

ADHD, a Food-Induced Hypersensitivity Syndrome: in Quest of a Cause

**The effects of a restricted elimination diet (RED) on ADHD,
ODD and comorbid somatic complaints,
and a preliminary survey of the mechanisms of an RED**

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

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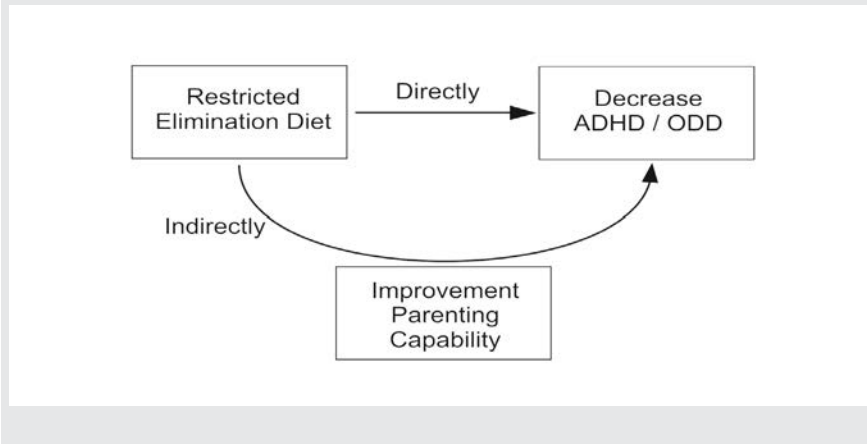
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Figure 3 Mechanism of action of an RED on ADHD and ODD

9.6. Follow-up research

The RED studies have unequivocally established that an RED shows considerable and favourable effects on ADHD and ODD, in selected as well as in unselected groups of children. Consequently, an important question, i.e., to what extent may food be causal of ADHD, now has been answered satisfactorily. Still, the answers to questions may lead to even more questions; how true this is regarding this issue. In this part of the thesis the do's and don'ts regarding follow-up research will be discussed on the strength of the main points considered in this thesis, as listed below:

- ADHD is not caused or cured by specific food components like additives or fish oil;
- Both ADHD and comorbid ODD may be caused by food;
- Comorbid physical complaints and sleep problems may be caused by food;
- The mechanisms of food in ADHD involve neither an IgE- or an IgG-mediated allergic mechanism, nor are the behavioural improvements due to improved parenting capabilities;
- In 40% of young children with ADHD the behavioural problems are not caused by food.

First of all this thesis may result in some “don’ts”. Although it seems to be customary in scientific research to end a manuscript with the closing remark “more research is necessary”, it is timely to acknowledge that in some cases the conclusion to reconsider the performance of further research may be warranted. This reconsideration might be applicable to the issues of additives and ADHD and fatty acids and ADHD. All in all, the results of additive and fatty acid studies in ADHD may be considered conclusive: in numerous studies (see *Chapter 1*) has convincingly been established that neither elimination of additives nor supplementation of fatty acids are effective treatments of ADHD. Consequently, it is worth considering to no longer focus further studies involving additives or fatty acids on children with ADHD, but to pivot these studies on children of the general population (additive studies),^{47,48} or on children with learning problems (fatty acids).⁴⁹ Thus, recent developed research models concerning the effect of additives in children with ADHD,⁵⁰ primed by the European Food Safety Authority advice to remove six colours from food and drink in the United Kingdom,⁵¹ might shift focus from ADHD to the effect of both colourings and preservatives in children of the general population.^{47,48} In addition, it might be prudent for additive researchers to collectively stand up against policymakers who, impulsively and with apparent deficit of attention to the evidence available (i.e. colourings do not cause ADHD and either colourings or preservatives or both may cause a minimal increase of hyperactivity in *all* children), stubbornly focus on colourings only, and suggest far-reaching and definitely not evidence based measures.

Similarly, fatty acid researchers might shift focus from increasing omega-3 to a neglected area that may be worthwhile to investigate when fatty acids are concerned, i.e. the at least ten to twentyfold increased ratio of omega-6 to omega-3 during the 20th century.^{52,53,54} Data suggest that until 100 years ago the omega 6/3 ratio was 1:1,⁵³ and it is not inconceivable that decreasing omega-6 in our foods may eventually prove to be more beneficial to our health than increasing omega-3, in particular because omega-6 fatty acids are known to increase inflammation,⁵⁵⁻⁵⁸ which is an important underlying problem of many lifestyle diseases.⁵⁹⁻⁶² Consequently, fatty acid researchers might consider to shift focus from supplementing omega-3 to elimination of omega-6 fatty acids.

Another “don’t” concerns further research on whether or not an RED may have a beneficial effect on the behaviour of children with ADHD. It is now timely to acknowledge that sufficient evidence is available to underline the relationship

between an RED and ADHD. Consequently further research should not focus on the question *if* an RED may be effective in children with ADHD, but on the important question *how* food exerts its effects. Below the suggestions for follow-up research concentrating on this issue will be discussed.

9.6.1. Suggestions for follow-up research regarding the RED mechanism

The exact way in which food exerts its effects is not clear yet. In [Chapter 6](#) and [Chapter 7](#) it has been discussed that IgE, IgG and change in family structure are not the underlying mechanism of the RED effects. More research is necessary to investigate how an RED brings its impressive effect about and to define the role of gut, brain and genes in children with FI-ADHD. Furthermore the epigenetic effects of food might be investigated. Finally, a search for biomarkers might offer the opportunity to differentiate between FI-ADHD and C-ADHD.

First of all, the gut may play an important role in the FI-ADHD mechanism. Many children with ADHD report gastrointestinal problems and further research is required to define whether this association is a matter of comorbidity, of co-occurrence, or whether there is a causal connection. In this light, an interesting object of study would be the effect of food on the gut flora and the consequential effect of the gut flora on ADHD. Metagenomics (studying the microbiome, i.e. the collective genome of all intestinal microbiota)⁶³ and nutrigenomics (studying the effects of food on the microbiome)⁶⁴ may lead to interesting new perspectives.⁶⁵

Second, research might focus on the brain of children with FI-ADHD. Functional magnetic resonance imaging (MRI) studies, in children before and after an RED, are necessary to answer this question. Even more important: how does food affect the brain and which food components actually pass the blood brain barrier? Or may other pathways be involved, e.g. the gut-brain axis, and may in children with FI-ADHD food result in a dysfunction of the pathway between the gastrointestinal tract and the central nervous system?

Third, future research is necessary to find out into what extent genes are involved in FI-ADHD. Of course, considering that FI-ADHD may be present in 60% of children with ADHD and that ADHD is a disorder with many genes involved – the genetic heterogeneity even broader than expected –,⁶⁶ it is likely that an association will be found between food and genes in children with FI-ADHD. Therefore, it is first of all important to focus on genetic differences between children with FI-ADHD and children with C-ADHD. In addition, research should

focus on the occurrence of FI-ADHD in siblings of children with FI-ADHD. If genetic factors are involved in FI-ADHD, it is expected to run in the family. Furthermore, several genes involved in the regulation of the immune system are associated with the development of ADHD symptoms,^{67,68} and the further unravelling of the relationship between genes, ADHD and the immune system is also an important area of research. Considering that dopamine, a neurotransmitter involved in ADHD, and dopaminergic receptors are found on human T-cells, genes may be involved in a cell-mediated immune response which may be underlying FI-ADHD.

When focussing on genetics, another intriguing subject of research may be the epigenetic effects of food. Considering that dietary factors may induce epigenetic alterations,⁶⁹ it would be challenging to investigate whether ADHD may be mediated by epigenetic mechanisms influenced by specific foods. In light of epigenetic changes, parental nutrition may be an important area for research. Our food, that used to be a hunter-gatherer diet, has changed profoundly during the agricultural and industrial revolution in the past centuries. These changes may instigate epigenetic alterations⁷⁰ which may affect the offspring. It is tempting to hypothesise that, if epigenetic alterations prove to be part of the FI-ADHD mechanism and considering that epigenetic changes are reversible,⁷¹ a child who adheres to his or her diet for a longer period of time might “overgrow” the hypersensitivity to food. Indeed, it would even be conceivable that the child’s offspring might not inherit the specific genetic vulnerability anymore, thus breaking out of the heritability spiral. If this were the case, then the long-term effects of an RED would be immense.

9.6.2. Suggestions for follow-up research regarding the challenge period

In addition to further research focussing on the mechanism of food, additional research should also focus on the challenge period, following the RED in RED responders. It is important to emphasise that the RED never lasts longer than 5 weeks, after which nonresponders (children with C-ADHD) may eat anything again and after which responders (children with FI-ADHD) start the challenge period. During this challenge period one food a week is added to the RED in order to investigate the behavioural consequences of the added food, i.e. to investigate to which specific foods each child reacts. Each child tends to respond differently to different foods, mostly to more than one food and in a for each child different

combination of foods.^{1,4} It may take a year to define to which food a child responds unfavourably. Parents find this trial-and-error period very strenuous; the behavioural relapses during the challenge period are dreaded and are burdensome for the whole family. Unfortunately, at this moment no method is available to anticipate *which* foods may cause a relapse in behaviour or *when* (i.e. after which amount of food) this behavioural relapse will happen. Further research should focus on an easier method to define the incriminated foods and on a way to establish the individual sensibility of each child.

Furthermore, research should focus on expert coaching of parents, child, siblings and teachers in order to increase the feasibility of the challenge period and to help parents and teachers to see this period through. Although the follow-up results of the INCA study have not been analysed yet, it is already clear that at least 50% of the responders actually finished the follow-up period which lasted 10 months. Families who left the trial prematurely indicated that they did not leave the study because the diet ceased to be effective, but they left because the recurrent behavioural relapses caused too much stress and disquietude in the family, or because their child's teacher found the relapses in behaviour difficult to handle and preferred medication. It is important to note that, until an easier method is available, the challenge period is crucial to determine the incriminated foods and thereby compose a feasible diet. At the end of the challenge period the child's diet will be practically normal and the child will have to avoid the incriminated foods only, thus, compared to the RED and the challenge period the final dietary restrictions will be "a piece of cake". Relapses will only occur if the child does not stick to the diet. Concluding, facilitating the challenge period is an important aim for further research.

9.6.3. Suggestions for follow-up research regarding the long-term effect of food and the financial consequences of RED research implementation

More research is necessary to establish the long-term effect of foods. Some RED studies have already shown that the RED effects continue unabated during a follow-up period of one year.^{2,4} The preliminary results of the INCA 10-month follow-up study also show that the behavioural effects, in children who stick to their diet, persist. Still, it is imperative to investigate the effects of an RED after a longer period of time, and to investigate whether children may overgrow the sensitivity to specific foods when avoiding the incriminated foods for a longer

period of time. In addition, during long-term research a comparison might be made of the prospects of children treated with a diet with those of children treated with medication, and of the financial consequences of both treatments.

It is calculated that the direct medical costs of children with ADHD are 11 times higher than the costs of children without behavioural problems,⁷² as discussed in *Chapter 1.4*. The estimated costs of ADHD when most other societal costs like special education, behavioural interventions, placing in care, associated costs in adulthood, substance use and costs of crime are included, may vary from \$12,005.- to \$17,458.- 2005 dollars per individual per year.⁷³ The Dutch Foundation of Child and Behaviour already has calculated some financial benefits of RED research implementation in children with ADHD, which may amount to € 280 million per year.⁷⁴ In sum, it is obvious that the costs of ADHD are considerable and that prevention of ADHD may offer opportunities to decrease the costs of illness. A comprehensive study including all costs of both treatment as usual and RED research, may shed more light on the cost effectiveness of implementation of RED research in children with ADHD.

9.6.4. Suggestions for follow-up research regarding the effects of food on other psychiatric disorders and on somatic problems

Another important objective of further research will be the effect of an RED on other psychiatric disorders as well as on somatic problems. In two RCTs (see *Chapter 3* and *Chapter 6*) and in one pilot study (see *Chapter 2*) the effect of an RED on comorbid ODD has already been investigated, resulting in 74% responders¹ who all showed impressive improvements of behaviour (89%). Considering the high percentage of responders, and considering that children with disorders like ODD give rise to substantial parenting stress and are more at risk for long-term maladjustment,⁷⁵⁻⁷⁷ it may be important to investigate the effects of an RED on ODD in children without ADHD. Interventions that may reduce ODD have great clinical potential, reducing long-term risks and improving the perspectives of these children.

Furthermore, further research may focus on the effects of an RED on other child psychiatric problems (e.g. Conduct Disorder, Autism Spectrum Disorder, Obsessive-Compulsive behaviours and mood and anxiety disorders). Many associations have been found between various psychiatric conditions and comorbidity is a general phenomenon, rule rather than exception. It is important

to define whether the effects of food may exceed the borders of ADHD and ODD and may affect other disorders as well.

In addition, the effects of an RED on physical complaints and sleep problems in children with and without ADHD need to be investigated. Physical complaints like gastrointestinal disorders occur frequently in children with⁷⁸ and without⁷⁹⁻⁸² psychiatric disorders, and functional somatic symptoms are common health complaints in young children.⁸³ It has already been shown that dietary intervention may result in a decrease of physical complaints in children and adults without ADHD,^{79,82} consequently, further research into the effects of an RED on physical problems in children with and without ADHD is important.

Finally, considering the high comorbidity between ADHD and physical complaints it is tempting to hypothesise that physical complaints in children with ADHD may be considered an exophenotype (on the analogy of endophenotype) of FI-ADHD, i.e. indicative of a hypersensitivity to food. If so, physical complaints or combinations of complaints might offer the opportunity to predict the results of an RED in children with ADHD.

9.6.5. Suggestions for follow-up research regarding the phenotypic manifestation of a hypersensitivity reaction to food

Another intriguing issue and subject of further research where the posited (epi)genetic contribution to FI-ADHD is concerned, is the assumption that the genetic constitution or the epigenetic alterations might define the phenotypic expression of food in individuals. Could it be that in child A food may trigger ADHD, while in child B food may be the underlying cause of ODD, or compulsive behaviour, or depression? In other words, can a child's genetic predisposition determine which disorder actually will manifest itself as a consequence of the food hypersensitivity? Moreover, considering the fact that in girls the prevalence of ADHD is smaller but the prevalence of mood disorders is higher than in boys,⁸⁴ the effect of food might even be determined by a genetic predisposition associated with the sex of a child, i.e. in boys resulting in ADHD, in girls resulting in mood disorders. Thus, the relevant phenotype may be broader than just ADHD and ODD and include mood and anxiety disorders and maybe even autism spectrum disorders. Indeed, the phenotypic expression might also involve physical complaints, consequently, the phenotypic manifestation of a hypersensitivity reaction to food is a fascinating and challenging subject of research.

9.6.6. Suggestions for follow-up research regarding biological markers

Finally, further research is recommended to answer the question whether any biological markers may be found. Extensive blood, urine, saliva and faeces tests in children with FI-ADHD, C-ADHD and their siblings is of the essence and will hopefully lead to tests that can predict whether RED research or treatment as usual should be first choice for each individual child. Hypothetically, biological markers may even provide information that could answer the questions which foods in which amount cause which trouble in which child. If further research would lead to such a marker, then in future a simple test might suffice to answer these questions.

9.6.7. Suggestions for follow-up research regarding the characteristics of food that triggers FI-ADHD and for RED research in other continents

More research is needed to define the characteristics of food that instigates ADHD in children with FI-ADHD. For example, does the reaction of a child, showing ADHD behaviour when eating potatoes, only depends on the amount of potatoes eaten (i.e. every day or once a week), or may the kind, or the quality (old or new), or the method of preparation of the potatoes be of importance as well? And will any similarities be found between the different foods a child reacts to, i.e. do these foods have a common component that may cause the change in behaviour?

Another subject worth mentioning concerns RED research in other continents. Most RED studies (6/8) were executed in Western-Europe and the RED was based on the specific eating habits in this part of the world. In most follow-up studies children showed behavioural relapses after eating common everyday and frequently eaten foods. It is conceivable that in other continents, with different eating habits and other daily foods (i.e. rice or corn instead of wheat and potatoes), other (epi)genetic vulnerabilities may exist. If this would be the case, then these children might react to different foods, implicating that a different RED composition based on the specific eating habits in that part of the world may be needed in order to investigate the effect of food on the behaviour of these children.

9.6.8. Suggestions for follow-up research regarding children diagnosed with C-ADHD

According to the results of the RED studies 40% of children with ADHD do not respond favourably to an RED and may be diagnosed with C-ADHD. The aetiology

of ADHD in these children needs further attention and may focus on the following six questions. 1) Is the threshold model applicable to this group of children? 2) Are other (necessary) causal factors yet to be discovered? Some environmental factors are associated with hypersensitivity reactions in children (e.g. propylene glycol and glycol ether in indoor air⁸⁵) or may affect the central nervous system (e.g. thinner inhalation in painters⁸⁶ or solvents in glue sniffers⁸⁷). For this reason it is conceivable that other environmental factors yet to be discovered are involved in ADHD. Furthermore, in children using anti-asthma medication behavioural problems appear to be more common than in children who do not use this medication.⁸⁸ In children not responding to an RED and using anti-asthma medication it is conceivable that the behavioural problems may be an adverse effect of the medication, and a temporary change of anti-asthma medication might be considered. 3) Does the disorder manifest itself independent of the child's genetic constitution? 4) Is it possible that mentally challenged children, highly talented children or children suffering from learning disabilities like dyslexia or dyscalculia may show symptoms of ADHD as a consequence of their learning problem? If the learning problems are not recognised and treated, the children may show ADHD behaviour (i.e. become restless, inattentive and so on) as a result of the learning problems and consequentially may be wrongfully diagnosed with C-ADHD. 5) Is an inadequate family environment or are parenting problems, which may be due to parental psychiatric problems, underlying the child's behavioural problems? 6) Would in some children the old and abandoned diagnosis minimal brain damage (MBD-ADHD) be appropriate? For instance, in children physically abused or in children with unfavourable prenatal or natal conditions like severe dysphyxia and hypoxia, the brain may have been damaged to such an extent that this may lead to abnormal behaviour and ADHD.

9.6.9. In conclusion

In conclusion, the RED studies have provided valuable information that contributes to our understanding of ADHD. In addition they have also provided worthwhile indications for further research into the mechanisms in which food may exert its effects. The results of further research will lead to better understanding of FI-ADHD as well as of C-ADHD, and will improve the diagnostic procedure and treatment of these children.