

Biomarker Research in ADHD: the Impact of Nutrition (BRAIN)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03440346

Recruitment Status : Recruiting

First Posted : February 21, 2018

Last Update Posted : February 22, 2018

See **Contacts and Locations**

Sponsor:

Wageningen University

Collaborator:

ADHD Research Centre

Information provided by (Responsible Party):

Wageningen University

• Study Details

• Tabular View

• No Results Posted

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Study Description

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Brief Summary:

Attention deficit hyperactivity disorder (ADHD) is the most common childhood behavioural disorder, causing significant impediment to a child's development. The exact aetiology of ADHD is still unknown. It is a complex disorder with numerous contributing (epi)genetic and environmental factors. Currently, treatment predominantly consists of behavioural and pharmacological therapy. However, medication use is associated with several side effects and concerns about long-term effects and efficacy exist. Therefore, there is considerable interest in the development of alternative treatment options.

Double-blind research investigating the effect of a few-foods diet (FFD) has demonstrated large improvements in ADHD symptoms. However, following an FFD requires great effort of both the child and parents. To make this treatment easier or potentially obsolete, it is important to understand how and in which children an FFD affects ADHD symptoms.

The investigators hypothesise that an FFD affects brain function and behaviour, including ADHD symptoms, via the complex network of communication between the microbiota, gut and brain, i.e. the MGB axis. The aim of this study is to identify potential mechanism(s) underlying the impact of an FFD on ADHD symptoms and to identify biomarkers that predict the response to the FFD.

100 boys with ADHD will follow the FFD for 5 weeks. After inclusion, all participants will start with a baseline period, during which they will maintain their regular diet. The baseline period ends at the end of week 2. Thereafter, participants will follow a 5-week FFD, preceded by a 1-week transition period. The FFD period ends at the end of week 8.

At the end of the baseline period (i.e. at the end of week 2) and at the end of the FFD (i.e. at the end of week 8), fMRI scans will be made, blood and buccal saliva will be collected, and stool and urine will be handed in. Children will do computer tasks and parents will complete questionnaires to monitor ADHD and physical complaints. All samples will be analysed by researchers blinded to behavioural responses to the FFD. To assess the impact of the

FFD on brain function and the MGB axis, associations between ADHD behavioural changes and changes in other primary and secondary study outcomes will be analysed.

This study may lead to the identification of biomarkers that can predict the response to an FFD. Understanding which changes - induced by an FFD - lead to improvements in ADHD symptoms may provide new avenues for developing treatments. Ultimately, the findings may enable personalised intervention strategies based on an individuals' configuration of the MGB axis.

Condition or disease	Intervention
Attention Deficit-Hyperactivity Disorder	Other: Few-foods diet

Study Design

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Study Type : Interventional (Clinical Trial)

Estimated Enrollment : 100 participants

Intervention Model: Single Group Assignment

Masking: None (Open Label)

Primary Purpose: Basic Science

Official Title: Biomarker Research in ADHD: the Impact of Nutrition (BRAIN). An Open-label Trial to Investigate the Mechanisms Underlying the Effects of a Few-foods Diet on ADHD Symptoms in Children

Actual Study Start Date : February 19, 2018

Estimated Primary Completion Date : February 2020

Estimated Study Completion Date : February 2020

Resource links provided by the National Library of Medicine

MedlinePlus related topics: Attention Deficit Hyperactivity Disorder

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Few-foods diet intervention	<p>Other: Few-foods diet</p> <p>The few-foods diet (FFD) is followed for 5-weeks preceded by a 1-week transition period during which the child's eating pattern will be gradually adjusted. The diet consists of rice, meat (turkey and lamb), a range of vegetables, pear, rice milk with added calcium and water, and is complemented with foods such as potatoes, fruits, corn, some sweets and wheat, which are allowed in small quantities only. Normal quantities of vegetables, rice and meat are allowed every day. If necessary the diet will be adjusted to avoid foods that the child dislikes or has cravings for. If the child does not respond to the initial FFD, i.e. no change in behaviour after the first two weeks, interim adjustments to the FFD will be made in consultation with the parents.</p> <p>Other Name: Restricted Elimination Diet</p>

Outcome Measures

Primary Outcome Measures :

1. Change in neural activation patterns during execution of tasks [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Using fMRI, blood oxygen-level-dependent (BOLD) signal changes will be measured whilst performing cognitive tasks that assess inhibitory control and selective attention, i.e. a stop-signal task (response inhibition) and a Flanker task (response conflict and associated error monitoring). fMRI BOLD responses will be assessed between variable task-elements and performance. Region of interest (ROI; anatomically defined regions in the brain) analyses of the BOLD responses will be performed.

2. Change in peripheral blood metabolite concentrations [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Global metabolite profiles will be examined in plasma (or alternatively serum) obtained from whole blood using mass-spectrometry profiling. Phenylalanine and tyrosine plasma levels represent primary outcomes.

3. Change in functional composition of the gut microbiota [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Metagenome profiling will be performed on stool samples, leveraging Illumina next-generation sequencing technology. Sequence read data will be used for abundance profiling of microbiota genes that encode enzymes directly involved in the production or degradation of the dopamine and noradrenaline precursors phenylalanine and tyrosine.

4. Change in ADHD symptom scores [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

ADHD symptoms will be scored using the 18-item ADHD rating scale, which is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and consists of 9 items that assess inattention and 9 items that focus on hyperactivity and impulsivity.

Secondary Outcome Measures :

1. Change in whole brain neural activation patterns during the execution of tasks [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

fMRI BOLD responses, assessed between variable task-elements, will be explored using whole brain imaging analyses.

2. Change in whole brain functional connectivity at rest [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

A resting-state fMRI scan will be performed to analyse the networks of brain structures that are active during the resting-state.

3. Change in taxonomic and functional composition of the gut microbiota [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Stool metagenome and/or 16S ribosomal ribonucleic acid (rRNA) gene profiling will be performed using Illumina sequencing. Metagenome data will be used to determine the taxonomic and functional composition of the gut microbiota.

4. Change in metabolite profiles [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Global metabolite profiles will be examined in plasma (or alternatively serum) obtained from whole blood, urine and optionally in stool using mass-spectrometry profiling.

5. Change in peripheral blood cell gene expression profiles [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Peripheral blood mononuclear cells will be isolated from fasting blood samples and gene expression profiles will either be determined using Affymetrix gene expression arrays or by RNA-sequencing.

6. Change in a panel of peripheral blood protein biomarkers related to immune, metabolic and neurological status [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

A large panel of proteins will be profiled using quantitative immunoassays or proteomics on blood plasma or serum.

7. DNA genotype [Time Frame: Before the FFD diet intervention (i.e. at the end of week 2)]

Genotyping will be conducted using a microarray platform on DNA isolated from buccal cells or on DNA isolated from whole blood.

8. Change in DNA methylation profiles [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Genome-wide profiling of DNA methylation status will be conducted using the Illumina Infinium MethylationEPIC beadchip microarray platform in DNA isolated from buccal cells or alternatively on DNA isolated from whole blood.

9. Change in executive function [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Executive functioning will be measured using a continuous performance test that assesses executive functions such as sustained attention and behavioural inhibition.

10. Change in ADHD symptoms [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Change will be scored using the Abbreviated Conners' scale

11. Change in oppositional defiant disorder symptoms [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Change will be scored using a validated questionnaire.

12. Change in social behavioural problems [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Change will be scored using the children's social and behavioural questionnaire.

13. Change in physical complaints [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

Change will be scored using a validated questionnaire.

14. Change in stool frequency [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

The child will record the frequency of defaecations for one week.

15. Change in stool type [Time Frame: Before and at the end of the FFD intervention (i.e. at the end of week 2 and at the end of week 8)]

The child will type each stool using the modified Bristol stool scale form for children, which comprises 5 stool form types described and depicted in drawings.

Other Outcome Measures:

1. IQ-score [Time Frame: At the screening session, prior to inclusion of participant in the study]

If no intelligence quotient (IQ) test has been conducted in the past year, an abbreviated form of the Wechsler Intelligence Scale III IQ test will be conducted.

2. Change in taxonomic and functional composition of the gut microbiota [Time Frame: Prior to the screening (i.e. week 0) and after the baseline period (i.e. at the end of week 2)]

Stool metagenome and/or 16S rRNA gene profiling will be performed using Illumina sequencing. Metagenome data will be used to determine the taxonomic and functional composition of the gut microbiota. The change in gut microbiota composition will be assessed between stools sampled prior to the screening and after the baseline period (i.e. before the start of the FFD intervention).

Eligibility Criteria

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Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, [Learn About Clinical Studies](#).

Ages Eligible for Study: 8 Years to 10 Years (Child)
Sexes Eligible for Study: Male
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Meeting DSM-IV ADHD criteria
- Male
- Aged 8 up to and including 10 years
- Right-handed
- Available to visit Wageningen University for 4 sessions (i.e. intake, screening, T1 and T2), of which 3 sessions including the child (screening, T1, T2)
- Upon study start, fully understanding and agreeing to the study objectives and having dated and signed an informed consent to participate in the study, including permission that material will be used or archived for (epi)genetic testing
- Willing to be informed about chance-findings that may have implications for the health of the child or his family, and approving of reporting this to the child's medical specialist or family's general physician.
- If the child uses "over the counter" medication, e.g. laxatives, melatonin for sleeping problems or hay fever medication, parents are asked to share the information leaflet, and if necessary participants are asked to change to alternatives that are free of additives that may affect ADHD, e.g. laxatives free of artificial sweeteners, sugar and cacao.

Exclusion Criteria:

- Diagnosis Autism Spectrum Disorder
- Diagnosis Developmental Coordination Disorder
- Premature birth (< 36 weeks) and/or oxygen deprivation during birth
- Diagnosed chronic gastrointestinal disorder, i.e. inflammatory bowel disease, irritable bowel syndrome, celiac disease, non-celiac gluten-intolerance (gluten-sensitivity) or lactose-intolerance
- Auto-immune disorder (e.g. diabetes mellitus type 1)
- Vegetarian/vegan
- Diagnosis dyslexia and/or dyscalculia
- IQ < 85

- Following behavioural therapy
- Use of ADHD medication
- Use of systemic antibiotics, antifungals, antivirals or antiparasitics in the past six months
- Insufficient command of the Dutch language by either parents or child that may affect understanding and execution of study and dietary instructions
- Family circumstances that may compromise following or completion of the diet, including but not limited to family relational problems
- Having a contra-indication to MRI scanning (including, but not limited to): pacemakers and defibrillators, intraorbital or intraocular metallic fragments, ferromagnetic implants, claustrophobia.
- Two weeks prior to the start of the study, dietary supplements (e.g. antioxidants, minerals, vitamins) or pro- or prebiotics use has to be stopped.

Contacts and Locations

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Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

*Please refer to this study by its ClinicalTrials.gov identifier (NCT number): **NCT03440346***

Contacts

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Locations

Netherlands

Wageningen University **Recruiting**
Wageningen, Netherlands

Sponsors and Collaborators

Wageningen University
ADHD Research Centre

Investigators

Principal Investigator: Michiel Kleerebezem, Prof. dr. Wageningen University

More Information

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Additional Information:

BRAIN-study website [EXIT](#)

Publications:

Pelsser LM, Frankena K, Toorman J, Savelkoul HF, Dubois AE, Pereira RR, Haagen TA, Rommelse NN, Buitelaar JK. Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. *Lancet*. 2011 Feb 5;377(9764):494-503. doi: 10.1016/S0140-6736(10)62227-1.

Pelsser LM, Frankena K, Toorman J, Rodrigues Pereira R. Diet and ADHD, Reviewing the Evidence: A Systematic Review of Meta-Analyses of Double-Blind Placebo-Controlled Trials Evaluating the Efficacy of Diet Interventions on the Behavior of Children with ADHD. *PLoS One*. 2017 Jan 25;12(1):e0169277. doi: 10.1371/journal.pone.0169277. eCollection 2017. Review.

Responsible Party: Wageningen University

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Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

Keywords provided by Wageningen University:

Attention Deficit Hyperactivity Disorder

ADHD

child

human

diet

few-foods diet

brain

gut

microbiota

Additional relevant MeSH terms:

Attention Deficit Disorder with Hyperactivity

Hyperkinesia

Attention Deficit and Disruptive Behavior Disorders

Neurodevelopmental Disorders

Mental Disorders

Dyskinesias

Neurologic Manifestations

Nervous System Diseases

Signs and Symptoms