored_data$sos5 <- ordered(factored_data$sos5)
factored_data$sos6 <- ordered(factored_data$sos6)
factored_data$sos7 <- ordered(factored_data$sos7)
factored_data$sos8 <- ordered(factored_data$sos8)
factored_data$sos9 <- ordered(factored_data$sos9)
factored_data$sos10 <- ordered(factored_data$sos10)
factored_data$bpm1 <- ordered(factored_data$bpm1)
factored_data$bpm2 <- ordered(factored_data$bpm2)
factored_data$bpm3 <- ordered(factored_data$bpm3)
factored_data$bpm4 <- ordered(factored_data$bpm4)
factored_data$bpm5 <- ordered(factored_data$bpm5)
factored_data$bpm6 <- ordered(factored_data$bpm6)
factored_data$bpm7 <- ordered(factored_data$bpm7)
factored_data$bpm8 <- ordered(factored_data$bpm8)
factored_data$bpm9 <- ordered(factored_data$bpm9)
factored_data$bpm10 <- ordered(factored_data$bpm10)
```

```
factored_data$bpm11 <- ordered(factored_data$bpm11)
factored_data$bpm12 <- ordered(factored_data$bpm12)
factored_data$bpm13 <- ordered(factored_data$bpm13)
factored_data$bpm14 <- ordered(factored_data$bpm14)
factored_data$bpm15 <- ordered(factored_data$bpm15)
factored_data$bpm16 <- ordered(factored_data$bpm16)
factored_data$bpm17 <- ordered(factored_data$bpm17)
factored_data$bpm18 <- ordered(factored_data$bpm18)
factored_data$bpm19 <- ordered(factored_data$bpm19)
factored_data$psi1 <- ordered(factored_data$psi1)
factored_data$psi2 <- ordered(factored_data$psi2)
factored_data$psi3 <- ordered(factored_data$psi3)
factored_data$psi4 <- ordered(factored_data$psi4)
factored_data$psi5 <- ordered(factored_data$psi5)
factored_data$psi6 <- ordered(factored_data$psi6)
factored_data$psi7 <- ordered(factored_data$psi7)
factored_data$psi8 <- ordered(factored_data$psi8)
factored_data$psi9 <- ordered(factored_data$psi9)
factored_data$psi10 <- ordered(factored_data$psi10)
factored_data$psi11 <- ordered(factored_data$psi11)
factored_data$psi12 <- ordered(factored_data$psi12)
factored_data$psi13 <- ordered(factored_data$psi13)
factored_data$psi14 <- ordered(factored_data$psi14)
factored_data$psi15 <- ordered(factored_data$psi15)
factored_data$psi16 <- ordered(factored_data$psi16)
factored_data$psi17 <- ordered(factored_data$psi17)
factored_data$psi18 <- ordered(factored_data$psi18)
factored_data$psi19 <- ordered(factored_data$psi19)
factored_data$psi20 <- ordered(factored_data$psi20)
factored_data$psi21 <- ordered(factored_data$psi21)
factored_data$psi22 <- ordered(factored_data$psi22)
factored_data$psi23 <- ordered(factored_data$psi23)
factored_data$psi24 <- ordered(factored_data$psi24)
factored_data$psi25 <- ordered(factored_data$psi25)
factored_data$psi26 <- ordered(factored_data$psi26)
factored_data$psi27 <- ordered(factored_data$psi27)
factored_data$psi28 <- ordered(factored_data$psi28)
factored_data$psi29 <- ordered(factored_data$psi29)
factored_data$psi30 <- ordered(factored_data$psi30)
factored_data$psi31 <- ordered(factored_data$psi31)
factored_data$psi32 <- ordered(factored_data$psi32)
factored_data$psi33 <- ordered(factored_data$psi33)
factored_data$psi34 <- ordered(factored_data$psi34)
factored_data$psi35 <- ordered(factored_data$psi35)
factored_data$psi36 <- ordered(factored_data$psi36)
factored_data$kid1 <- ordered(factored_data$kid1)
factored_data$kid2 <- ordered(factored_data$kid2)
factored_data$kid3 <- ordered(factored_data$kid3)
factored_data$kid4 <- ordered(factored_data$kid4)
factored_data$kid5 <- ordered(factored_data$kid5)
factored_data$kid6 <- ordered(factored_data$kid6)
factored_data$kid7 <- ordered(factored_data$kid7)
factored_data$kid8 <- ordered(factored_data$kid8)
factored_data$kid9 <- ordered(factored_data$kid9)
factored_data$kid10 <- ordered(factored_data$kid10)
factored_data$kid11 <- ordered(factored_data$kid11)
factored_data$cur1 <- ordered(factored_data$cur1)
```

```r
factored_data$cur2 <- ordered(factored_data$cur2)
factored_data$cur3 <- ordered(factored_data$cur3)
factored_data$cur4 <- ordered(factored_data$cur4)
factored_data$cur5 <- ordered(factored_data$cur5)
factored_data$cur6 <- ordered(factored_data$cur6)
factored_data$cur7 <- ordered(factored_data$cur7)
factored_data$cur8 <- ordered(factored_data$cur8)
factored_data$cur9 <- ordered(factored_data$cur9)
factored_data$cur10 <- ordered(factored_data$cur10)
factored_data$diet1 <- factor(factored_data$diet1)
factored_data$diet7 <- ordered(factored_data$diet7)
factored_data$diet8 <- ordered(factored_data$diet8)
factored_data$diet9 <- ordered(factored_data$diet9)
factored_data$diet10 <- ordered(factored_data$diet10)
factored_data$diet11 <- ordered(factored_data$diet11)
factored_data$diet12 <- ordered(factored_data$diet12)
factored_data$diet13 <- ordered(factored_data$diet13)
factored_data$diet14 <- ordered(factored_data$diet14)
factored_data$diet15 <- ordered(factored_data$diet15)
factored_data$diet16 <- ordered(factored_data$diet16)
factored_data$gsrs1 <- ordered(factored_data$gsrs1)
factored_data$gsrs2 <- ordered(factored_data$gsrs2)
factored_data$gsrs3 <- ordered(factored_data$gsrs3)
factored_data$gsrs4 <- ordered(factored_data$gsrs4)
factored_data$gsrs5 <- ordered(factored_data$gsrs5)
factored_data$gsrs6 <- ordered(factored_data$gsrs6)
factored_data$gsrs7 <- ordered(factored_data$gsrs7)
factored_data$gsrs8 <- ordered(factored_data$gsrs8)
factored_data$gsrs9 <- ordered(factored_data$gsrs9)
factored_data$gsrs10 <- ordered(factored_data$gsrs10)
factored_data$gsrs11 <- ordered(factored_data$gsrs11)
factored_data$gsrs12 <- ordered(factored_data$gsrs12)
factored_data$gsrs13 <- ordered(factored_data$gsrs13)
factored_data$gsrs14 <- ordered(factored_data$gsrs14)
factored_data$gsrs15 <- ordered(factored_data$gsrs15)
factored_data$slp2 <- ordered(factored_data$slp2)
factored_data$slp3 <- ordered(factored_data$slp3)
factored_data$som1 <- ordered(factored_data$som1)
factored_data$som2 <- ordered(factored_data$som2)
factored_data$som3 <- ordered(factored_data$som3)
factored_data$som4 <- ordered(factored_data$som4)
factored_data$som5 <- ordered(factored_data$som5)
factored_data$som6 <- ordered(factored_data$som6)
factored_data$som7 <- ordered(factored_data$som7)
factored_data$som8 <- ordered(factored_data$som8)
factored_data$som9 <- ordered(factored_data$som9)
factored_data$dominant_handrl <- factor(factored_data$dominant_handrl)

factored_data$ID <- data$ID

#meth <- vector(mode = "list", var_count)
#for(i in 1:var_count){
 #meth[[i]] <- "pmm"
  #print((is.numeric(factored_data[[i]])|(is.ordered(factored_data[[i]]))))

#}
#names(meth) <- names(factored_data)
```

```
#names(meth)
#is.data.frame(factored_data)

imp <- mice(factored_data,m=1, maxit=0, remove.colinear=FALSE)
meth <- imp$method
print(meth)
imp$loggedEvents

meth["sos3"] <- "logreg"
meth["sos5"] <- "polyreg"
meth["sos6"] <- "polyreg"
meth["sos7"] <- "polyreg"
meth["sos8"] <- "polyreg"
meth["sos9"] <- "polyreg"
meth["sos10"] <- "polyreg"
meth["bpm1"] <- "polyreg"
meth["bpm2"] <- "polyreg"
meth["bpm3"] <- "polyreg"
meth["bpm4"] <- "polyreg"
meth["bpm5"] <- "polyreg"
meth["bpm6"] <- "polyreg"
meth["bpm7"] <- "polyreg"
meth["bpm8"] <- "polyreg"
meth["bpm9"] <- "polyreg"
meth["bpm10"] <- "polyreg"
meth["bpm11"] <- "polyreg"
meth["bpm12"] <- "polyreg"
meth["bpm13"] <- "polyreg"
meth["bpm14"] <- "polyreg"
meth["bpm15"] <- "polyreg"
meth["bpm16"] <- "polyreg"
meth["bpm17"] <- "polyreg"
meth["bpm18"] <- "polyreg"
meth["bpm19"] <- "polyreg"
meth["psi1"] <- "polyreg"
meth["psi2"] <- "polyreg"
meth["psi3"] <- "polyreg"
meth["psi4"] <- "polyreg"
meth["psi5"] <- "polyreg"
meth["psi6"] <- "polyreg"
meth["psi7"] <- "polyreg"
meth["psi8"] <- "polyreg"
meth["psi9"] <- "polyreg"
meth["psi10"] <- "polyreg"
meth["psi11"] <- "polyreg"
meth["psi12"] <- "polyreg"
meth["psi13"] <- "polyreg"
meth["psi14"] <- "polyreg"
meth["psi15"] <- "polyreg"
meth["psi16"] <- "polyreg"
meth["psi17"] <- "polyreg"
meth["psi18"] <- "polyreg"
meth["psi19"] <- "polyreg"
meth["psi20"] <- "polyreg"
meth["psi21"] <- "polyreg"
meth["psi22"] <- "polyreg"
meth["psi23"] <- "polyreg"
```

```
meth["psi24"] <- "polyreg"
meth["psi25"] <- "polyreg"
meth["psi26"] <- "polyreg"
meth["psi27"] <- "polyreg"
meth["psi28"] <- "polyreg"
meth["psi29"] <- "polyreg"
meth["psi30"] <- "polyreg"
meth["psi31"] <- "polyreg"
meth["psi32"] <- "polyreg"
meth["psi33"] <- "polyreg"
meth["psi34"] <- "polyreg"
meth["psi35"] <- "polyreg"
meth["psi36"] <- "polyreg"
meth["kid1"] <- "polyreg"
meth["kid2"] <- "polyreg"
meth["kid3"] <- "polyreg"
meth["kid4"] <- "polyreg"
meth["kid5"] <- "polyreg"
meth["kid6"] <- "polyreg"
meth["kid7"] <- "polyreg"
meth["kid8"] <- "polyreg"
meth["kid9"] <- "polyreg"
meth["kid10"] <- "polyreg"
meth["kid11"] <- "polyreg"
meth["cur1"] <- "polyreg"
meth["cur2"] <- "polyreg"
meth["cur3"] <- "polyreg"
meth["cur4"] <- "polyreg"
meth["cur5"] <- "polyreg"
meth["cur6"] <- "polyreg"
meth["cur7"] <- "polyreg"
meth["cur8"] <- "polyreg"
meth["cur9"] <- "polyreg"
meth["cur10"] <- "polyreg"
meth["diet1"] <- "logreg"
meth["diet7"] <- "polyreg"
meth["diet8"] <- "polyreg"
meth["diet9"] <- "polyreg"
meth["diet10"] <- "polyreg"
meth["diet11"] <- "polyreg"
meth["diet12"] <- "polyreg"
meth["diet13"] <- "polyreg"
meth["diet14"] <- "polyreg"
meth["diet15"] <- "polyreg"
meth["diet16"] <- "polyreg"
meth["gsrs1"] <- "polyreg"
meth["gsrs2"] <- "polyreg"
meth["gsrs3"] <- "polyreg"
meth["gsrs4"] <- "polyreg"
meth["gsrs5"] <- "polyreg"
meth["gsrs6"] <- "polyreg"
meth["gsrs7"] <- "polyreg"
meth["gsrs8"] <- "polyreg"
meth["gsrs9"] <- "polyreg"
meth["gsrs10"] <- "polyreg"
meth["gsrs11"] <- "polyreg"
meth["gsrs12"] <- "polyreg"
```

```
meth["gsrs13"] <- "polyreg"
meth["gsrs14"] <- "polyreg"
meth["gsrs15"] <- "polyreg"
meth["slp2"] <- "polyreg"
meth["slp3"] <- "polyreg"
meth["som1"] <- "polyreg"
meth["som2"] <- "polyreg"
meth["som3"] <- "polyreg"
meth["som4"] <- "polyreg"
meth["som5"] <- "polyreg"
meth["som6"] <- "polyreg"
meth["som7"] <- "polyreg"
meth["som8"] <- "polyreg"
meth["som9"] <- "polyreg"
meth["dominant_handrl"] <- "logreg"
meth["bpm"] <- ""
meth["psi"] <- ""
meth["cur"] <- ""
meth["kidscreen"] <- ""
meth["sleep"] <- ""
meth["gluten"] <- ""
meth["gsrs"] <- ""
meth["meaneducation"] <- ""
meth["ZRTI_mean"] <- ""
meth["ZPAL_mean"] <- ""
meth["gscore"] <- ""
meth["bscore"] <- ""
meth["Zslp1"] <- ""
meth["Zslp2"] <- ""
meth["Zslp3"] <- ""
meth["ZPALFAMS"] <- ""
meth["ZPALTEA28"] <- ""
meth["ZRTIFMDMT"] <- ""
meth["ZRTIFMDRT"] <- ""
meth["ZSSPFSR"] <- ""
meth["Zverbal"] <- ""
meth["Zmatrix"] <- ""
meth["Z9HPT"] <- ""
meth["ZIgA_gluten"] <- ""
meth["ZIgG_gluten"] <- ""
meth["Age"] <- ""
meth["Age_years"] <- ""
meth["Parent_education_sum"] <- ""
meth["ID"] <- ""

#view(sapply(factored_data, class))

imputations <- 20

imp <- mice(factored_data,m=imputations,
maxit=10,method=meth,remove.colinear=FALSE)
imp$method

#pool
pooling <- with(data = imp,exp=lm(sos3 ~ IgG_gluten))
estimate <- pool(pooling)
estimate
```

```r
pooling <- with(data = imp,exp=lm(bpm1 ~ bpm19))
estimate <- pool(pooling)
estimate

completed <- NULL
i <- 1
repeat{
  if(i<=imputations){
  completed[[i]] <- mice::complete(imp,action=i,include=FALSE)
  i = i+1
  }else{
    break
  }
}

#view(completed[1])

#save
setwd("N:/durable/Statistics/r")
saveRDS(completed,file="dataimp.Rda")
saveRDS(imp,file="imp.Rda")
```

G4 Script R: Statistical analysis

```
####PREPARING SCRIPT####
setwd("N:/durable/Statistics/r")
imp <- readRDS(file="imp.Rda")

#Defining nr of imputations, adding one for original dataset
imputations <- imp$m+1

#Loading libraries
library(mice)
library(miceadds)
library(dplyr)
library(Amelia)
library(car)
library(QuantPsyc)
library(MASS)
library(xlsx)
library(semTools)
library(lavaan)
library(tidyverse)


#####RANKING BIOLOGICAL MEASURES####
looped <- data.frame()

i <- 1
repeat{
  if(i<=imputations){
    #Pulling imputation
    imputation <- mice::complete(imp,i-1)

    #Ranking variables
    imputation$R_IgA_gluten <-
rank(imputation$IgA_gluten,na.last="keep",ties.method="first")
    imputation$R_IgG_gluten <-
rank(imputation$IgG_gluten,na.last="keep",ties.method="first")

    #Re-creating .imp and .id-variables
    imputation$.id <- rownames(imputation)
    imputation$.imp <- i-1

    #Appending imputations together
    looped <- rbind(looped, imputation)

    i = i+1
  }else{
    break
  }
}

##Turning looped into .mids-object, before turning .mids object into long
form.
data.ranked <- as.mids(looped, where = NULL, .imp = ".imp", .id = ".id")
completed <- mice::complete(data.ranked, 'long', include=TRUE)

####SCALING AND REVERSING MEASURES####
```

```
##Scaling sleep, then reversing slp1 (total amount of sleep, so higher score -
> less sleep)
completed$Zslp1 <- as.vector(scale(subset(completed, select =(slp1), center =
TRUE, scale = TRUE)))
completed$Zslp2 <- as.vector(scale(as.numeric(unlist(completed$slp2)), center
= TRUE, scale = TRUE))
completed$Zslp3 <- as.vector(scale(as.numeric(unlist(completed$slp3)), center
= TRUE, scale = TRUE))

##Creating zscores for results cognitive tests..
completed$ZPALFAMS <- as.vector(scale(subset(completed, select =(PALFAMS),
center = TRUE, scale = TRUE)))
completed$ZPALTEA28 <- as.vector(scale(subset(completed, select =(PALTEA28),
center = TRUE, scale = TRUE)))
completed$ZRTIFMDMT <- as.vector(scale(subset(completed, select =(RTIFMDMT),
center = TRUE, scale = TRUE)))
completed$ZRTIFMDRT <- as.vector(scale(subset(completed, select =(RTIFMDRT),
center = TRUE, scale = TRUE)))
completed$ZSSPFSR <- as.vector(scale(subset(completed, select =(SSPFSR),
center = TRUE, scale = TRUE)))
completed$Zverbal <- as.vector(scale(subset(completed, select =(verbal_sum),
center = TRUE, scale = TRUE)))
completed$Zmatrix <- as.vector(scale(subset(completed, select =(matrix_sum),
center = TRUE, scale = TRUE)))
completed$Z9HPT <- as.vector(scale(subset(completed, select =(time_dominant),
center = TRUE, scale = TRUE)))

##Reversing scaled scores for selected CANTAB-scores and 9HPT
completed$ZPALTEA28 <- 100 - completed$ZPALTEA28 - 100
completed$ZRTIFMDMT <- 100 - completed$ZRTIFMDMT - 100
completed$ZRTIFMDRT <- 100 - completed$ZRTIFMDRT - 100
completed$Z9HPT <- 100 - completed$Z9HPT - 100


####LOGARTMIC TRANSFORMATION AND SCALING OF BIOLOGICAL MEASURES####
##log10 transforms
# completed$IgG_flagellin <- log10(completed$IgG_flagellin)
# completed$IgM_flagellin <- log10(completed$IgM_flagellin)
 completed$L_IgA_gluten <- log10(completed$IgA_gluten)
 completed$L_IgG_gluten <- log10(completed$IgG_gluten)
# completed$Scd14 <- log10(completed$Scd14)
# completed$I_FABP <- log10(completed$I_FABP)
# completed$LBP <- log10(completed$LBP)

##Creating zscores for biomarkers
completed$ZIgA_gluten <- as.vector(scale(subset(completed, select
=(IgA_gluten), center = TRUE, scale = TRUE)))
completed$ZIgG_gluten <- as.vector(scale(subset(completed, select
=(IgG_gluten), center = TRUE, scale = TRUE)))
completed$L_ZIgA_gluten <- as.vector(scale(subset(completed, select
=(L_IgA_gluten), center = TRUE, scale = TRUE)))
completed$L_ZIgG_gluten <- as.vector(scale(subset(completed, select
=(L_IgG_gluten), center = TRUE, scale = TRUE)))


####CREATING COMPOSITES####
bpm_arr <- dplyr::select(completed, bpm1,bpm2,bpm3,bpm4,bpm5,bpm6,bpm7,bpm8,
```

```
bpm9,bpm10,bpm11,bpm12,bpm13,bpm14,bpm15,bpm16,bpm17,bpm18,bpm19)
for(j in 1:length(bpm_arr)){
  bpm_arr[j] <- as.numeric(unlist(bpm_arr[j]))
}
psi_arr <- dplyr::select(completed, psi1:psi36)
for(j in 1:length(psi_arr)){
  psi_arr[j] <- as.numeric(unlist(psi_arr[j]))
}
cur_arr <- dplyr::select(completed, cur1:cur10)
for(j in 1:length(cur_arr)){
  cur_arr[j] <- as.numeric(unlist(cur_arr[j]))
}
kid_arr <- dplyr::select(completed, kid1:kid10)
for(j in 1:length(kid_arr)){
  kid_arr[j] <- as.numeric(unlist(kid_arr[j]))
}
gluten_arr <- dplyr::select(completed, diet10,diet11,diet12,diet15)
for(j in 1:length(gluten_arr)){
  gluten_arr[j] <- as.numeric(unlist(gluten_arr[j]))
}
gsrs_arr <- dplyr::select(completed, gsrs1:gsrs15)
for(j in 1:length(gsrs_arr)){
  gsrs_arr[j] <- as.numeric(unlist(gsrs_arr[j]))
}
sos_arr <- dplyr::select(completed, sos9,sos10)
for(j in 1:length(sos_arr)){
  sos_arr[j] <- as.numeric(unlist(sos_arr[j]))
}

#rude variables
completed$bpm <- rowMeans(bpm_arr)
completed$psi <- rowMeans(psi_arr)
completed$cur <- rowMeans(cur_arr)
completed$kidscreen <- rowMeans(kid_arr)
completed$gluten <- rowMeans(gluten_arr)
completed$gsrs <- rowMeans(gsrs_arr)
completed$meaneducation <- rowMeans(sos_arr)

#nice variables
completed$sleep <- rowMeans(subset(completed, select = c(Zslp1:Zslp3)), na.rm
= TRUE)
completed$ZRTI_mean <- rowMeans(subset(completed, select =
c(ZRTIFMDMT,ZRTIFMDRT)), na.rm = TRUE)
completed$ZPAL_mean <- rowMeans(subset(completed, select =
c(ZPALFAMS,ZPALTEA28)), na.rm = TRUE)
completed$gscore <- rowMeans(subset(completed, select =
c(Zmatrix,Zverbal,ZRTI_mean,ZPAL_mean,ZSSPFSR,Z9HPT)), na.rm = TRUE)
completed$bscore <- rowMeans(subset(completed, select =
c(ZIgA_gluten,ZIgG_gluten)), na.rm = TRUE)
completed$L_bscore <- rowMeans(subset(completed, select =
c(L_ZIgA_gluten,L_ZIgG_gluten)), na.rm = TRUE)
completed$R_bscore <- rowMeans(subset(completed, select =
c(R_IgA_gluten,R_IgG_gluten)), na.rm = TRUE)
completed$cantab <- rowMeans(subset(completed, select =
c(ZRTI_mean,ZPAL_mean,ZSSPFSR)), na.rm = TRUE)
```

```
completed$sb5 <- rowMeans(subset(completed, select = c(Zverbal,Zmatrix)),
na.rm = TRUE)


#Standarized variables for linear regression (standarized coefficents). NOT
CENTERED.
completed$Zage <- scale(as.numeric(unlist(completed$Age)), center = TRUE,
scale = TRUE)
completed$Zmeaneducation <- scale(as.numeric(unlist(completed$meaneducation)),
center = TRUE, scale = TRUE)
completed$Zpsi <- scale(as.numeric(unlist(completed$psi)), center = TRUE,
scale = TRUE)
completed$Zcur <- scale(as.numeric(unlist(completed$cur)), center = TRUE,
scale = TRUE)
completed$Zkidscreen <- scale(as.numeric(unlist(completed$kidscreen)), center
= TRUE, scale = TRUE)
completed$Zbpm <- scale(as.numeric(unlist(completed$bpm)), center = TRUE,
scale = TRUE)
completed$Zgsrs <- scale(as.numeric(unlist(completed$gsrs)), center = TRUE,
scale = TRUE)
completed$ZR_bscore <- scale(as.numeric(unlist(completed$R_bscore)), center =
TRUE, scale = TRUE)
completed$Zpsi <- 100 - completed$Zpsi - 100
completed$Zbpm_reverse <- 100 - completed$Zbpm - 100

#Creating means to remove matrix from variables (creating error when turning
into .mids)
completed$Zage <- rowMeans(subset(completed, select = c(Zage)), na.rm = TRUE)
completed$Zmeaneducation <- rowMeans(subset(completed, select =
c(Zmeaneducation)), na.rm = TRUE)
completed$Zpsi <- rowMeans(subset(completed, select = c(Zpsi)), na.rm = TRUE)
completed$Zcur <- rowMeans(subset(completed, select = c(Zcur)), na.rm = TRUE)
completed$Zkidscreen <- rowMeans(subset(completed, select = c(Zkidscreen)),
na.rm = TRUE)
completed$Zbpm <- rowMeans(subset(completed, select = c(Zbpm)), na.rm = TRUE)
completed$Zgsrs<- rowMeans(subset(completed, select = c(Zgsrs)), na.rm = TRUE)
completed$Zbpm_reverse <- rowMeans(subset(completed, select =
c(Zbpm_reverse)), na.rm = TRUE)
completed$ZR_bscore <- rowMeans(subset(completed, select = c(ZR_bscore)),
na.rm = TRUE)

completed$sos3 <- as.numeric(as.character(completed$sos3))


#Creating .mids object
data.mids <- as.mids(completed, where = NULL, .imp = ".imp", .id = ".id")



####RANKING VARIABLES FOR SPEARMAN RANKED####
#Clearing loop
looped <- data.frame()

###Ranking composites variables for correlations
i <- 1
repeat{
  if(i<=imputations){
```

```
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)

    #Ranking variables for correlations
    imputation$R_PALFAMS <-
rank(imputation$ZPALFAMS,na.last="keep",ties.method="first")
    imputation$R_PALTEA28 <-
rank(imputation$ZPALTEA28,na.last="keep",ties.method="first")
    imputation$R_RTIFMDMT <-
rank(imputation$ZRTIFMDMT,na.last="keep",ties.method="first")
    imputation$R_RTIFMDRT <-
rank(imputation$ZRTIFMDRT,na.last="keep",ties.method="first")
    imputation$R_SSPFSR <-
rank(imputation$ZSSPFSR,na.last="keep",ties.method="first")
    imputation$R_verbal <-
rank(imputation$Zverbal,na.last="keep",ties.method="first")
    imputation$R_matrix <-
rank(imputation$Zmatrix,na.last="keep",ties.method="first")
    imputation$R_cantab <-
rank(imputation$cantab,na.last="keep",ties.method="first")
    imputation$R_sb5 <-
rank(imputation$sb5,na.last="keep",ties.method="first")
    imputation$R_9HPT <-
rank(imputation$Z9HPT,na.last="keep",ties.method="first")
    imputation$R_gscore <-
rank(imputation$gscore,na.last="keep",ties.method="first")
    imputation$R_psi <-
rank(imputation$Zpsi,na.last="keep",ties.method="first")
    imputation$R_cur <-
rank(imputation$cur,na.last="keep",ties.method="first")
    imputation$R_kidscreen <-
rank(imputation$kidscreen,na.last="keep",ties.method="first")
    imputation$R_bpm <-
rank(imputation$bpm,na.last="keep",ties.method="first")
    imputation$R_gsrs <-
rank(imputation$gsrs,na.last="keep",ties.method="first")
    imputation$R_sleep <-
rank(imputation$sleep,na.last="keep",ties.method="first")
    imputation$R_Age <-
rank(imputation$Age,na.last="keep",ties.method="first")
    imputation$R_meaneducation <-
rank(imputation$meaneducation,na.last="keep",ties.method="first")

    #Re-creating .imp and .id-variables
    imputation$.id <- rownames(imputation)
    imputation$.imp <- i-1

    #Appending imputations together
    looped <- rbind(looped, imputation)

    i = i+1
  }else{
    break
  }
}

#Creating back into .mids-object
```

```
data.mids <- as.mids(looped, where = NULL, .imp = ".imp", .id = ".id")

####RUN SCRIPT TO HERE TO CREATE AND SAVE ALL VARIABLES####
saveRDS(data.mids,file="datamids.Rda")



#Creating dataset containing only those with blood samples results for gluten
antibodies.
completed <- mice::complete(data.mids, 'long', include=TRUE)
fulldata <- subset(completed, ID %in% c("G003", "G004", "G006", "G016",
"G021", "G023", "G024"))
data.full <- as.mids(fulldata, where = NULL, .imp = ".imp", .id = ".id")



####CORRELATIONS####
##Pearson correlations
pearson <- miceadds::micombine.cor(mi.res=data.mids,
                                   variables
=c(1,6,154,138,145:153,155:158,173:175,179:183))

write.xlsx(attr(pearson, "r_matrix"), file = "output/correlations.xlsx",
           sheetName = "Correlations", append = FALSE)

##Partial correlations. Controlling for gender and mean education, Age.
partial <- miceadds::micombine.cor(mi.res=data.mids,

variables=c(138,140:153,155:158,173:175,179:183,189),
                                   partial=~sos3+meaneducation+Age)
write.xlsx(attr(partial, "r_matrix"), file = "output/correlations.xlsx",
           sheetName = "Partial cor", append = TRUE)

##Spearman correlations
spearman <- miceadds::micombine.cor(mi.res=data.mids, variables
=c(6,180,189:207), method="spearman")

write.xlsx(attr(spearman, "r_matrix"), file = "output/correlations.xlsx",
           sheetName = "Ranked", append = TRUE)

##Partial spearman correlations. Controlling for gender and mean education,
Age.
partial_s <- miceadds::micombine.cor(mi.res=data.mids,
variables=c(173,174,180,189:205), method="spearman",
                                   partial=~sos3+R_meaneducation+R_Age)
write.xlsx(attr(partial_s, "r_matrix"), file = "output/correlations.xlsx",
           sheetName = "Partial ranked", append = TRUE)

##Correlations sensitivity, only participants with biological measures
##Partial correlations. Controlling for gender and mean education, Age.
partial_full <- miceadds::micombine.cor(mi.res=data.full,

variables=c(145:153,157,158,173:175,179:183),
                                   partial=~sos3+meaneducation+Age)
write.xlsx(attr(partial_full, "r_matrix"), file = "output/correlations.xlsx",
           sheetName = "Pearson full", append = TRUE)
```

```r
##Partial spearman correlations. Controlling for gender and mean education,
Age.
partial_s_full <- miceadds::micombine.cor(mi.res=data.full,
variables=c(173,174,180,189:205), method="spearman",
                                          partial=~sos3+R_meaneducation+R_Age)
write.xlsx(attr(partial_s_full, "r_matrix"), file =
"output/correlations.xlsx",
           sheetName = "Spearman full", append = TRUE)



####LINEAR MODELS####
##Multivariate model. Output save to "linear models.xlsx". First model does
not append, overwriting old .txt. Includes baseline models separating effect
of confounding variables.
mod.total <- with(data.mids, lm(gscore + Zcur + Zbpm_reverse + Zkidscreen +
Zpsi ~ Zage + sos3 + Zmeaneducation + Zgsrs + ZR_bscore))
output.total <- c(summary(pool(mod.total), conf.int = TRUE),
pool.r.squared(mod.total))
write.xlsx(output.total, "output/linear models.xlsx", sheetName="Total",
col.names=TRUE, row.names=TRUE)

baseline.total <- with(data.mids, lm(gscore + Zcur + Zbpm_reverse + Zkidscreen
+ Zpsi ~ Zage + sos3 + Zmeaneducation))
output.btotal <- c(summary(pool(baseline.total), conf.int = TRUE),
pool.r.squared(baseline.total))
write.xlsx(output.btotal, "output/linear models.xlsx", sheetName="Baseline
Total", append = TRUE, col.names=TRUE, row.names=TRUE)

##G-score model
mod.gscore <- with(data.mids, lm(gscore ~ Zage + sos3 + Zmeaneducation +
ZR_bscore + Zgsrs))
output.gscore <- c(summary(pool(mod.gscore), conf.int = TRUE),
pool.r.squared(mod.gscore))
write.xlsx(output.gscore, "output/linear models.xlsx", sheetName="G-score",
append = TRUE, col.names=TRUE, row.names=TRUE)

baseline.gscore <- with(data.mids, lm(gscore ~ Zage + sos3 + Zmeaneducation))
output.bgscore <- c(summary(pool(baseline.gscore), conf.int = TRUE),
pool.r.squared(baseline.gscore))
write.xlsx(output.bgscore, "output/linear models.xlsx", sheetName="Baseline G-
score", append = TRUE, col.names=TRUE, row.names=TRUE)

##BPM-model
mod.bpm <- with(data.mids, lm(Zbpm ~ Zage + sos3 + meaneducation + ZR_bscore +
Zgsrs))
output.bpm <- c(summary(pool(mod.bpm), conf.int = TRUE),
pool.r.squared(mod.bpm))
write.xlsx(output.bpm, "output/linear models.xlsx", sheetName="BPM", append =
TRUE, col.names=TRUE, row.names=TRUE)

baseline.bpm <- with(data.mids, lm(Zbpm ~ Zage + sos3 + meaneducation))
output.bbpm <- c(summary(pool(baseline.bpm), conf.int = TRUE),
pool.r.squared(baseline.bpm))
write.xlsx(output.bbpm, "output/linear models.xlsx", sheetName="Baseline BPM",
append = TRUE, col.names=TRUE, row.names=TRUE)
```

```
##KIDSCREEN-model
mod.kidscreen <- with(data.mids, lm(Zkidscreen ~ Zage + sos3 + Zmeaneducation
+ ZR_bscore + Zgsrs))
output.kidscreen <- c(summary(pool(mod.kidscreen), conf.int = TRUE),
pool.r.squared(mod.kidscreen))
write.xlsx(output.kidscreen, "output/linear models.xlsx",
sheetName="KIDSCREEN", append = TRUE, col.names=TRUE, row.names=TRUE)

baseline.kidscreen <- with(data.mids, lm(Zkidscreen ~ Zage + sos3 +
Zmeaneducation))
output.bkidscreen <- c(summary(pool(baseline.kidscreen), conf.int = TRUE),
pool.r.squared(baseline.kidscreen))
write.xlsx(output.bkidscreen, "output/linear models.xlsx", sheetName="Baseline
KIDSCREEN", append = TRUE, col.names=TRUE, row.names=TRUE)

##PSI-model
mod.psi <- with(data.mids, lm(Zpsi ~ Zage + sos3 + Zmeaneducation + ZR_bscore
+ Zgsrs))
output.psi <- c(summary(pool(mod.psi), conf.int = TRUE),
pool.r.squared(mod.psi))
write.xlsx(output.psi, "output/linear models.xlsx", sheetName="PSI", append =
TRUE, col.names=TRUE, row.names=TRUE)

baseline.psi <- with(data.mids, lm(Zpsi ~ Zage + sos3 + Zmeaneducation))
output.bpsi <- c(summary(pool(baseline.psi), conf.int = TRUE),
pool.r.squared(baseline.psi))
write.xlsx(output.bpsi, "output/linear models.xlsx", sheetName="Baseline PSI",
append = TRUE, col.names=TRUE, row.names=TRUE)

##Curiosity model
mod.cur <- with(data.mids, lm(Zcur ~ Zage + sos3 + Zmeaneducation + ZR_bscore
+ Zgsrs))
output.cur <- c(summary(pool(mod.cur), conf.int = TRUE),
pool.r.squared(mod.cur))
write.xlsx(output.cur, "output/linear models.xlsx", sheetName="Curiosity",
append = TRUE, col.names=TRUE, row.names=TRUE)

baseline.cur <- with(data.mids, lm(Zcur ~ Zage + sos3 + Zmeaneducation))
output.bcur <- c(summary(pool(baseline.cur), conf.int = TRUE),
pool.r.squared(baseline.cur))
write.xlsx(output.bcur, "output/linear models.xlsx", sheetName="Baseline
Curiosity", append = TRUE, col.names=TRUE, row.names=TRUE)

##SB5
mod.sb5 <- with(data.mids, lm(sb5 ~ Zage + sos3 + Zmeaneducation + ZR_bscore +
Zgsrs))
output.sb5 <- c(summary(pool(mod.sb5), conf.int = TRUE),
pool.r.squared(mod.sb5))
write.xlsx(output.sb5, "output/linear models.xlsx", sheetName="sb5", append =
TRUE, col.names=TRUE, row.names=TRUE)

baseline.sb5 <- with(data.mids, lm(sb5 ~ Zage + sos3 + Zmeaneducation))
output.bsb5 <- c(summary(pool(baseline.sb5), conf.int = TRUE),
pool.r.squared(baseline.sb5))
write.xlsx(output.bsb5, "output/linear models.xlsx", sheetName="Baseline sb5",
append = TRUE, col.names=TRUE, row.names=TRUE)
```

```r
##CANTAB
mod.cantab <- with(data.mids, lm(cantab ~ Zage + sos3 + Zmeaneducation +
ZR_bscore + Zgsrs))
output.cantab <- c(summary(pool(mod.cantab), conf.int = TRUE),
pool.r.squared(mod.cantab))
write.xlsx(output.cantab, "output/linear models.xlsx", sheetName="cantab",
append = TRUE, col.names=TRUE, row.names=TRUE)

baseline.cantab <- with(data.mids, lm(cantab ~ Zage + sos3 + Zmeaneducation))
output.bcantab <- c(summary(pool(baseline.cantab), conf.int = TRUE),
pool.r.squared(baseline.cantab))
write.xlsx(output.bcantab, "output/linear models.xlsx", sheetName="Baseline
cantab", append = TRUE, col.names=TRUE, row.names=TRUE)

##9hpt
mod.9hpt <- with(data.mids, lm(Z9HPT ~ Zage + sos3 + Zmeaneducation +
ZR_bscore + Zgsrs))
output.9hpt <- c(summary(pool(mod.9hpt), conf.int = TRUE),
pool.r.squared(mod.9hpt))
write.xlsx(output.9hpt, "output/linear models.xlsx", sheetName="9hpt", append
= TRUE, col.names=TRUE, row.names=TRUE)

baseline.9hpt <- with(data.mids, lm(Z9HPT ~ Zage + sos3 + Zmeaneducation))
output.b9hpt <- c(summary(pool(baseline.9hpt), conf.int = TRUE),
pool.r.squared(baseline.9hpt))
write.xlsx(output.b9hpt, "output/linear models.xlsx", sheetName="Baseline
9hpt", append = TRUE, col.names=TRUE, row.names=TRUE)


####STRUCTURAL EQUATION MODELING####
###SEM-models for investigating relationship between variables for
psychological functioning and gluten sensitivity.
sink("output/SEM analyses.txt")

###SEM-model investigating facets of psychological functioning
print("ELEMENT \n")
model.element <- '
# measurement model
glutenprob =~ gsrs + R_bscore
g =~ gscore
hrqol =~ kidscreen
parentstress =~ psi
behavior =~ bpm
curiosity =~ cur
# regressions
g ~ glutenprob
hrqol ~ glutenprob
curiosity ~ glutenprob
parentstress ~ glutenprob
behavior ~ glutenprob
# residual correlations
glutenprob ~~ Age + sos3 + meaneducation
g ~~ Age + sos3 + meaneducation
hrqol ~~ Age + sos3 + meaneducation
parentstress ~~ Age + sos3 + meaneducation
behavior ~~ Age + sos3 + meaneducation
curiosity ~~ Age + sos3 + meaneducation
```

```
'
require(lavaan)
out.elements <- runMI(model.element,
                      data = data.mids,
                      fun = "sem",
                      meanstructure=TRUE)
summary(out.elements)

##printing estimates and outcomes for model elements
fitMeasures(out.elements, c("chisq", "df", "pvalue", "cfi", "rmsea"),
            output = "matrix")
print(fitMeasures(out.elements, c("chisq", "df", "pvalue", "cfi", "rmsea"),
                  output = "text"), add.h0 = TRUE)
parameterEstimates(out.elements)



###SEM-model with latent variables
print("TOTAL \n")
model.total <- '
#measurement model
glutenprob =~ gsrs + R_bscore
psychfunctioning =~ gscore + kidscreen + bpm + psi + cur
#regressions
psychfunctioning ~ glutenprob
#residual correlations
glutenprob ~~ Age + sos3 + meaneducation
psychfunctioning ~~ Age + sos3 + meaneducation
 '
require(lavaan)
out.total <- runMI(model.total,
                   data = data.mids,
                   fun = "sem",
                   meanstructure=TRUE)
summary(out.total)

##printing estimates and outcomes for model total
fitMeasures(out.total, c("chisq", "df", "pvalue", "cfi", "rmsea"),
            output = "matrix")
print(fitMeasures(out.total, c("chisq", "df", "pvalue", "cfi", "rmsea"),
                  output = "text"), add.h0 = TRUE)
parameterEstimates(out.total)


###SEM-model with latent g-structure
print("G-structure \n")
model.total <- '
#measurement model
glutenprob =~ gsrs + R_bscore
psychfunctioning =~ kidscreen + bpm + psi + cur
cognitive =~ Z9HPT + cantab + sb5
#regressions
psychfunctioning ~ glutenprob
#residual correlations
glutenprob ~~ Age + sos3 + meaneducation
psychfunctioning ~~ Age + sos3 + meaneducation
cognitive ~~ Age + sos3 + meaneducation
```

```
'
require(lavaan)
out.cog <- runMI(model.total,
                  data = data.mids,
                  fun = "sem",
                  meanstructure=TRUE)
summary(out.cog)

##printing estimates and outcomes for model total
fitMeasures(out.cog, c("chisq", "df", "pvalue", "cfi", "rmsea"),
            output = "matrix")
print(fitMeasures(out.cog, c("chisq", "df", "pvalue", "cfi", "rmsea"),
                  output = "text"), add.h0 = TRUE)
parameterEstimates(out.cog)
sink()



####MEDIATION MODELS IN LAVAAN####
sink("output/Mediation analyses.txt")

#Mediation analysis with latent dependent variable
print("MEDIATION WITH LATENT CONSTRUCT\n")
model.mediation.lat <- '
# measurement model latent variable
Glutensensitivity =~ gscore + R_bscore
#direct effect
gscore ~ c*Glutensensitivity
#mediator
cur ~ a*Glutensensitivity
gscore ~ b*cur
#indirect effect
indirect := a * b
#Total effect
totalE := c + (a*b)
#residual correlations
gscore ~~ Age + sos3+ meaneducation
R_bscore ~~ Age + sos3+ meaneducation
gsrs ~~ Age + sos3+ meaneducation
cur ~~ Age + sos3+ meaneducation
'
out1 <- runMI(model.mediation.lat, data = data.mids, fun="cfa", meanstructure
= TRUE)
summary(out1)
print(fitMeasures(out1, c("chisq", "df", "pvalue", "cfi", "rmsea"),
                  output = "text"), add.h0 = TRUE)
parameterEstimates(out1)

#Mediation analysis
print("MEDIATION WITHOUT LATENT CONSTRUCT\n")
model.mediation <-
'#direct effect
gscore ~ c1*R_bscore + c2*gsrs
#mediator
cur ~ a1*R_bscore + a2*gsrs
gscore ~ b*cur
#indirect effect
```

```
indirectB := a1 * b
indirectG := a2 * b
#contrasts
contrast := a1*b - a2*b
#Total effect
totalB := c1 + (a1*b)
totalG := c2 + (a2*b)
#residual correlations
gscore ~~ Age + sos3+ meaneducation
R_bscore ~~ Age + sos3+ meaneducation
gsrs ~~ Age + sos3+ meaneducation
cur ~~ Age + sos3+ meaneducation
'

require(lavaan)
out2 <- runMI(model.mediation, data = data.mids, fun="cfa", meanstructure =
TRUE)
summary(out2, standardized=TRUE)
unclass(vcov(out2))

fitMeasures(out2, c("chisq", "df", "pvalue", "cfi", "rmsea"), output =
"matrix")
print(fitMeasures(out2, c("chisq", "df", "pvalue", "cfi", "rmsea"),
                  output = "text"), add.h0 = TRUE)
parameterEstimates(out2)
# running model with MI (from article)
fitmeasures(out2, c("chisq", "df", "pvalue", "cfi", "rmsea"),
            output = "matrix")

#OUT: Numbers not semplot maybe later significance indirect effect alle
correlasjonene a,b og c paths
#fit <- sem(model.mediation,data=completed)#check if correct dataframe
#summary(fit)
#Summary(fit, standardized=T, fit.measures=T, rsq=T)
sink()

#Inderect effect bscore path
################################################
# This code can be edited in this window and   #
# submitted to Rweb, or for faster performance #
# and a nicer looking histogram, submit        #
# directly to R.                               #
################################################
require(MASS)
a=-0.004
b=0.082
rep=20000
conf=95
pest=c(a,b)
acov <- matrix(c(
  0.0005028816, -0.0000161497,
  -0.0000161497, 0.05272927
),2,2)
mcmc <- mvrnorm(rep,pest,acov,empirical=FALSE)
ab <- mcmc[,1]*mcmc[,2]
low=(1-conf/100)/2
upp=((1-conf/100)/2)+(conf/100)
```

```
LL=quantile(ab,low)
UL=quantile(ab,upp)
LL4=format(LL,digits=4)
UL4=format(UL,digits=4)
################################################
# The number of columns in the histogram can   #
# be changed by replacing 'FD' below with      #
# an integer value.                            #
################################################
hist(ab,breaks='FD',col='skyblue',xlab=paste(conf,'% Confidence Interval
','LL',LL4,'  UL',UL4),
     main='Distribution of Indirect Effect')



#Inderect effect GSRS path
################################################
# This code can be edited in this window and   #
# submitted to Rweb, or for faster performance #
# and a nicer looking histogram, submit        #
# directly to R.                               #
################################################
require(MASS)
a=0.142
b=0.082
rep=20000
conf=95
pest=c(a,b)
acov <- matrix(c(
  0.05140909, 0.0005885866,
  0.0005885866, 0.05272927
),2,2)
mcmc <- mvrnorm(rep,pest,acov,empirical=FALSE)
ab <- mcmc[,1]*mcmc[,2]
low=(1-conf/100)/2
upp=((1-conf/100)/2)+(conf/100)
LL=quantile(ab,low)
UL=quantile(ab,upp)
LL4=format(LL,digits=4)
UL4=format(UL,digits=4)
################################################
# The number of columns in the histogram can   #
# be changed by replacing 'FD' below with      #
# an integer value.                            #
################################################
hist(ab,breaks='FD',col='skyblue',xlab=paste(conf,'% Confidence Interval
','LL',LL4,'  UL',UL4),
     main='Distribution of Indirect Effect')

#Mediation analasys of data.full
sink("output/Model ABC paths.txt")
#Linear regressions
# model 1 C path
print("Model 1 c path:")
fit1m <- with(data.full, lm(gscore ~ Age + sos3 + meaneducation + R_bscore))
fit1 <- pool(fit1m)
summary(fit1,conf.int=TRUE)
```

```
print("RSQUARED:")
print(pool.r.squared(fit1m))

# model 2 a path
print("Model 2 a path:")
fit2m <- with(data.full,lm(Zcur ~ Age + sos3 + meaneducation + R_bscore))
fit2 <- pool(fit2m)
summary(fit2, conf.int=TRUE)
print("RSQUARED:")
print(pool.r.squared(fit2m))

#model 3 b path
print("Model 3 b path:")
fit3m <- with(data.full,lm(gscore ~ Age + sos3 + meaneducation + R_bscore +
Zcur, data = full))
fit3 <- pool(fit3m)
summary(fit3, conf.int=TRUE)
print("RSQUARED:")
print(pool.r.squared(fit3m))
sink()




####VALIDITY ANALYSIS OF COMPOSITES####
sink("output/CFA.txt")


##CFA BPM
print("BPM \n")
model.bpm <- '
internalizing =~ bpm9 + bpm11 + bpm12 + bpm13 + bpm18 + bpm19
externalizing =~ bpm2 + bpm6 + bpm7 + bpm8 + bpm15 + bpm16 + bpm17
attention =~ bpm1 + bpm3 + bpm4 + bpm5 + bpm10 + bpm14
 BPM =~ internalizing + externalizing + attention
'

fit.bpm <- runMI(model.bpm, data=data.mids, fun="cfa")
summary(fit.bpm, fit.measures=TRUE, standardized=TRUE)

##CFA I/D-YC Epistemic curiosity
print("I/D-YC \n")
model.cur <- '
curiosity =~ cur1 + cur2 + cur3 + cur4 + cur5 + cur6 + cur7 + cur8 + cur9 +
cur10
'

fit.cur <- runMI(model.cur, data=data.mids, fun="cfa")
summary(fit.cur, fit.measures=TRUE, standardized=TRUE)

##CFA KIDSCREEN-10
print("KIDSCREEN \n")
model.kidscreen <- '
hrqol =~ kid1 + kid2 + kid3 + kid4 + kid5 + kid6 + kid7 + kid8 + kid9 + kid10
+ kid11
'
```

```
fit.kidscreen <- runMI(model.kidscreen, data=data.mids, fun="cfa")
summary(fit.kidscreen, fit.measures=TRUE, standardized=TRUE)

##CFA PSI-4-SF
print("PSI-4-SF \n")
model.psi <- '
stress =~ psi1 + psi2 + psi3 + psi4 + psi5 + psi6 + psi7 + psi8 + psi9 + psi10
+ psi11 + psi12 + psi13 + psi14 + psi15 + psi16 + psi17 + psi18 + psi19 +
psi20 + psi21 + psi22 + psi23 + psi24 + psi25 + psi26 + psi27 + psi28 + psi29
+ psi30 + psi31 + psi32 + psi33 + psi34 + psi35 + psi36
'
fit.psi <- runMI(model.psi, data=data.mids, fun="cfa")
summary(fit.psi, fit.measures=TRUE, standardized=TRUE)

##CFA GSRS
print("GSRS \n")
model.gsrs <- '
gastrosymptoms =~ gsrs1 + gsrs2 + gsrs3 + gsrs4 + gsrs5 + gsrs6 + gsrs7 +
gsrs8 + gsrs9 + gsrs10 + gsrs11 + gsrs12 + gsrs13 + gsrs14 + gsrs15
'
fit.gsrs <- runMI(model.gsrs, data=data.mids, fun="cfa")
summary(fit.gsrs, fit.measures=TRUE, standardized=TRUE)

##CFA GSRS
print("GSRS rev \n")
model.gsrsrev <- '
gastrosymptoms =~ gsrs6 + gsrs8 + gsrs9 + gsrs10 + gsrs11 + gsrs12 + gsrs13 +
gsrs14
'
fit.gsrsrev <- runMI(model.gsrsrev, data=data.mids, fun="cfa")
summary(fit.gsrsrev, fit.measures=TRUE, standardized=TRUE)


##CFA Gluten
print("Gluten \n")
model.gluten <- '
glutenindiet =~ diet10 + diet11 + diet12 + diet15
'
fit.gluten <- runMI(model.gluten, data=data.mids, fun="cfa")
summary(fit.gluten, fit.measures=TRUE, standardized=TRUE)

##CFA Sleep
print("Sleep \n")
model.sleep <- '
sleepissues =~ slp1 + slp2 + slp3
'
fit.sleep <- runMI(model.sleep, data=data.mids, fun="cfa")
summary(fit.sleep, fit.measures=TRUE, standardized=TRUE)

##CFA composite cognitive development score
print("G-score \n")
model.cog <- '
Gscore =~ Zverbal + Zmatrix + ZPAL_mean + ZRTI_mean + ZSSPFSR + Z9HPT
'
fit.cog <- runMI(model.cog, data=data.mids, fun="cfa")
summary(fit.cog, fit.measures=TRUE, standardized=TRUE)
```

```r
##CFA Biomarkers
print("Biomarkers \n")
model.biomarker <- '
biomarker =~ ZIgA_gluten + ZIgG_gluten
'
fit.biomarker <- runMI(model.biomarker, data=data.mids, fun="cfa")
summary(fit.biomarker, fit.measures=TRUE, standardized=TRUE)
sink()

#save
setwd("N:/durable/Statistics/r")
saveRDS(data.mids,file="datamids.Rda ")
```

G5 Script R: Regression diagnostics

```
####PREPARING SCRIPT####
setwd("N:/durable/Statistics/r")
data.mids <- readRDS(file="datamids.Rda")

#Defining nr of imputations, adding one for original dataset
imputations <- imp$m+1

library(R.utils)
library(mice)
library(car)
library(QuantPsyc)
library(MASS)
library(skedastic)
library(car)
library(QuantPsyc)
library(psych)
library(ggpubr)
library(tidyverse)

##Shapiro-Wilks variables
capture.output(print("B-score"),
file="output/normality/ShapiroWilksBscore.txt")
capture.output(print("Ranked B-score"),
file="output/normality/ShapiroWilksRankedB.txt")
capture.output(print("Log B-score"),
file="output/normality/ShapiroWilksLogB.txt")
capture.output(print("G-score"),
file="output/normality/ShapiroWilksGscore.txt")
capture.output(print("Sleep"), file="output/normality/ShapiroWilksSleep.txt")

i <- 2
repeat {
  if (i<=imputations) {
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)
    imputation <- as.data.frame(imputation)

    #Calculating and printing shapiro wilks
    capture.output(print(shapiro.test(imputation$bscore)),
file="output/normality/ShapiroWilksBscore.txt", append = TRUE)
    capture.output(print(shapiro.test(imputation$R_bscore)),
file="output/normality/ShapiroWilksRankedB.txt", append = TRUE)
    capture.output(print(shapiro.test(imputation$L_bscore)),
file="output/normality/ShapiroWilksLogB.txt", append = TRUE)
    capture.output(print(shapiro.test(imputation$gscore)),
file="output/normality/ShapiroWilksGscore.txt", append = TRUE)
    capture.output(print(shapiro.test(imputation$sleep)),
file="output/normality/ShapiroWilksSleep.txt", append = TRUE)

    pdf(toString(c("output/normality/gscore",i-1,".pdf"),sep=""))
    ggqqplot(imputation$gscore)
    ggdensity(imputation$gscore)
    dev.off()

    pdf(toString(c("output/normality/bscore",i-1,".pdf"),sep=""))
```

```
    ggqqplot(imputation$bscore)
    ggdensity(imputation$bscore)
    dev.off()

    pdf(toString(c("output/normality/r_bscore",i-1,".pdf"),sep=""))
    ggqqplot(imputation$R_bscore)
    ggdensity(imputation$R_bscore)
    dev.off()

    pdf(toString(c("output/normality/r_bscore",i-1,".pdf"),sep=""))
    ggqqplot(imputation$L_bscore)
    ggdensity(imputation$L_bscore)
    dev.off()

    pdf(toString(c("output/normality/sleep",i-1,".pdf"),sep=""))
    ggqqplot(imputation$sleep)
    ggdensity(imputation$sleep)
    dev.off()

  i = i+1
  } else {
    break
  }
}

####ASSSUMPTIONS####
##Creating loop
write(NA, file="output/assumptions/VIF.txt")
sink("output/assumptions/assumptions.txt")

##Model 1: ass.total - All variables
print("Model 1: All variables")
capture.output(print("Model 1: All variables"),
file="output/assumptions/Durbinwatson.txt")
capture.output(print("Model 1: All variables"),
file="output/assumptions/NCV.txt")
capture.output(print("Model 1: All variables"),
file="output/assumptions/ShapiroWilks.txt")
capture.output(print("Model 1: All variables"),
file="output/assumptions/Whites.txt")


i <- 2
repeat {
  if (i<=imputations) {
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)


    ##Defining Model
    ass.total <- lm(gscore + Zcur + Zbpm + Zkidscreen + Zpsi ~ Age + sos3 +
meaneducation + Zgsrs + R_bscore, data=imputation)

    #Multi-collinearity predictor variables (constant across)
    vif.tot <- vif(ass.total)
    write(vif.tot, file="output/assumptions/VIF.txt", append=TRUE)
```

```
    #Shapiro-Wilks
    capture.output(print(durbinWatsonTest(ass.total)),
file="output/assumptions/Durbinwatson.txt", append = TRUE)
    capture.output(print(ncvTest(ass.total)),
file="output/assumptions/NCV.txt", append = TRUE)
    capture.output(print(shapiro.test(ass.total$residuals)),
file="output/assumptions/ShapiroWilks.txt", append = TRUE)
    capture.output(print(white_lm(ass.total)),
file="output/assumptions/Whites.txt", append = TRUE)


pdf(toString(c("output/assumptions/total",toString(i),"plots.pdf"),sep=""))
    #Non-normality
    print(qqPlot(ass.total, main="QQ Plot"))
    # distribution of studentized residuals
    sresid <- studres(ass.total)
    hist(sresid, freq=FALSE,
         main="Distribution of Studentized Residuals")
    xfit<-seq(min(sresid),max(sresid),length=40)
    yfit<-dnorm(xfit)
    lines(xfit, yfit)
    # plot studentized residuals vs. fitted values
    print(spreadLevelPlot(ass.total))
    #Evaluate Nonlinearity through component + residual plot
    print(crPlots(ass.total))
    dev.off()

    i = i+1
  } else {
    break
  }
}

##Model 2: G-score model
print(" ")
print("Model 2: G-score model")
capture.output(print("Model 2: G-score model"),
file="output/assumptions/Durbinwatson.txt", append=TRUE)
capture.output(print("Model 2: G-score model"),
file="output/assumptions/NCV.txt", append=TRUE)
capture.output(print("Model 2: G-score model"),
file="output/assumptions/ShapiroWilks.txt", append=TRUE)
capture.output(print("Model 2: G-score model"),
file="output/assumptions/Whites.txt", append=TRUE)

i <- 2
repeat {
    if (i<=imputations) {
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)

    ##Defining Model
    ass.gscore <- lm(gscore ~ Age + sos3 + meaneducation + Zgsrs + R_bscore,
data=imputation)

    #Shapiro-Wilks, ncvTest, Durbin Watson Test
```

```
    capture.output(print(durbinWatsonTest(ass.gscore)),
file="output/assumptions/Durbinwatson.txt", append = TRUE)
    capture.output(print(ncvTest(ass.gscore)),
file="output/assumptions/NCV.txt", append = TRUE)
    capture.output(print(shapiro.test(ass.gscore$residuals)),
file="output/assumptions/ShapiroWilks.txt", append = TRUE)
    capture.output(print(white_lm(ass.gscore)),
file="output/assumptions/Whites.txt", append = TRUE)

    ##Model 2: Gscore

pdf(toString(c("output/assumptions/gscore",toString(i),"plots.pdf"),sep=""))
#Non-normality
    print(qqPlot(ass.gscore, main="QQ Plot"))
    # distribution of studentized residuals
    sresid <- studres(ass.gscore)
    hist(sresid, freq=FALSE,
         main="Distribution of Studentized Residuals")
    xfit<-seq(min(sresid),max(sresid),length=40)
    yfit<-dnorm(xfit)
    lines(xfit, yfit)
    # plot studentized residuals vs. fitted values
    print(spreadLevelPlot(ass.gscore))
    #Evaluate Nonlinearity through component + residual plot
    print(crPlots(ass.gscore))
    dev.off()

    i = i+1
    } else {
      break
    }
}

##Model 3: Curiosity
print(" ")
print("Model 3: Curiosity")
capture.output(print("Model 3: Curiosity"),
file="output/assumptions/Durbinwatson.txt", append=TRUE)
capture.output(print("Model 3: Curiosity"), file="output/assumptions/NCV.txt",
append=TRUE)
capture.output(print("Model 3: Curiosity"),
file="output/assumptions/ShapiroWilks.txt", append=TRUE)
capture.output(print("Model 3: Curiosity"),
file="output/assumptions/Whites.txt", append=TRUE)

i <- 2
  repeat {
    if (i<=imputations) {

    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)

    ##Defining Model
    ass.cur <- lm(Zcur ~ Age + sos3 + meaneducation + Zgsrs + R_bscore,
data=imputation)

    #Shapiro-Wilks, ncvTest, Durbin Watson Test
```

```
    capture.output(print(ncvTest(ass.cur)), file="output/assumptions/NCV.txt",
append = TRUE)
    capture.output(print(shapiro.test(ass.cur$residuals)),
file="output/assumptions/ShapiroWilks.txt", append = TRUE)
    capture.output(print(durbinWatsonTest(ass.cur)),
file="output/assumptions/Durbinwatson.txt", append = TRUE)
    capture.output(print(white_lm(ass.cur)),
file="output/assumptions/Whites.txt", append = TRUE)

    ##Model 3: Curiosity
    pdf(toString(c("output/assumptions/cur",toString(i),"plots.pdf"),sep=""))
    #Non-normality
    print(qqPlot(ass.cur, main="QQ Plot"))
    # distribution of studentized residuals
    sresid <- studres(ass.cur)
    hist(sresid, freq=FALSE,
         main="Distribution of Studentized Residuals")
    xfit<-seq(min(sresid),max(sresid),length=40)
    yfit<-dnorm(xfit)
    lines(xfit, yfit)
    # plot studentized residuals vs. fitted values
    print(spreadLevelPlot(ass.cur))
    #Evaluate Nonlinearity through component + residual plot
    print(crPlots(ass.cur))
    dev.off()

    i = i+1
      } else {
        break
      }
    }

##Model 4: BPM"
print(" ")
print("Model 4: BPM")
capture.output(print("Model 4: BPM"),
file="output/assumptions/Durbinwatson.txt", append=TRUE)
capture.output(print("Model 4: BPM"), file="output/assumptions/NCV.txt",
append=TRUE)
capture.output(print("Model 4: BPM"),
file="output/assumptions/ShapiroWilks.txt", append=TRUE)
capture.output(print("Model 4: BPM"), file="output/assumptions/Whites.txt",
append=TRUE)

i <- 2
  repeat {
    if (i<=imputations) {
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)

    ##Defining Model
    ass.bpm <- lm(Zbpm ~ Age + sos3 + meaneducation + Zgsrs + R_bscore,
data=imputation)

    #Shapiro-Wilks, ncvTest, Durbin Watson Test
    capture.output(print(ncvTest(ass.bpm)), file="output/assumptions/NCV.txt",
append = TRUE)
```

```
    capture.output(print(shapiro.test(ass.bpm$residuals)),
file="output/assumptions/ShapiroWilks.txt", append = TRUE)
    capture.output(print(durbinWatsonTest(ass.bpm)),
file="output/assumptions/Durbinwatson.txt", append = TRUE)
    capture.output(print(white_lm(ass.bpm)),
file="output/assumptions/Whites.txt", append = TRUE)

    ##Model 4: BPM
    pdf(toString(c("output/assumptions/bpm",toString(i),"plots.pdf"),sep=""))
#Non-normality
    print(qqPlot(ass.bpm, main="QQ Plot"))
    # distribution of studentized residuals
    sresid <- studres(ass.bpm)
    hist(sresid, freq=FALSE,
         main="Distribution of Studentized Residuals")
    xfit<-seq(min(sresid),max(sresid),length=40)
    yfit<-dnorm(xfit)
    lines(xfit, yfit)
    # plot studentized residuals vs. fitted values
    print(spreadLevelPlot(ass.bpm))
    #Evaluate Nonlinearity through component + residual plot
    print(crPlots(ass.bpm))
    dev.off()

    i = i+1
      } else {
        break
      }
    }

##Model 5: KIDSCREEN
print(" ")
print("Model 5: KIDSCREEN")
capture.output(print("Model 5: KIDSCREEN"),
file="output/assumptions/Durbinwatson.txt", append=TRUE)
capture.output(print("Model 5: KIDSCREEN"), file="output/assumptions/NCV.txt",
append=TRUE)
capture.output(print("Model 5: KIDSCREEN"),
file="output/assumptions/ShapiroWilks.txt", append=TRUE)
capture.output(print("Model 5: KIDSCREEN"),
file="output/assumptions/Whites.txt", append=TRUE)

i <- 2
  repeat {
    if (i<=imputations) {
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)

    ##Defining Model
    ass.kidscreen <- lm(Zkidscreen ~ Age + sos3 + meaneducation + Zgsrs +
R_bscore, data=imputation)

    #Shapiro-Wilks, ncvTest, Durbin Watson Test
    capture.output(print(ncvTest(ass.kidscreen)),
file="output/assumptions/NCV.txt", append = TRUE)
    capture.output(print(shapiro.test(ass.kidscreen$residuals)),
file="output/assumptions/ShapiroWilks.txt", append = TRUE)
```

```
    capture.output(print(durbinWatsonTest(ass.kidscreen)),
file="output/assumptions/Durbinwatson.txt", append = TRUE)
    capture.output(print(white_lm(ass.kidscreen)),
file="output/assumptions/Whites.txt", append = TRUE)

    ##Model 5: KIDSCREEN

pdf(toString(c("output/assumptions/kidscreen",toString(i),"plots.pdf"),sep="")
)
    #Non-normality
    print(qqPlot(ass.kidscreen, main="QQ Plot"))
    # distribution of studentized residuals
    sresid <- studres(ass.kidscreen)
    hist(sresid, freq=FALSE,
         main="Distribution of Studentized Residuals")
    xfit<-seq(min(sresid),max(sresid),length=40)
    yfit<-dnorm(xfit)
    lines(xfit, yfit)
    # plot studentized residuals vs. fitted values
    print(spreadLevelPlot(ass.kidscreen))
    #Evaluate Nonlinearity through component + residual plot
    print(crPlots(ass.kidscreen))
    dev.off()

    i = i+1
      } else {
        break
      }
    }

##Model 6: PSI
print(" ")
print("Model 6: PSI")
capture.output(print("Model 6: PSI"),
file="output/assumptions/Durbinwatson.txt", append=TRUE)
capture.output(print("Model 6: PSI"), file="output/assumptions/NCV.txt",
append=TRUE)
capture.output(print("Model 6: PSI"),
file="output/assumptions/ShapiroWilks.txt", append=TRUE)
capture.output(print("Model 6: PSI"), file="output/assumptions/Whites.txt",
append=TRUE)

i <- 2
  repeat {
    if (i<=imputations) {
    #Pulling imputation
    imputation <- mice::complete(data.mids,i-1)


    ass.psi <- lm(Zpsi ~ Age + sos3 + meaneducation + Zgsrs + R_bscore,
data=imputation)

    #Shapiro-Wilks, ncvTest, Durbin Watson Test
    capture.output(print(ncvTest(ass.psi)), file="output/assumptions/NCV.txt",
append = TRUE)
    capture.output(print(shapiro.test(ass.psi$residuals)),
file="output/assumptions/ShapiroWilks.txt", append = TRUE)
```

```
    capture.output(print(durbinWatsonTest(ass.psi)),
file="output/assumptions/Durbinwatson.txt", append = TRUE)
    capture.output(print(white_lm(ass.psi)),
file="output/assumptions/Whites.txt", append = TRUE)

    ##MODEL 6: PSI
    pdf(toString(c("output/assumptions/psi",toString(i),"plots.pdf"),sep=""))
    #Non-normality
    print(qqPlot(ass.psi, main="QQ Plot"))
    # distribution of studentized residuals
    sresid <- studres(ass.psi)
    hist(sresid, freq=FALSE,
         main="Distribution of Studentized Residuals")
    xfit<-seq(min(sresid),max(sresid),length=40)
    yfit<-dnorm(xfit)
    lines(xfit, yfit)
    # plot studentized residuals vs. fitted values
    print(spreadLevelPlot(ass.psi))
    #Evaluate Nonlinearity through component + residual plot
    print(crPlots(ass.psi))
    dev.off()

    i = i+1
      } else {
        break
      }
  }

sink()

#Checking linearity of data with biological data
data.original <- mice::complete(data.full,0)

ass.total2 <- lm(gscore + Zcur + Zbpm + Zkidscreen + Zpsi ~ Age + sos3 +
meaneducation + Zgsrs + R_bscore, data=data.original)
ass.gscore2 <- lm(gscore ~ Age + sos3 + meaneducation + Zgsrs + bscore,
data=data.original)
ass.cur2 <- lm(Zcur ~ Age + sos3 + meaneducation + Zgsrs + bscore,
data=data.original)
ass.bpm2 <- lm(Zbpm ~ Age + sos3 + meaneducation + Zgsrs + bscore,
data=data.original)
ass.kidscreen2 <- lm(Zkidscreen ~ Age + sos3 + meaneducation + Zgsrs + bscore,
data=data.original)
ass.psi2 <- lm(Zpsi ~ Age + sos3 + meaneducation + Zgsrs + bscore,
data=data.original)

pdf("output/assumptions/crPlots.pdf")
print(crPlots(ass.total2))
print(crPlots(ass.gscore2))
print(crPlots(ass.cur2))
print(crPlots(ass.bpm2))
print(crPlots(ass.kidscreen2))
print(crPlots(ass.psi2))
dev.off()


setwd("N:/durable/Statistics/r")
```

```r
dataimp <- readRDS(file="impwithz.Rda")
standard_length <- length(dataimp)

print(is.list(dataimp[1]))
#test <- list(list(standard_length))
#imputethis <- lapply(1:imputations, data=NA,
nrow=observations,ncol=(standard_length+new_col_count), function(f))

#dataimp <- as.matrix(dataimp)

participants <- length(dataimp[[1]][[1]])
print(length(dataimp))
imputations <- 20


library(lavaan)
library(mice)
library(miceadds)
library(dplyr)
library(semTools)
library(Amelia)
library(car)
library(QuantPsyc)
library(psych)
library(ggpubr)



empty_vector <- vector(mode = "numeric", imputations+1)

bpms <- empty_vector
kids <- empty_vector
psis <- empty_vector
gsrss <- empty_vector
slps <- empty_vector
zvm <- empty_vector
zh <- empty_vector
cur <- empty_vector
gscore <- empty_vector
bscore <- empty_vector

alpha_vars <- 10
df <- NULL
.imp <- vector(mode = "numeric", ((imputations+1)*alpha_vars))
.id <- vector(mode = "numeric", ((imputations+1)*alpha_vars))

i <- 1
repeat{
  if(i<=(imputations+1)){
    ##If getting error unused arguments restart session with ctrl+shift+f10
    ##Cronbachs_alpha run in imputation

    imput <- mice::complete(dataimp,i-1)
    #imput <- as.data.frame(imput)
    for(j in 1:length(imput)){
      imput[[j]] <- as.numeric(imput[[j]])
    }
```

```
    bpms[i] <- psych::alpha(dplyr::select(imput, bpm1:bpm19),check.keys=TRUE)
    kids[i] <- psych::alpha(dplyr::select(imput, kid1:kid11),check.keys=TRUE)
    psis[i] <- psych::alpha(dplyr::select(imput, psi1:psi36),check.keys=TRUE)
    gsrss[i] <- psych::alpha(dplyr::select(imput,
gsrs1:gsrs15),check.keys=TRUE)
    slps[i] <- psych::alpha(dplyr::select(imput, slp1:slp3),check.keys=TRUE)
    zvm[i] <- psych::alpha(dplyr::select(imput, Zverbal, Zmatrix, ZPALFAMS,
ZPALTEA28, ZRTIFMDMT, ZRTIFMDRT, ZSSPFSR, Z9HPT),check.keys=TRUE)
    zh[i] <- psych::alpha(dplyr::select(imput, ZIgA_gluten,
ZIgG_gluten),check.keys=TRUE)
    cur[i] <- psych::alpha(dplyr::select(imput, cur1, cur2, cur3, cur4, cur5,
cur6, cur7, cur8, cur9, cur10),check.keys=TRUE)

    gscore[i] <-
psych::alpha(dplyr::select(imput,Zmatrix,Zverbal,ZRTI_mean,ZPAL_mean,ZSSPFSR,Z
9HPT),check.keys=TRUE)
    bscore[i] <-
psych::alpha(dplyr::select(imput,R_IgA_gluten,R_IgG_gluten),check.keys=TRUE)


    for(j in 1:alpha_vars){
      .imp[(alpha_vars*(i-1))+j] <- i-1
    }
    for(j in 1:alpha_vars){
      .id[(alpha_vars*(i-1))+j] <- j
    }

    rbind(df,bpms[[i]]) -> df
    rbind(df,kids[[i]]) -> df
    rbind(df,psis[[i]]) -> df
    rbind(df,gsrss[[i]]) -> df
    rbind(df,slps[[i]]) -> df
    rbind(df,zvm[[i]]) -> df
    rbind(df,zh[[i]]) -> df
    rbind(df,cur[[i]]) -> df
    rbind(df,gscore[[i]]) -> df
    rbind(df,bscore[[i]]) -> df

    i <- i+1

  }else{
    break
  }
}

df$.imp <- .imp
df$.id <- .id

bpmsf <- empty_vector
kidsf <- empty_vector
psisf <- empty_vector
gsrssf <- empty_vector
slpsf <- empty_vector
zvmf <- empty_vector
zhf <- empty_vector
curf <- empty_vector
```

```
gscoref <- empty_vector
bscoref <- empty_vector

sink("output/normality/alphas.txt")
### PRINTING ALPHAS
for(i in 1:(length(kids))){
  bpmsf[i] <- bpms[[i]]["raw_alpha"]
  kidsf[i] <- kids[[i]]["raw_alpha"]
  psisf[i] <- psis[[i]]["raw_alpha"]
  gsrssf[i] <- gsrss[[i]]["raw_alpha"]
  slpsf[i] <- slps[[i]]["raw_alpha"]
  zvmf[i] <- zvm[[i]]["raw_alpha"]
  zhf[i] <- zh[[i]]["raw_alpha"]
  curf[i] <- cur[[i]]["raw_alpha"]
  gscoref[i] <- gscore[[i]]["raw_alpha"]
  bscoref[i] <- bscore[[i]]["raw_alpha"]
}

bpmsf <- as.numeric(bpmsf)
kidsf <- as.numeric(kidsf)
psisf <- as.numeric(psisf)
gsrssf <- as.numeric(gsrssf)
slpsf <- as.numeric(slpsf)
zvmf <- as.numeric(zvmf)
zhf <- as.numeric(zhf)
curf <- as.numeric(curf)
gscoref <- as.numeric(gscoref)
bscoref <- as.numeric(bscoref)

bpmsf <- mean(bpmsf)
kidsf <- mean(kidsf)
psisf <- mean(psisf)
gsrssf <- mean(gsrssf)
slpsf <- mean(slpsf)
zvmf <- mean(zvmf)
zhf <- mean(zhf)
curf <- mean(curf)
gscoref <- mean(gscoref)
bscoref <- mean(bscoref)

print("RAW")
print(toString(c("bpm: ",bpmsf)))
print(toString(c("kid: ",kidsf)))
print(toString(c("psi: ",psisf)))
print(toString(c("gsrss: ",gsrssf)))
print(toString(c("slp: ",slpsf)))
print(toString(c("Zvm: ",zvmf)))
print(toString(c("Zh: ",zhf)))
print(toString(c("Cur: ",curf)))
print(toString(c("Gscore: ",gscoref)))
print(toString(c("Ranked Bscore: ",bscoref)))


for(i in 1:(length(kids))){
  bpms[i] <- bpms[[i]]["std.alpha"]
  kids[i] <- kids[[i]]["std.alpha"]
  psis[i] <- psis[[i]]["std.alpha"]
```

```
  gsrss[i] <- gsrss[[i]]["std.alpha"]
  slps[i] <- slps[[i]]["std.alpha"]
  zvm[i] <- zvm[[i]]["std.alpha"]
  zh[i] <- zh[[i]]["std.alpha"]
  cur[i] <- cur[[i]]["std.alpha"]
  gscore[i] <- gscore[[i]]["std.alpha"]
  bscore[i] <- bscore[[i]]["std.alpha"]
}

bpms <- as.numeric(bpms)
kids <- as.numeric(kids)
psis <- as.numeric(psis)
gsrss <- as.numeric(gsrss)
slps <- as.numeric(slps)
zvm <- as.numeric(zvm)
zh <- as.numeric(zh)
cur <- as.numeric(cur)
gscore <- as.numeric(gscore)
bscore <- as.numeric(bscore)

bpms <- mean(bpms)
kids <- mean(kids)
psis <- mean(psis)
gsrss <- mean(gsrss)
slps <- mean(slps)
zvm <- mean(zvm)
zh <- mean(zh)
cur <- mean(cur)
gscore <- mean(gscore)
bscore <- mean(bscore)

print("STD")
print(toString(c("bpm: ",bpms)))
print(toString(c("kid: ",kids)))
print(toString(c("psi: ",psis)))
print(toString(c("gsrss: ",gsrss)))
print(toString(c("slp: ",slps)))
print(toString(c("Zvm: ",zvm)))
print(toString(c("Zh: ",zh)))
print(toString(c("Cur: ",cur)))
print(toString(c("Gscore: ",gscore)))
print(toString(c("Ranked Bscore: ",bscore)))
sink()


#TEST OF NORMALITY
#comp <- mice::complete(dataimp, 'long', include=TRUE)

sink("output/normality/shapiro.txt")
i <- 1
#for(i in 1:(imputations+1)){
#### REPEAT THIS SECTION MANUALLY ONCE FOR EACH IMPUTATION +1(Yes, it needs to
be done manually to work)
imput <- mice::complete(dataimp,i-1)
imput <- as.data.frame(imput)
# for(j in 1:length(imput)){
#   imput[[j]] <- as.numeric(imput[[j]])
```

```
# }
pdf(toString(c("output/normality/gscore",i-1,".pdf"),sep=""))
ggqqplot(imput$gscore)
ggdensity(imput$gscore)
dev.off()

pdf(toString(c("output/normality/R_bscore",i-1,".pdf"),sep=""))
ggqqplot(imput$R_bscore)
ggdensity(imput$R_bscore)
dev.off()

pdf(toString(c("output/normality/bscore",i-1,".pdf"),sep=""))
ggqqplot(imput$bscore)
ggdensity(imput$bscore)
dev.off()

#sink(toString(c("output/normality/shapiros",i,".txt"),sep=""))
print(shapiro.test(imput$gscore))
print(shapiro.test(imput$R_bscore))
print(shapiro.test(imput$bscore))


#sink()
i <- i+1
print(i)
####
#}

sink()
```

Appendix H: Supplementary tables

Table H1: *Linear models of confounding variables and measures of psychological functioning*

		95% CI					
	Coefficient	*LL*	*UL*	SE	*df*	*p*	Model r^2
Covariate model 1: CM-score							.24
Intercept	-0.41	-1.00	0.17	0.27	15.21	.151	
Age [a]	0.11	-0.22	0.44	0.15	15.30	.500	
Gender	0.58	-0.19	1.35	0.36	15.20	.132	
Parent's education [a]	0.09	-0.29	0.47	0.18	15.07	.611	
Covariate model 2: Brief Problem Monitor							.10
Intercept	1.13	-1.00	3.26	1.00	15.23	.277	
Age [a]	0.17	-0.32	0.66	0.23	15.28	.465	
Gender	0.00	-1.14	1.15	0.54	15.22	.994	
Parent's education [a]	-0.37	-1.12	0.39	0.35	15.20	.315	
Covariate model 3: KIDSCREEN-10							0.11
Intercept	0.11	-0.75	0.98	0.41	15.25	.785	
Age [a]	-0.31	-0.80	0.18	0.23	15.29	.198	
Gender	-0.18	-1.33	0.96	0.54	15.22	.741	
Parent's education [a]	0.12	-0.45	0.68	0.27	14.82	.667	
Covariate model 4: Parenting Stress Index 4th Edition Short form							.16
Intercept	-0.52	-1.36	0.32	0.39	15.25	.207	
Age [a]	-0.15	-0.63	0.32	0.22	15.28	.498	
Gender	0.84	-0.27	1.95	0.52	15.19	.129	
Parent's education [a]	-0.19	-0.74	0.37	0.26	14.44	.485	
Covariate model 5: I/D-Young Children							.08
Intercept	0.07	-0.80	0.95	0.41	15.15	.860	
Age [a]	-0.28	-0.77	0.22	0.23	15.30	.249	
Gender	-0.12	-1.28	1.05	0.55	15.11	.835	
Parent's education [a]	0.09	-0.49	0.67	0.27	14.59	.743	

Note. N = 21. CI = confidence interval; *LL* = lower limit; *UL* = upper limit. All outcome variables are Z-scored.

[a] Z-scored variables

Table H2: *Factor loadings for the CM-score*

Variables	Factor loadings	Standardized factor loadings	*SE*	*t*	*p*
Sum score from Vocabulary subtest	1.000	0.67			
Sum score from Object Series/Matrices	0.93	0.62	0.49	1.91	0.056
PAL mean [a]	0.76	0.53	0.48	1.72	0.085
RTI mean [b]	0.85	0.68	0.42	2.01	0.046*
SSP Forward Span Reached	0.97	0.65	0.48	2.03	0.042*
Nine-Hole Peg Test	0.99	0.65	0.50	1.96	0.042*

Note: PAL = Paired Associates Learning; RTI = Reaction Time Index; SSP = Spatial Span.

[a] Averaged composite created from PAL First Attempt Memory Score and PAL Total Errors (Adjusted)

[b] Averaged composite created from RTI Median Five-Choice Reaction Time and RTI Median Five-Choice Reaction Time

*p < .05.

Table H3: *Pearson Product Moment Correlations between known confounders and psychometric and biological measures.*

	Age	Gender	Parent's level of education
Biomarker composite [a]	.04	-.12	.35
Anti-gliadin IgA [a]	.10	-.07	.25
Anti-gliadin IgG [a]	-.02	-.13	.32
Gastrointestinal symptom rating scale	.28	-.31	-.12
CM-score	.15	.45*	.32
Brief Problem Monitor	.16	-.13	-.26
KIDSCREEN-10	-.30	-.03	.06
Parenting Stress Index 4 Short form	-.17	.32	.00
I/D-YC epistemic curiosity	-.28	-.01	.05

Note: N = 21.

[a] Rank transformed variables.

*p < .05. ** p <.01.

Table H4: Pearson product moment correlation coefficients and Spearman's rank correlation coefficient between measures of NCGS and psychological functioning on the seven participants with full biological data.

	1	2	3	4	5	6	7	8	9
1. Biomarker composite [a]	-	.75	.42	.31	-.55	.76	-.51	-.58	-.39
2. Anti-gliadin IgA [a]	.73	-	-.16	.22	-.56	.89**	.08	.02	-.46
3. Anti-gliadin IgG [a]	.51	-.22	-	.09	-.19	.04	-.92*	-.87**	.23
4. Gastrointestinal symptom rating scale [b]	.12	-.14	.34	-	.58	.54	-.46	-.44	-.86*
5. CM-score [b]	-.50	-.63	.07	.80*	-	-.29	-.05	-.01	-.41
6. Brief Problem Monitor [b]	.67	.98*	-.25	.08	-.50	-	-.25	-.29	-.64
7. KIDSCREEN-10 [b]	-.93*	-.50	-.67	-.45	.14	-.55	-	-	.60
8. Parenting Stress Index 4 Short form [b]	-.94*	-.72	-.42	.08	.64	-.70	.84*	-	.22
9. I/D-YC epistemic curiosity [b]	-.35	-.31	-.12	-.89**	-.53	-.53	.14	.16	-

Note. N = 21. Spearman's ρ correlations are in the top right section of the matrix (grey). Pearson's *r* correlations are in the bottom left section (white). Age, gender, and parent's level of education were included as partial correlations when calculating all correlations.

[a] Ranked version of variables used in both correlation analyses.

[b] Ranked version of variables only used when calculating Spearman's ρ.

* $p < .05$. ** $p < .01$