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

Lidy M.J. Pelsser

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Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

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Liduina Maria Josephina Pelsser
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Promotoren

Prof. dr. J.K. Buitelaar

Prof. dr. H.F. Savelkoul (Wageningen Universiteit)

Copromotor

Dr. N.N. Lambregts-Rommelse

Manuscriptcommissie

Prof. dr. R. de Groot, voorzitter

Prof. dr. E. Taylor (King's College London, UK)

Prof. dr. J.J. van Binsbergen

Let medicine be thy food, and food be thy medicine

Hippocrates,
Greek physician (460 BC - 377 BC),
founder of medicine

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Preface: how it all began

When I practised as a veterinary surgeon it occurred to me that I often spent more time listening to the personal problems of the owner than treating their pets. Although I was not trained to be a human physician or psychiatrist, I felt that I failed in my duty. Consequently, in the evenings I took psychology classes and I became fascinated by one specific book, the *Modern Synopsis of the Comprehensive Textbook of Psychiatry* by Kaplan and Sadock. I was puzzled by the fact that in the human psychiatric diagnostic procedure it seemed to be common practice to start a therapy – of course after making an inventory of symptoms and their impact on everyday life – without a search for a cause. How totally different that was from what I had learned as a vet.

According to my veterinary medical education it was considered malpractice to start a therapy without at least trying to find a cause of the problems. This golden standard – first making an inventory of symptoms, then a search for the cause of the symptoms (i.e. differential diagnostic research), and finally starting a therapy specifically aimed at eliminating the cause – is common practice in both veterinary and human somatic medicine. Still, I now was dealing with psychiatric conditions. Could it be, so I pondered on this issue, that psychiatric diagnostic rules did not correspond to somatic diagnostic rules?

On the other hand, although we had not yet unravelled the mysteries of the brain, it is an organ like other organs, so there should be a cause to find in case of malfunction, even in psychiatric disorders. What did psychiatric researchers focus on to resolve this problem, I wondered. I remembered treating a little dog suffering from fly catcher's syndrome, compulsively trying to catch imaginary flies. Definitely mad. This dog happened to suffer from eczema as well and I prescribed a restricted elimination diet, an effective treatment of eczema in veterinary practice in many patients. What happened following a 6-week period of diet was striking: the dog trotted into the surgery without a twitch or snatch, the owner following with a big smile on his face. I was astounded to find that not only the eczema had vanished but also the fly catching. What a strange and puzzling coincidence it seemed to be at the time, but now I wondered whether there might have been a connection between the somatic and the psychiatric problems of the little dog.

Several weeks later I happened to hit upon a study investigating the effects of a restricted elimination diet on ADHD in children. Reading it I got truly interested, I searched for more literature on this subject, thought about the little mad dog and I kept on reading. That was how I spent my evenings, reading, writing, thinking and rethinking, with my children fast asleep. I discovered that the answers to my questions inevitably led to even more questions and I enjoyed it to the full. I realised I had found my future: science. You may find the results of my thoughts and research in this thesis, and I would highly recommend chapters 1, 8 and 9, which in particular comprise the results of my considerations on the cause of ADHD.

The Story of Fidgety Philip

A poem by Dr Heinrich Hoffman, a German physician, published in 1845

"Let me see if Philip can
Be a little gentleman;
Let me see if he is able
To sit still for once at table":
Thus Papa bade Phil behave;
And Mamma looked very grave.
But fidgety Phil,
He won't sit still;
He wriggles,
And giggles,
And then, I declare,
Swings backwards and forwards,
And tilts up his chair,
Just like any rocking horse—
"Philip! I am getting cross!"

See the naughty, restless child
Growing still more rude and wild,
Till his chair falls over quite.
Philip screams with all his might,
Catches at the cloth, but then
That makes matters worse again.
Down upon the ground they fall,
Glasses, plates, knives, forks, and all.
How Mamma did fret and frown,
When she saw them tumbling down!
And Papa made such a face!
Philip is in sad disgrace.

Where is Philip, where is he?
Fairly covered up you see!
Cloth and all are lying on him;
He has pulled down all upon him.
What a terrible to-do!
Dishes, glasses, snapt in two!
Here a knife, and there a fork!
Philip, this is cruel work.
Table all so bare, and ah!
Poor Papa, and poor Mamma
Look quite cross, and wonder how
They shall have their dinner now.

Chapter 1

General introduction

Introduction

In this general introduction a description is given of Attention-Deficit/Hyperactivity Disorder (ADHD) and ADHD Not Otherwise Specified (ADHD-NOS), of comorbid disorders often identified in children with ADHD, of the impact of ADHD on child and society, and of the aetiology, i.e. the genetic and environmental factors involved in ADHD. Subsequently, this introduction elaborates on one specific environmental risk factor of ADHD, i.e. food, on studies eliminating or supplementing food constituents like additives and fatty acids, on restricted elimination diet studies, on the current assessment and therapy of ADHD, and on the role of food in the current therapeutic approach of ADHD. Finally, the aim of this thesis, i.e. the relationship between ADHD and food in coherence with the objectives of each of the six studies involved, will be explained.

1.1 ADHD

1.1.1. From MBD to ADHD

The first description of hyperactive and ungovernable child behaviour was published in 1845, in a book written by Dr Heinrich Hoffman, a German physician.[1] This illustrated booklet comprised a series of 10 different poems, mostly about children showing inappropriate behaviour. Especially the poem about "Fidgety Philip" became well known, not only in Germany but throughout Europe,[2] although of course we do not know whether little Philip suffered from ADHD or whether he just choose an awkward way of telling his parents that he really disliked Brussels sprouts. Be that as it may, fact is that the symptoms described in the poem correspond with some of the ADHD symptoms described in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).[3]

The first detailed account of ADHD symptoms was given in 1902, by Dr George Still in a *Lancet* publication,[4] and up to the second half of the twentieth century these behavioural problems were thought to be caused by organic encephalic lesions, indicated as minimal brain damage (MBD).[5] As research showed that no organic neurological alterations could be detected in these children[6] the phrase "minimal brain damage" was changed into "minimal brain dysfunction". Still, as it was not easy to differentiate between minimal brain dysfunction and temperament,[7] and as in fact all psychiatric disorders may be the consequence of some

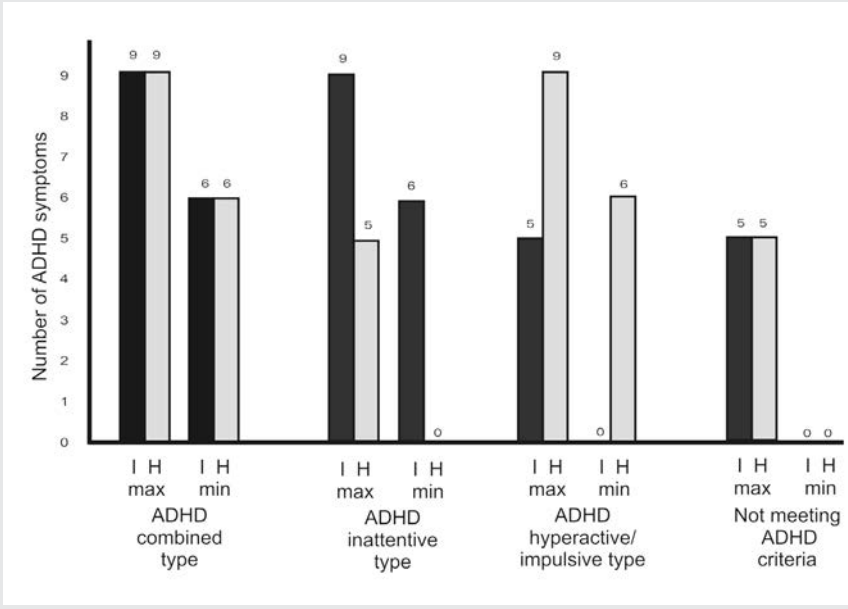
dysfunction of the brain, the aetiological formulation of the problem, i.e. MBD, evolved into a more descriptive formulation, making an inventory of symptoms without referring to a cause.

To date, inattention, overactivity and impulsivity symptoms are described in two generally accepted and overlapping concepts: Hyperkinetic Disorder, as described in the International Classification of Diseases (ICD),[8] and Attention-Deficit/Hyperactivity Disorder (ADHD), as described in the DSM.[3] Considering that the studies included in this thesis were based on the DSM, the terminology applied in this thesis is restricted to the DSM-terminology. In the DSM-III, the first manual including this behavioural disorder, the symptoms were represented as Attention Deficit Disorder with Hyperactivity (ADDH).[9] This description was not accepted without scrutiny[10] and the question was raised whether a clinical diagnosis could be made using behavioural instruments.[11] Some researchers preferred to refer to ADDH as ADDH-syndrome.[12] Nevertheless, despite some resistance, to date, in 2011, the DSM-III ADDH criteria have evolved into the DSM-IV ADHD criteria, and are based on behavioural symptoms and the concurrent impairment.

1.1.2. Diagnostic criteria

According to the DSM-IV criteria ADHD is a psychiatric disorder characterised by developmentally inappropriate symptoms of inattention, impulsive behaviour and hyperactivity.[3] In most children the behavioural problems start before the age of 5 (frequently before the age of 2 years), and the disorder often persists into adolescence and adulthood.[13] The ADHD symptoms comprise 18 characteristic features, i.e. 9 concerning inattentive behaviour and 9 concerning hyperactive/impulsive behaviour. The inattentive symptoms refer to children who: 1) are often careless, 2) often have difficulty in sustaining attention, 3) often do not seem to listen, 4) often fail to finish schoolwork, 5) often have difficulty organizing tasks, 6) often avoid tasks that require sustained mental efforts, 7) often lose things, 8) are often easily distracted, 9) are often forgetful in daily activities. The hyperactive/impulsive symptoms refer to children who: 1) often fidget with hands or feet, 2) often leave their seat when remaining seated is expected, 3) often run about or climb excessively, 4) often find it difficult to play quietly, 5) often act as if driven by a motor, 6) often talk excessively, 7) often blurt out answers before questions have been completed, 8) often have difficulty to await their turn, 9) often interrupt on others.

Figure Number of a child's inattentive (I) ADHD symptoms (0-9) and hyperactive/impulsive (H/I) ADHD symptoms (0-9), and the corresponding ADHD diagnosis



To meet the DSM-IV-diagnostic criteria of ADHD the child has to comply with five conditions:

A) the number of symptoms (see **figure**)

Based on the number and kind of symptoms which must have been manifest for at least the last 6 months, ADHD is divided into three different types.

1) Combined type: children who show at least 6 inattentive symptoms and at least 6 hyperactive/impulsive symptoms, may meet the criteria of the combined type.
2) Predominantly inattentive type: children who show at least 6 inattentive symptoms and less than 6 hyperactive/impulsive symptoms, may meet the criteria for the predominantly inattentive type.
3) Predominantly hyperactive/impulsive type: children who show at least 6 hyperactive/impulsive symptoms and less than 6 inattentive symptoms, may meet the criteria for the predominantly hyperactive/impulsive type.

B) the onset of symptoms
   Some symptoms that cause impairment were present before the age of 7.
C) the manifestation of the symptoms
   Some impairment has to be present in more than one setting, i.e. at home and at school or at day care.
D) the impairment caused by the symptoms
   The symptoms have to be more frequent and severe than in typically developing children at a comparable level of development, i.e. there must be clear evidence of clinically significant impairment in social and academic functioning.
E) the absence of Pervasive Developmental Disorder (PDD) and psychotic disorders
   Also, the symptoms must not be better accounted for by another mental disorder

In order to make reasonable decisions concerning ADHD, diagnostic thresholds, age and the impairment (e.g. at home, at school, with friends) as a result of the symptoms should be taken into account.[14] Consequently, it is important to emphasize that ADHD is more than the sum of symptoms. For instance, Fidgety Philip definitely showed a number of ADHD symptoms. He was careless and did not listen, he did not follow the instructions given, he fidgeted, he did not remain seated, he acted like he was driven by a motor and showed behaviour unsuitable for the occasion. Furthermore, father and mother expected him to behave badly, considering the father who bade his son to behave, and the mother who looked grave. Still, more information about the impact of his behaviour would be necessary, in order to establish the impact of Philip's behaviour and in order to decide whether ADHD would be the appropriate diagnosis.

1.1.3. Category or continuum

According to the ADHD guidelines of the National Institute for Health and Clinical Excellence (NICE) "ADHD is a valid clinical disorder that can be distinguished from comorbid conditions and the normal spectrum. ADHD differs from the normal spectrum because there are high levels of hyperactivity/impulsivity and/or inattention that result in significant psychological, social and/or occupational impairment that occurs across multiple domains and settings and persists over time".[15] Although ADHD is defined as a distinct category[16] epidemiological and twin studies have provided evidence for ADHD as a continuum rather than a

discrete category.[17-20] In a recent magnetic resonance imaging (MRI) study Shaw at al provided further neurobiological evidence for dimensionality of the disorder.[21] Lubke found that ADHD fitted best in three different classes, i.e. mild, moderate and severe, and most children with ADHD combined type belonged to the extreme end of the continuum.[20] Whether or not ADHD is considered a categoric or a dimensional disorder, the ADHD diagnosis has proved to be stable, in the sense of predicting the ADHD diagnosis;[22] children meeting the ADHD criteria were likely to continue to meet the criteria during a period of 8 years, thus supporting the predictive validity of the DSM-IV ADHD criteria.[23]

Conversely, this stability does not hold for the three types of ADHD (predominantly inattentive, hyperactive/impulsive, combined),[22,24,25] which were particularly defined to divide the heterogeneous group of children with ADHD in more homogeneous groups, in order to facilitate the diagnostic and therapeutic procedures.[22] Children with ADHD appeared to shift unsystematically from one type into another, consequently the typing of ADHD seems unpredictable and unstable over time.[22,24,25] Therefore it is advised to alter the current nominal typing into continuous typing, i.e. counting the numbers of both dimensions (inattentive and hyperactive/impulsive), because a robust association of symptom count with future impairment has been found.[22]

1.1.4. Prevalence

According to the DSM-IV ADHD affects 3 to 5% of all children,[3] but the prevalence of ADHD tends to increase. The worldwide prevalence is now estimated at 5.3%, and is associated with significant variability.[26] A recent report concerning the administrative ADHD prevalence, i.e. the number of parent reported children diagnosed with ADHD and taking ADHD medication, showed that in the USA this percentage had increased from 7.8% in 2003 to 9.5% in 2007, an increase of 21.8%.[27] In Germany the administrative prevalence of ADHD showed an increase of 45% during 2000-2007.[28]

The ADHD prevalence is 2.1 times greater in boys than in girls.[29] This difference might be explained by the higher prevalence of the predominantly inattentive type in girls,[30-32] which symptoms are less intruding or inconvenient than the more prominent hyperactive/impulsive symptoms. Consequently, girls are less likely to be referred for further diagnostic research and treatment.[32] According to the multiple threshold model, which implies that multiple factors (genetic as well as

environmental) are involved in the causation of ADHD and contribute additively to the liability for ADHD, girls may have a higher threshold for ADHD than boys,[33] which may be another explanation of the difference in occurrence between boys and girls. Still, although the differences in prevalence between boys and girls are well-established, more research is needed to explain these differences.[34] Unfortunately, the risks of non-treatment in both boys and girls are equal, and in 70-80% of children diagnosed with ADHD the symptoms and concomitant impairment will persist into adolescence and adulthood.[31]

1.2. ADHD-NOS

Some children do not meet the criteria for ADHD but nevertheless show prominent symptoms of inattention and/or hyperactivity/impulsivity, to such an extent that the child's development is negatively affected. In these children the diagnosis ADHD Not Otherwise Specified (ADHD-NOS) might be made.[3] This diagnosis may be applicable to children who meet the ADHD criteria but who show ADHD symptoms in one setting only (at home or at school), or to children who are too young to go to school. Of course the younger the child the more difficult it will be to establish the diagnosis, especially since the behaviour of young children may correspond with *some* ADHD symptoms. Still, according to the DSM-IV in toddlers the diagnosis may be established, because even children of 2 or 3 years old should be able to sit with an adult, or to listen to a story. The behavioural problems in young children may be assessed using the Preschool Age Psychiatric Assessment.[35] Furthermore, considering the medication studies that have been conducted in preschoolers, ADHD may be a real problem in young children. These medication studies have shown favourable effects of medication, although the effects seem to be smaller and some side effects seem to be greater than in school-age children.[36-38]

1.3. Comorbid disorders

ADHD is generally diagnosed in combination with other psychiatric disorders and co-occurrence of two or more child psychiatric disorders is common.[39] In the

majority of children with ADHD at least one comorbid condition is reported: according to a 2007 analysis in US children 33% suffered from one comorbid condition, 16% suffered from 2, and 18% reported 3 or more comorbid disorders.[40] Oppositional Defiant Disorder (ODD), affecting at least 40–60% of children with ADHD, and Conduct Disorder (CD) are the most frequent reported comorbid disorders in children with ADHD.[41] Although DSM-IV diagnostic criteria for ADHD exclude PDD,[42] children with ADHD often show symptoms of PDD Not Otherwise Specified (PDD-NOS)[42-45] and a high co-occurrence rate for ADHD and PDD-NOS exists. Furthermore, tic and anxiety disorder are comorbidities often reported[46] and the comorbitidy between ADHD and major depression disorder in children and adolescents is substantial.[47]

Other non-psychiatric common comorbid disorders include motor disorders like developmental coordination disorder (DCD)[48] and learning disorders like dyslexia and dyscalculia;[46] according to parent reports 46% of children with ADHD had a learning disorder, versus 5% of children without ADHD.[40] ADHD is overrepresented in children with coeliac disease[49,50] and, finally, sleep disorders[51] and physical complaints like eczema, asthma, headache, bellyache, enuresis and encopresis are conditions often reported by parents of children with ADHD.[52-54]

1.4. The impact of ADHD

ADHD is a disorder that affects the child and his or her environment substantially. The impairment is not limited to family life, but is also existing at school, play ground and in everyday life. Apart from the social consequences, preschool children with ADHD are more often referred to special education and need more physical and speech therapy than a control group without ADHD.[55] Furthermore, children with ADHD are more often visiting a general practitioner or a specialist, they are more often hospitalised and have more major injuries than a control group without ADHD.[56,57] Consequently, the demands for social and healthcare services are considerable,[58,59] concomitantly affecting the parents' professional productivity.[57] Children with comorbid psychiatric disorders like ODD and CD are even more difficult to handle by parents and teachers. They give rise to significant parenting stress, they have more problems, and need more health and educational

care than children with ADHD only.[40] These children have a worse prognosis compared to children without comorbidity.[60]

In most children the problems persist into adolescence and adulthood[27,31] and these children are even more at risk for long term negative outcomes.[60,61] Adolescents with ADHD show increased academic failure and an increased risk of driving accidents. They may develop aggressive and antisocial behaviour, resulting in a poorer social environment.[60] Research has shown that in particular ADHD with comorbid ODD or CD may predict an early onset of criminal behaviour[62] and children with or without comorbidity show worse delinquency outcomes.[63] Furthermore, in detained male adolescents, 90% of the subjects reported at least one psychiatric disorder –75% of which were ODD and/or CD–, and parent-reported ADHD, CD and childhood-onset CD predicted serious recidivism.[64,65] Finally, adults with ADHD are at risk of unemployment, problems at work, divorce and drug abuse.[66,67]

Not only the child and his or her environment suffer from ADHD, the societal costs of ADHD are considerable also. According to a Dutch study assessing the medical costs of ADHD patients and their mothers, the annual direct medical costs of children with ADHD were € 2040, which proved to be 11 times higher than the costs of children with no behavioural problems.[58] The mean annual medical costs of the mothers were € 728, almost 5 times higher than the costs of mothers of children without behavioural problems.[58] Additional other societal costs, like special education, behavioural interventions, placing in care, associated costs in adulthood, substance use and costs of crime[68] were not included in the calculations of the Dutch study. Summarizing, the impact of ADHD on everyday life is considerable for both the child and the child's environment, with significant social as well as economical consequences, resulting in impairment of life and substantial direct and indirect societal costs.

1.5. Aetiology: genetic and environmental factors involved

Since 1902, following the first description of the clinical symptoms of ADHD in *The Lancet*, the behavioural problems of children have been the subject of many investigations. Twin and adoption studies have provided evidence that genetic

factors play a dominant role in ADHD[69] with a heritability estimate of 75%.[70,71] Many genes of small effect are involved, interacting with each other and with environmental risk factors, but no genes of large effect have been found yet.[70] Furthermore, in children with ADHD a significantly increased rate of large, rare copy number variants (CNVs, i.e. chromosomal duplications and deletions) has been found,[72] especially in children with intellectual disability (IQ score <70), suggesting that routine genetic research and screening for these mutations could be helpful for children with ADHD.[71] Still, it is important to emphasize that high heritability and the presence of rare CNVs must not be confused with genetic determinism;[13] genomic risk prediction is obvious in Mendelian diseases, but in complex disorders genetic variants may explain the disease risk only partially.[73] Thus, the genetic architecture of ADHD is complex and not conclusive.[74]

Furthermore, considering that the increased rates of large CNVs were only found in the small minority (16%) of children with ADHD and were also found in 7% of the control group children without ADHD,[71,75] these additional results may serve as an example for the intricateness of this subject. Also, epigenetic changes may play a role in ADHD. Epigenetics is the process that governs the function of genes and is most commonly defined as the study of heritable changes in genome function that occur without a change in DNA sequence. Epigenetic effects in gene activation and inactivation are increasingly understood to be important in phenotype transmission and development. Considering the diversity of genotypes as well as phenotypes, ADHD sharing specific genes with autism, epilepsy, schizophrenia and mental retardation,[71,76] further studies investigating the associations between genotypes and phenotypes are important, perhaps resulting in previously overlooked similar phenotypic elements that might link the genotypic outcomes.[76]

Despite all scientific reseach and efforts to unravel the mysteries of ADHD the exact aetiological pathways of ADHD are still unknown.[13,77] To date, ADHD is considered a complex and multifactorial disorder in which genetic as well as environmental risk factors may be involved.[78] Although according to the Dutch ADHD guidelines environmental factors do not have a strong influence on the development of ADHD,[77] biological environmental factors (e.g. complications during pregnancy and delivery, smoking or alcohol use by the mother during pregnancy, and low birth weight, prematurity or dysmaturity) as well as psychosocial environmental factors (e.g. low social class, foster placement,

parental mental disorders, and family dysfunction) are associated with ADHD.[79] According to the polygenic multiple threshold model,[33] every risk factor (genetic, biological and psychosocial) may have a small effect on the increasing vulnerability to the disorder, additive as well as interactive, and the cumulative effect of these risk factors, if exceeding a threshold, may lead to ADHD.[70] Individuals may differ in their response to environmental factors, and some individuals who have ADHD related genes may only develop the disorder when they are exposed to risk factors.[80] I.e., it is conceivable that the child's genetic constituency may be interpreted as a genetic vulnerability to environmental risk factors.[69,74]

Not until recently specific gene-environment interactions have been studied in ADHD by means of "gene-environment" (GxE) studies. It is conceivable that the predominating negligence of environmental factors may have been caused by the very high heritability of ADHD.[79] Contrary to the posited notion that ADHD results from a cumulation or a confluence of genes and environment, which of course is true, the GxE theory goes a step further, i.e. genotype and environment may increase or decrease each others effect, resulting in an actual interplay between genes and environment.[79] Consequently, some genotypes may be disadvantageous, but only in combination with specific environmental factors, and some environments may be detrimental, but only to certain individuals with specific genotypes.[79] An appealing example is the Siamese cat, whose black tips are defined by the environment, to be more specific, by the temperature. A Siamese kept in the fridge will grow black hair only, but kept in the desert will be white as snow.[75]

On top of that, gene expression and epigenetic processes may be altered or induced by environmental factors,[75,81] indicating that GxE studies are very exciting and may be promising for the future. Concluding, genes and environmental factors may interact with each other in complex ways,[69] emphasizing the importance of studies into environmental factors.[79] More research is needed to define to what extent environmental factors may influence the genotype and play a role in ADHD, and to investigate whether risk reduction and treatment could be achieved by modifying the environment.[80]

1.6. Food as a specific environmental risk factor of ADHD

One of the environmental research areas meriting greater attention is the impact food may have on behaviour and behavioural disorders. There is growing awareness among healthcare providers that the composition and quality of our food may play a role in determining not only our physical well-being, but also our behaviour. The pharmacological effects of certain foods, like caffeine (improving concentration), chocolate (affecting mood), and alcohol (changing behaviour) are well known.[82] Foods are also involved in allergic and highly genetic diseases like asthma and eczema. Various environmental factors (e.g. dust mites, pet animals, pollen or foods) may play an important role and may contribute to the development of these disease.[83,84] Avoiding incriminated risk factors may reduce or even prevent the symptoms, thus offering the opportunity to reduce the intake of drugs to a minimum.

Based on the comorbidity of ADHD and allergic disorders which occurs in 40% of children with ADHD[85] a causal relationship between allergies and ADHD was suggested.[85-87] Conversely, other studies showed no conclusive evidence for this association[88,89] finding no discrepancy in the number of children showing ADHD behaviour with and without an allergic disorder.[54,88,89] The occurrence of adverse physical reactions to foods (e.g. eczema, asthma, allergic rhinitis, gastrointestinal disturbances)[90] in combination with the high comorbidity of behavioural and physical complaints,[46] stimulated speculation that foods might not only affect organs like the skin, the gastrointestinal tract and the respiratory system, but might also have an impact on the brain, resulting in adverse behavioural effects.[53] If so, in children (genetically) vulnerable to ADHD specific foods may trigger the disorder, commensurable with strawberry triggering eczema, orange triggering asthma, or wheat triggering coeliac disease. Consequently, avoiding the incriminated foods will lead to a decrease of symptoms. In order to investigate the relationship between food and behaviour in the previous century two types of studies have been performed; studies eliminating or supplementing one or several food components, i.e. additive and supplement studies, and studies eliminating many foods, i.e. restricted elimination diet (RED) studies.

1.7. Additive and supplement studies

Additive studies are defined as studies eliminating or provocating one or a few food components. Between 1970 and 2000 many additive studies investigated the effect of food dyes, preservatives or other specific food components (e.g. sugar or chocolate) on ADHD. These studies have convincingly shown that additives or specific food components are not to blame for ADHD.[91-97] Recent studies into the effects of additives showed that exposure to food colours *and* benzoate preservatives may result in some degree of hyperactivity in *all* children of the general population, but not specifically in children with ADHD.[98,99] Furthermore, the effect sizes were small, and it is undetermined whether either food colours, or preservatives, or both engendered the effect.[98,99] Other studies eliminating only one or a few diet components, like a gluten free diet or the Feingold diet, did not result in statistically significant and clinically relevant results on ADHD as well.[97,100] Concluding, despite the common association and the expectation of parents that sugar and additives may cause ADHD, a diet excluding just a few food components, like gluten, sugar or chocolate,[76,78] or an additive free diet is of no benefit to ADHD.[53] According to the European and the NICE guidelines there is no evidence for the effectiveness of these diets and they should not be prescribed.[13,15] The Dutch multidisciplinary ADHD guidelines, provided by the Trimbos Institute (Netherlands Institute of Mental Health and Addiction) are consistent with the European and the NICE guidelines.[77]

In addition to additive studies, eliminating some food components, supplement studies have been performed, characterised by supplementing a specific food component or nutrient. In short, no evidence exists for the effectiveness of supplementation of vitamins or herbs.[97,100] Furthermore, clinical effects of zinc, iron, or magnesium supplementation are equivocal,[101,102] not significant,[103] or too little studies are available to draw any conclusions.[101] Supplementation with poly-unsaturated fatty acids (PUFA), more specifically omega-3 and omega-6 fatty acids [essential fatty acids (EFA)], has also been studied as a treatment for ADHD. In fact, supplementation of omega-3 fatty acid or alpha-linolenic acid, mostly referred to as fish oil, is widely applied for all kinds of diseases, including ADHD. To date, fish oil appears to have grown into a panecea, of which the food industry is taking full advantage, adding fish oil to all kinds of foods, even to pet food. Contrary to the canvassing texts on foods, up to now research has shown

no convincing evidence for a clear effect of omega-3 fats on our health, neither on total mortality, cardiovascular events or cancer,[105] nor on ADHD.[106-109]

A recent randomised placebo-controlled trial in children and adolescents with ADHD showed that omega 3/6 supplementation (eye q) was not statistically superior to placebo. In children with comorbid ODD, i.e. the majority of children with ADHD, a clinical response was lacking altogether. In a subgroup of children without ODD but with comorbid reading and learning disorders, the supplement only just reached statisticial significance.[110] A review recently conducted by the National Institute for Public Health and the Environment in the Netherlands, found that omega 3/6 fatty acid supplementation does not show clinically relevant effects on ADHD.[104] Similarly, in a systematic review Raz et al concluded that omega 3/6 trials "have generally been unsuccesful in demonstrating any behavioural effects".[109] Overall, despite many trials supplementing either omega-3 fatty acids (fish oil) or omega-6 fatty acids or both, evidence for the effect on ADHD is limited and results are inconsistent.[107] Consequently, fatty acids are not recommended as a primary or supplementary treatment for children with ADHD.[15,77,104,109]

1.8. RED studies

Between 1985 and 2000 the effects of a restricted elimination diet (RED) on ADHD have been investigated in six randomised controlled dietary studies,[52,53,85,111-113] of which five studies used a double-blind placebo controlled design.[52,53,85,111,113] The rationale for using a highly restrictive diet was the assumption that a child might show adverse behavioural reactions after eating any foods. If so, this would explain why excluding just one or two different foods, as happened in the additive studies,[91-97] would not be an effective method to investigate the existence of a diet-behaviour connection in a child.[53] Consequently, contrary to the additive studies in which the children adhered to their normal diet, the RED studies involved a total change of diet, allowing only a few different foods and excluding not only additives but many different foods. In short, in the additive studies parents were told what the child should *not* eat, in the RED studies parents were told what the child was *allowed* to eat.

In the RED studies the children followed an individually composed restricted

elimination diet (RED) for 4 weeks at the most. Basic foods were rice, meat, vegetables, fruit and water, i.e. the few foods diet as described by Carter,[53] but most studies used a more elaborate diet and adapted the diet for each child individually. The RED trials have shown that in 24% (in the study using the most extensive diet which lasted 8 days only)[113] to 82% (in the study using the most restricted diet in a highly selected population)[85] of subjects significant behavioural improvements were established following the RED. A meta-analysis of the five double-blind placebo-controlled RED studies[52,53,85,111,113] resulted in an aggregated standardized mean difference of 0.80, which is a large effect size.[106] Considering that the majority of these studies (3/5) were conducted in children selected via diet clinics[53,85] or allergy clinics,[111] the results of the RED studies are applicable to a subgroup of children with ADHD, showing convincing controlled evidence of efficacy[97,114] Consequently, in 2001 application of an RED in predetermined cases was included in a basic algorithm for treatment of ADHD in the United Kingdom.[100]

The mechanism in which foods may exert their effects on ADHD has not been investigated yet. It is hypothesised that ADHD is allergy related[115] and that a shared genetic aetiology may be underlying both allergic conditions (e.g. asthma) and ADHD.[116] In allergic diseases like asthma, rhinitis and eczema environmental factors play an important triggering role.[117-119] According to the revised nomenclature of allergy, hypersensitivity is the coordinating term for all allergic and non-allergic reactions triggered by environmental factors, the definition being as follows: "Hypersensitivity describes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects."[120] The manifestation of asthma symptoms following exposure to dust mites, will meet the definition of hypersensitivity, the dust mite being the defined environmental stimulus. Similarly, if a child shows ADHD symptoms after eating normal amounts of specific foods, these foods may, like the dust mite in asthma, be considered as clearly identified stimuli tolerated by typical subjects. Consequently, in some children ADHD may be the result of a hypersensitive reaction as described in the definition above. The results of the RED studies, investigating the effects of food on ADHD symptoms, support the existence of a hypersensitivity mechanism. If a child shows ADHD after eating certain foods and if blood tests show increased levels of immunoglobulin (Ig) against the incriminated foods,[120] then in this specific child ADHD may be the consequence of an allergic reaction to foods. Allergy is a hypersensitivity reaction initiated by specific

immunologic mechanisms,[120] and may be antibody-mediated and/or cell-mediated. In antibody-mediated allergies immunoglobulins like IgE or IgG are involved.[121] According to Gaitens a behavioural response to food is probably not IgE-mediated, but there might well be a connection between ADHD and allergies based on a non-IgE-mediated mechanism.[122] Consequently, in children showing an ADHD-response to foods, cell-mediated allergy (i.e. mediated by a chronic immune stimulus to T cells) may be involved.

In children with food-induced ADHD but without an established allergic mechanism, a non-allergic hypersensitivity may be involved, in which pharmacologic, toxic,[53] or epigenetic [75,81] mechanisms may play a role. Considering the high comorbidity of functional gastrointestinal disorders and psychiatric disorders even the gut brain axis (i.e. the link between the gastrointestinal tract and the central nervous system), an unexplored area where ADHD is concerned, may play a role in ADHD.[123] Furthermore, modulation of behaviour via gut microbiotica is another new and interesting concept.[124] Concluding, more research is necessary to establish whether in children with food-induced ADHD an allergic or a non-allergic hypersensitivity mechanism is involved.

1.9. Current assessment and therapy of ADHD

According to the guidelines the ADHD diagnosis should only be made by a trained health care professional, with expertise in diagnosing ADHD. The ADHD assessments should comprise: 1) parent interview, including a developmental history of the child and family members, family functioning, social network, a psychiatric interview concerning DSM-IV-diagnoses and parent rating scales; 2) child interview, although the interviewer must realise that behavioural problems may not manifest themselves in a new and exciting setting; 3) school information about the functioning and the behaviour of the child at school and about the teacher-child relationship; 4) psychological tests if there are any problems related to learning or progress at school, 5) general examination of physical health, including weight and height, further investigations only to be executed on medical grounds (e.g. EEG in case of a history of seizures, gene assessments in case of developmental delay, audiograms in case of hearing problems, and neuro-psychological tests in case of suspicion of brain lesions).[13,77]

To date, the management of ADHD is generally based on multimodal treatments.[115] According to the NICE ADHD guidelines the order of treatment should depend on the severity of symptoms and the level of impairment of functioning. In children with moderate ADHD and moderate impairment parent training and parent education, if desired combined with child group treatment (cognitive behavioural therapy), should be the first-line treatment. In children with severe ADHD and severe impairment drug treatment should be first-line, preferably combined with group based parent training.[15] According to the European guidelines for hyperkinetic disorder psycho-education should be the base of treatment, followed by psychological and behavioural interventions (i.e. parent training and behavioural interventions in the family; behavioural interventions at school; cognitive behaviour therapy of the child).[13] Psychopharmacological treatment should be considered if the effects of psychological interventions are insufficient or if the case meets the criteria for severity of symptoms and of impairment of functioning that warrant direct medication treatment.[13,77]

1.10. The role of food in the current therapy of ADHD

As yet not any diet is part of the current therapy of ADHD. So far only seldom an elimination diet is referred to as a possible treatment for ADHD.[125] Indeed, in an analysis of the current literature by the American Academy of Pediatrics' Committee on Quality Improvement, conducted for the purpose of developing an evidence-based clinical practice guideline for the treatment of the school-aged child with ADHD, the results of the RED studies were not mentioned at all.[126] In a recent "balanced review of the literature, both in support and against the possibility of foods or additives causing behavior disorders" all RED studies were ignored.[127] Furthermore, in a review "emphasising new developments and focusing on pathways of discovery that could lead to improved treatments for patients with ADHD" the authors referred to additive studies only in order to deduce that there are "mostly negative studies of dietary factors".[70] Of course, it is correct that the additive studies, investigating the effect of elimination of additives or other food components on the behaviour of children with ADHD, have convincingly shown not to be effective and are not considered part of the treatment

of ADHD.[13,15] Conversely, convincing evidence exists for the effectiveness of an individually constructed elimination diet in selected groups of children.[97,114] Moreover, in 2001 an RED was incorporated in an algorithm for ADHD treatment if: 1) there was a clue in history that dietary factors might be involved; 2) a paediatric dietician was available to monitor the diet; 3) the child and family were motivated to follow a diet.[100] Considering the existing evidence available at the time of the above-mentioned reviews, it is amazing that all RED studies have been disregarded by the reviewers.

Despite the recommendation in the UK ADHD algorithm[100] the European guidelines state that: "there is not yet enough scientific evidence to establish guidelines for dietary approach, more research is needed".[13] More amazing still is the guidelines' advice that a diary approach is considered applicable if parents suspect that foods affect their child's behaviour, to investigate whether a link exists between behaviour and food intake.[13,15] This recommendation appears to be consensus based rather than evidence based, because no scientific evidence exists for a relationship between keeping a diary and finding foods that may cause ADHD. Concluding, despite convincing evidence for the effects of an RED in subgroups of children with ADHD, the current ADHD therapy does not comprise an RED.

1.11. Aim and structure of this thesis

This thesis comprises two main aims. First, the relationship between ADHD and food and the relationship between psychiatric and/or physical comorbid disorders and food is examined, in heterogeneous groups of young children with ADHD, using an individually constructed RED. The hypothesis is tested that a restricted elimination diet may have a beneficial effect on both the behavioural problems and the somatic complaints in an unselected group of children with ADHD. Second, two possible mechanisms of action in which food may exert its effects are investigated, i.e. a direct immunological mechanism and an indirect mechanism, affecting family structure. The hypotheses are tested that 1) an immunological mechanism is involved in food-induced ADHD, and 2) the effects of an RED may be mediated by changes in family environment. Consequently, the thesis is divided in two parts corresponding with the main aims.

1.11.1. Part 1:
the effect of an RED on ADHD, ODD and comorbid complaints

Most previously performed studies applying an RED focussed on selected subgroups, e.g. the participants were recruited via diet or allergy clinics. In Chapter 2, a pilot study is described investigating the effects of an RED on ADHD, ODD and physical complaints in a group of children not selected for atopic constitution or diet affinity. Only children familiar with risk factors for ADHD, e.g. prematurity, dysmaturity, alcohol use during pregnancy or foster placing, were excluded. This study focuses on the question whether nutrition can be regarded as a potential ADHD risk factor in a heterogeneous group of children and whether it is recommendable to execute a follow up study with a randomised controlled design. Chapter 3 describes the follow up study, a randomised controlled trial (RCT) executed in a comparable heterogeneous group of children with ADHD and comorbid complaints. The aim was to investigate whether the results of the previous open study could be replicated in a randomised controlled design. In Chapter 4 the RED results on sleep problems and physical complaints are investigated, in the group of children described in Chapter 3.

1.11.2. Part 2:
the potential working mechanisms of an RED on ADHD and ODD

In Chapter 5, based on the results of all previous RED studies in children with ADHD, showing evidence of efficacy on both psychiatric and physical conditions, the hypothesis is postulated that ADHD, like asthma and eczema, might be considered a (non-)allergic hypersensitivity disorder. Based on definitions of allergic conditions this hypothesis is explained and motivated. Chapter 6 describes the Impact of Nutrition on Children with ADHD (INCA) study. In this pragmatic study, using a randomised controlled design with blinded measurements by a paediatrician, the effects of the RED are investigated in an unselected group of children with ADHD. Contrary to the studies described in Chapters 2 and 3, children familiar with risk factors for ADHD are not excluded, in order to determine how generally applicable this RED treatment will be within a general group of young children with ADHD. Furthermore, it is investigated whether an immunological mechanism may be involved, using IgE and IgG blood tests. The results of the blood tests may provide additional information about the mechanisms of foods in children with ADHD, may enable us to segregate between non-allergic

or allergic mechanisms in food-induced ADHD and may eventually facilitate the RED procedure. Finally, in Chapter 7 another possible mechanism in which food may exert its effects is explored, i.e. a change in family structure and family environment. It is conceivable that behavioural improvements after following an RED may also be mediated by changes in family environment due to the strict scheme the family has to follow during the RED. This study aimed to investigate whether changes in family environment may contribute to the positive behavioural effects of an RED in children with ADHD, in a subsample of the INCA study.

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Chapter 2

Favourable effects of an elimination diet on the behaviour of young children with ADHD: an exploratory study

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Pelsser, L.M.J. & Buitelaar, J.K.

Gunstige invloed van een standaardeliminatiedieet op het gedrag van jonge kinderen met aandachtstekort-hyperactiviteitsstoornis (ADHD), een verkennend onderzoek.

Nederlands Tijdschrift voor Geneeskunde 2002;146:2543-47 (in Dutch).

Abstract

Objective. To determine whether a standard elimination diet can decrease ADHD symptoms in a heterogeneous group of young children with ADHD.
Design. Open, descriptive.
Method. 40 children, 36 boys and 4 girl, aged 3-7 (average 4.8 years), who met the DSM-IV criteria for ADHD, followed their usual diet for 2 weeks (the baseline period) and thereafter a 2-week elimination diet, based on the few foods diet (rice, turkey, pear and vegetables). The behaviour of the child was evaluated at study entry, at the end of the baseline period and at the end of the diet by means of three measurements: the abbreviated Conners' scale, the ADHD Rating Scale and a physical complaints questionnaire. Teachers completed the abbreviated Conners' scale and the ADHD Rating Scale twice, at start and at the end of the diet.
Results. According to the parent ratings, 25 children (62%) showed at the end of the elimination diet an improvement in behaviour of at least 50% on both the Conners' scale and the ADHD Rating Scale. Nine children (23%) withdrew from the study because the parents were unable to stick to the diet or because the child fell ill. Ten of 15 children with both parent and teacher ratings responded at home as well as at school.
Conclusion. In young children with ADHD an elimination diet can lead to a statistically significant decrease in symptoms.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common child psychiatric disorder, characterized by hyperactive behaviour, impulsivity and inattention [1]. Genetic factors play an important part in the development of ADHD. Besides genetic factors, pre- and postnatal environmental risk factors may be involved in the development of the disorder [2].

In the seventies of the previous century, the relationship between food colourings and behaviour has been thoroughly investigated, and no significant effect of food additives on ADHD was found [3-5]. The hypothesis that any food component may cause behavioural problems led to research into the effect of a diet consisting of hypo-allergenic foods, such as rice, turkey, vegetables and pear, i.e. the few foods diet. In double-blind, placebo controlled research, approximately 70% of the participants responded to this diet with statistically significant behavioural improvements [6-9]. However, the participating children were children with an atopic constitution or were selected via diet clinics.

The objective of this pilot study was to establish the effects of a standard elimination diet on ADHD symptoms in a heterogeneous and non-selected group of young children with ADHD. The hypothesis was tested that in young children with ADHD, an elimination diet leads to a decrease of symptoms of at least 50% on the abbreviated Conners' scale (ACS) [10] and on the ADHD rating scale (ARS) [11].

Subjects and methods

Subjects

Children were recruited through media announcements or were referred by child psychiatrists. Children were included if (1) they met the DSM-IV ADHD criteria [12], (2) they were between 3 and 7 years old, and (3) they did not use psychotropic medication. Children were excluded if any biological environmental factors that can contribute to the development of ADHD, such as prematurity of the child or alcohol abuse by the mother during pregnancy, were reported [13].

Forty children were enrolled in the trial: 36 boys and 4 girls, aged 3-7 (average: 4.8). Eleven out of 40 children were clinically diagnosed with ADHD prior to study

entry. In all children the diagnosis was confirmed by means of a structured child psychiatric interview (SPI) [14]. Thirty-six children met the criteria for ADHD combined subtype, 4 children met the criteria for ADHD hyperactive impulsive subtype, and 31 children also met the criteria for Oppositional Defiant Disorder (ODD). In 24 children an atopic constitution was reported, whereby the existence of a clinically manifested allergy in at least one first grade relative (a parent or sibling) was used as a criterion. All parents gave informed consent.

End points

The most important end point was the score on the ACS [10]. This questionnaire has been frequently used in ADHD treatment research and consists of 10 questions, concerning the core symptoms restlessness, impulsivity and inattention, using a four-point rating scale. The total score may range between 0 and 30. The ACS was completed by the parents at study entry, at the end of the baseline period and at the end of the elimination diet (**table 1**).

The second end point was the score on the ARS [11]. This questionnaire consists of the 9 DSM-IV-items regarding inattention and the 9 DSM-IV-items regarding impulsivity and hyperactivity, each marked out on a four-point rating scale. The parents completed the ARS in accordance with the ACS, the teachers completed both questionnaires at start and the end of the diet period.

The third questionnaire concerned comorbid physical complaints of the child. An inventory was made of physical complaints in the past year, such as gastro-intestinal problems, headache, stomach-ache, eczema, asthma, excessive perspiration and sleeping problems [15]. Each question was to be answered with ‘no’, ‘sometimes’, or ‘often’. There were two measurement moments: at start and end of the trial. The questionnaire was completed by the parents only.

Finally, the SPI was repeated at the end of the elimination diet in order to establish whether or not the children still met the criteria for ADHD and ODD.

Procedure and intervention

At start the SPI was used to verify the child’s behavioural problems, i.e. ADHD with or without ODD. Three questionnaires were completed by the parents, after which the child started a 2-week baseline period in which no foods were to be eliminated. The parents kept an extended food and behaviour diary and had to observe the child closely. At the end of the baseline period the ACS and ARS were

completed for the second time. Subsequently, the children started the 2-week elimination diet. The elimination diet was based on the 'few foods' diet, consisting of rice, turkey, pear, vegetables and water [8, 16]. In order to create a more comprehensive and more feasible diet, the few foods diet was complemented wit specific foods, such as corn, apple, wheat and honey, which were allowed according to a strict schedule. All children followed the same diet, and parents kept an extensive diary during the elimination diet.

Statistical analysis

The parent questionnaires which were completed at the end of the baseline period and at the end of the elimination diet were compared using a paired t-test. The teacher questionnaires were compared using the Wilcoxon test because of the smaller numbers. The binary end points (number of responders and nonresponders and children with or without an atopic constitution) were compared using Fisher's exact test. A participant was defined a responder if the behavioural improvement was at least 50%, at both the ACS and the ARS. The statistical analyses were done with SPSS (version 9.0 for Windows).

Table 1 Time table and questionnaire moments

Questionnaires	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Physical complaints		x					x
ARS parents		x		x			x
ARS teacher				x			x
ACS parents		x		x			x
ACS teacher				x			x
SPI	x						x
		Baseline period			Elimination diet		

ARS = ADHD rating scale
ACS = abbreviated Conners' scale;
SPI = Structured Psychiatric Interview

Results

Nine of 40 children (23%) who started the trial withdrew prematurely from the study: 3 children withdrew before the start of the trial because their parents lacked the motivation to start a diet; 3 children withdrew in course of the study due to illness of the child or lack of motivation of the child; and 3 children left the trial during the elimination diet period. Thirty-one children completed the study. Teacher data were available of 15/31 children, teacher data were missing due to holidays or because the child was younger than 4 years old.

ADHD symptoms

The parents' (n = 31; **table 2**) and teacher's (n = 15; **table 3**) ACS and ARS scores were significantly lower at measurement point 3 (end of elimination diet period) when compared to measurement point 2 (end of baseline period). The improvements concerned both inattentive and hyperactive-impulsive symptoms. At the end of the study 4/31 children still met the criteria for ADHD ($p<0.0001$). According to the parent measurements 25 children belonged to the responders, i.e. 62% of all 40 children and 81% of 31 children who completed the study. Fifteen of 40 children (38%) belonged to the nonresponders: 9/40 were dropouts and 6/40 completed the diet but did not respond favourably. According to the teacher data 10/15 children were responders at home as well as at school; 1/15 child responded at home but not at school, 4/15 children were nonresponders both at home and at school.

ODD symptoms

A significant decrease of ODD symptoms was observed at the end of the elimination diet (see **table 2**). At the start of the trial 26/31 children met the ODD criteria and 2/26 children still met the ODD criteria at the end of the diet ($p<0.0001$): 21/26 were responders (81%), showing behavioural improvements of at least 50%.

Physical complaints

At the start of the trial 20/31 children suffered from 3 or more physical complaints, such as stomach-ache, headache, unusual thirst and/or excessive perspiration, diarrhoea, eczema or asthma. At the end of the elimination diet all 20 children showed a significant decrease in physical complaints (**table 4**). In 13 children,

9 responders and 4 nonresponders, the physical complaints had disappeared completely. The number of children with an atopic constitution did not differ between the responders (13/25) and nonresponders [4/6, (p = 0.43)].

Table 2 Parent measurements (n=31); average symptom scores on the abbreviated Conners' scale (ACS), the ADHD rating scale (ARS), and the number of ADHD and oppositional defiant disorder (ODD) criteria

	start trial	end baseline diet	end elimination diet	95%-CI
	mean (SD)	mean (SD)	mean (SD)	
ACS	24.13 (3.29)	25.35 (2.42)	8.84 (5.98)	14.28-18.75*
ARS inattention	19.10 (4.25)	20.58 (4.21)	7.81 (5.53)	10.36-15.19*
ARS hyperactivity/ impulsivity	22.42 (3.65)	23.35 (2.39)	8.42 (5.95)	12.86-17.01*
ARS total score	41.52 (6.60)	43.61 (5.12)	16.23 (11.04)	23.18-31.59*
ADHD	15.03 (2.27)	-	3.49 (4.75)	9.74-13.42†
ODD	6 (1.4)	-	1.3 (1.8)	3.86-5.60†

*p = 0.0001 (difference end baseline diet vs end elimination diet, paired t-test);
†p = 0.0001 (difference number of criteria start trial *vs* end elimination diet, Wilcoxon test)

Table 3 Teacher measurements (n=15); average symptom scores on the abbreviated Conners' scale (ACS) and the ADHD rating scale (ARS)

	end baseline diet	end elimination diet	95%-CI	p*
	mean (SD)	mean (SD)		
ACS	18.13 (3.60)	10.27 (4.57)	5.94-9.79	0.001
ARS inattention	13.27 (5.26)	8.40 (5.53)	2.39-7.34	0.007
ARS hyperactivity/impulsivity	16.73 (4.79)	9.80 (5.45)	4.18-9.68	0.001
ARS total score	30.00 (7.16)	18.20 (9.56)	7.40-16.20	0.001

*p-value Wilcoxon Test

Table 4 Physical complaints* at start trial and end elimination diet, in diet responders and diet nonresponders

number of physical complaints	responders (n = 25)		nonresponders (n = 6)	
	start trial	end diet	start trial	end diet
	n (%)	n (%)	n (%)	n (%)
3 or more	20 (80)	0 (0)	0 (0)	0 (0)
1-2	5 (20)	16 (64)	5 (83)	2 (34)
0	0 (0)	9 (36)	1 (17)	4 (66)

*Gastro-intestinal problems, headache, stomach ache, eczema, asthma and excessive perspiration

Discussion

This open pilot study showed that an elimination diet may affect behavioural problems of young children with ADHD in a favourable way. The number of responders was considerably, and in accordance with results of previous diet studies [6-9]. Still, the high number of responder might be due to the selection procedure, excluding children with known pre- and postnatal risk factors for ADHD. Furthermore, the high responder rate might be consequential of the strictness of the elimination diet; in another elimination diet study, allowing foods which may trigger ADHD behaviour [17], a response percentage of 24 was found [10].

At the start of the study 84% (26/31) of children also met the criteria for ODD. Children with comorbid ODD have a worse prognosis compared to children without ODD [18, 19]. In this study the elimination diet showed a favourable effect on both ADHD and ODD symptoms.

Children were not selected for affinity with dietary intervention, atopic background or allergies. According to previous studies, atopic children with ADHD might [9] or might not [20] respond to an elimination diet. In this study no association was found between an atopic constitution and response to the diet. Furthermore, although the participants were not selected for physical complaints, these complaints occurred frequently. As children suffering from physical

symptoms tend to respond less to medication [21], an elimination diet might be especially worth trying in these children.

An important limitation of this study is the open design, without a control group and with open measurements. Still, the teacher's observations confirmed the observations by the parents, and previous studies have shown that parental observations could be confirmed in a double-blind placebo controlled design, with objective tests [22]. In fact, hypo-allergenic diets have already provided convincing, double-blind placebo controlled evidence as a treatment of ADHD in selected subgroups of children with ADHD [23].

The mechanism of food in children with ADHD is not clear yet. It is hypothesised that the increase of atopic disorders may be due to a more general hypersensitivity of man to foods [24]. Allergic, pharmacological or toxic mechanisms may be involved in ADHD, i.e. an immunologic mechanism of food [16], or a direct mechanism of food components targeting the neurotransmitter system in the brain [25]. Laboratory studies have shown that certain additives, such as erythrosine, may affect the neurotransmitters release in the brain [26].

The results of this exploratory study elucidate the need for further controlled studies into the effect of an elimination diet on ADHD and into the long-term effect of foods. Furthermore, it is advised to investigate whether an elimination diet may cause nutrient deficiencies. Additionally, although children may show statistically significant improvements in behaviour following an elimination diet, it is important to emphasize that the diet does not eliminate the underlying vulnerability to food, i.e. commensurable to medication treatment a diet is not a cure of ADHD [13]. The diet has some advantages: the duration of action of an elimination diet is 24 hours a day and the diet reduces comorbid ODD and physical complaints. However, when children do not stick to the dietary restrictions, the symptoms will return, and high levels of motivation and perseverance of parents and children are required in order to see a diet intervention through.

Considering that a diet may play a role in prevention of ADHD, follow-up studies might focus on young children again [19]. In young children, with less freedom of movement, the compliance to the elimination diet is easier to control and the impact of the diet on their social activities will be less intrusive. The extent of the effects of an elimination diet on ADHD are not quit clear yet, and the diet demands a lot from parents and children. Therefore, as yet caution is advised in the application of the elimination diet in practice.

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Chapter 3

A randomised controlled trial into the effects of food on ADHD

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Pelsser LM, Frankena K, Toorman J, Savelkoul HF, Pereira RR, Buitelaar JK.

A randomised controlled trial into the effects of food on ADHD.

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Abstract

The aim of this study is to assess the efficacy of a restricted elimination diet in reducing symptoms in an unselected group of children with Attention deficit/ hyperactivity disorder (ADHD). Dietary studies have already shown evidence of efficacy in selected subgroups.

Twenty-seven children (mean age 6.2) who all met the DSM-IV criteria for ADHD, were assigned randomly to either an intervention group (15/27) or a waiting-list control group (12/27). Primary endpoint was the clinical response, i.e. a decrease in the symptom scores by 50% or more, at week 9 based on parent and teacher ratings on the abbreviated ten-item Conners Scale and the ADHD DSM- IV Rating Scale.

The intention-to-treat analysis showed that the number of clinical responders in the intervention group was significantly larger than that in the control group [parent ratings 11/ 15 (73%) versus 0/12 (0%); teacher ratings, 7/10 (70%) versus 0/7 (0%)]. The Number of ADHD criteria on the ADHD Rating Scale showed an effect size of 2.1 (Cohen's *d*) and a scale reduction of 69.4%. Comorbid symptoms of oppositional defiant disorder also showed a significantly greater decrease in the intervention group than it did in the control group (Cohen's *d* 1.1, scale reduction 45.3%).

A strictly supervised elimination diet may be a valuable instrument in testing young children with ADHD on whether dietary factors may contribute to the manifestation of the disorder and may have a beneficial effect on the children's behaviour.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common behavioural disorders in childhood, with symptoms often persisting across adolescence into adulthood [16]. Long-term risk outcomes of children with ADHD include underachievement at school and antisocial personality disorder, delinquency and substance abuse, marital breakdown and unemployment at adult life [19].

ADHD is a multifactorial disorder in which genetic risk factors predominate and various other environmental factors may be involved [5, 32]. The exact aetiological pathways of ADHD, however, are still unknown [22, 31]. According to current professional guidelines, medication and psychosocial interventions are the methods of treatment mostly recommended and most frequently used [12, 18, 31]. According an expert opinion, it is important to avoid overreliance on currently available pharmacological approaches, suggesting that, among others, more research on dietary effects is essential [29].

There is evidence for the effectiveness of an individually constructed elimination diet, the ''few foods'' approach [15]. Dietary studies using a few foods diet, i.e. a restricted elimination diet consisting of a limited number of foods [7, 8, 14, 17, 25, 26], have shown evidence of efficacy in subgroups selected for history of food sensitivity or atopic constitution [2]. A Dutch open pilot study in which 40 children with ADHD followed a few foods diet [23], resulted in a reduction of at least 50% in the symptom scores on rating scales completed by parents and teachers in 62% of the subjects. The present randomised controlled trial study was designed to assess the efficacy of a few foods diet in a group of ADHD children unselected for affinity with dietary interventions or the presence of physical problems. This study has been registered as an International Standard Randomised Controlled Trial, number ISRCTN47247160.

Methods

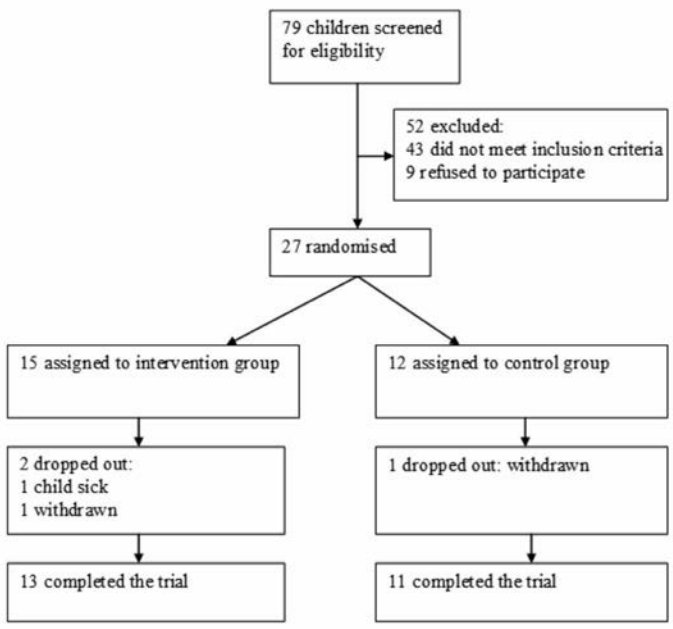
Study population

Participants were selected from a consecutive series of 79 Dutch children who were referred to the ADHD Research Centre between January and June 2006. Of

these children, 27 were enrolled in the trial (**figure 1**). They were between 3.8 and 8.5 years old and they all met the criteria as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for ADHD Combined Type or Predominantly Hyperactive-Impulsive Type [1]. The following exclusion criteria were used: adopted or foster children, co-existing neurological diseases, an IQ below 70, prematurity or dysmaturity, use of alcohol, or smoking by mother during pregnancy [31], and co-existence of other psychiatric disorders, except for oppositional defiant disorder (ODD) and conduct disorder (CD). The screening involved a systematic and complete review of the symptoms and diagnostic criteria of all DSM-IV axis I disorders occurring in childhood. None of the children used psychotropic medication.

Parents were given verbal and written information about the study, and duly signed informed parental consent forms were obtained before randomisation. Children who were already on a diet had to cease this diet at least 2 weeks before the start of the trial.

Figure 1 Trial profile



Design and procedures

The efficacy of an elimination diet in children with ADHD was tested by comparing outcomes in the children randomly assigned to the intervention group to the outcomes in those assigned to the waiting-list (control) group. Subjects were randomly allocated to one of the two groups by means of a sequence of numbered cards in sealed unmarked envelopes that were prepared by an independent paediatrician. Each card contained a reference to the group to which the child would be allocated, and for each allocation an equal number of cards [21] was used. The envelopes were picked and opened by the parents in the presence of the researcher, and treatment was then dispensed in accordance to the allocation on the card.

There were three measurement points: at study entrance (week 0), after the baseline diet (week 3) and after the elimination diet or waiting period (week 9). An overview of the time schedule regarding measure points and rating scales is presented in **table 1**.

Table 1 Time table

	Measure points	Rating scales parents	Rating scales teacher	Intervention group	Control group
Week 1	1 Entrance trial	ACS-1, ARS-1		Start of baseline diet	
Week 2				Baseline diet	
Week 3	2 After baseline	ACS-2, ARS-2, SPI	ACS-2, ARS-2	Baseline diet ends Elimination diet starts	Baseline diet ends Waiting list starts
Week 4-9				Elimination diet	Waiting list
Week 9	3 At endpoint	ACS-3, ARS-3, SPI	ACS-3, ARS-3	Elimination diet ends	Waiting list ends Elimination diet starts (if desired)

ACS: Abbreviated Conners Scale; ARS: ADHD Rating Scale; SPI: Structured Psychiatric Interview

After the first assessments all children started with a 2-week baseline diet in which they adhered to their normal diet, no foods were eliminated. During the

baseline diet the parents kept an extended diary in order to enable an assessment of the child's normal diet, its behaviour and activities. After the baseline diet and the second assessment, the intervention group started with an individually composed elimination diet [15], which had to be followed for a period of 5 weeks. The elimination diet consisted of rice, turkey, lamb, vegetables, fruits, margarine, vegetable oil, tea, pear juice and water [8, 23]. The control group was placed on a waiting list and continued their own, freely chosen diet. At the start of the trial the parents of the control group were informed that they could start with the elimination diet immediately after the last assessment if they so wished.

Primary endpoints were the parent and teacher ratings on the Abbreviated ten-item Conners Scale (ACS) and the ADHD Rating Scale (ARS) before and after the elimination diet or the waiting period. The ACS [9], has often been used in ADHD treatment studies [7, 8, 14, 23, 25]. It consists of ten items of behaviour, focusing on overactivity, impulsivity and inattention, and uses a four-point rating scale (0 never, 1 sometimes, 2 often, 3 always). The ARS is a frequently used rating scale based on the DSM-IV criteria for ADHD [21, 29]. The scores are divided in three parts: the Number of ADHD criteria (18 in all), the nine items regarding inattention and the nine items regarding impulsivity and hyperactivity, the latter both marked out on a four-point rating scale [13].

Secondary endpoints were parent ratings on ODD symptoms measured by a structured psychiatric interview (SPI) based on the DSM-IV criteria for ODD. The parents and teachers who filled in the questionnaires could not be blinded as they had to supervise the food intake of the child and knew whether the child was following an elimination diet.

Statistical analysis

SPSS version 9.0 was used for all statistical analyses. Data was analysed on an intention-to-treat basis, with last observations carried forward in cases of missing data. Descriptive parameters for indicating effect size were % scale reduction and Cohen's *d*. Effects were tested at $P < 0.05$; all testing was two-tailed. Subjects were defined as showing clinically significant improvement (responders) if the difference between measure point 3 (after the elimination diet) and measure point 2 (after the baseline diet) was 50% or more on both the ACS and the ARS. Data was analysed by Student's *t* test and Fisher's exact test.

Results

In sum 79 children were screened for eligibility, 43 of these failed to meet the inclusion criteria, and 9 refused to participate. As a result 27 children entered the study and were randomised to the intervention group [15] or the control group [12]. The descriptive characteristics of the subjects enrolled are presented in **table 2**. Of the 27 children, 3 (11%) were lost to follow up: one child assigned to the control group withdrew after randomisation, whilst two children assigned to the intervention group dropped out, one because of illness, the other because the parents lacked motivation to stick to the diet (see **figure 1**). For 17 of the 27 children, teacher data was available, in the other cases school contact at both Baseline and Endpoint rating was not possible due to holidays or teacher's illness.

Table 2 Descriptive characteristics of study participants at time of inclusion

	Intervention group N (%)		Control group N (%)	
Number of participants	15		12	
Boys	12/15	(80.0%)	10/12	(83.3%)
Age (mean, (SD))	6.3	(1.6)	6.1	(1.7)
ADHD combined type	10/15	(66.7%)	8/12	(66.7%)
ADHD predominantly hyperactive-impulsive type	5/15	(33.3%)	4/12	(33.3%)
Co-morbid ODD	12/15	(80.0%)	10/12	(83.3%)
On dietary restriction	0/15	(0%)	1/12	(8.3%)

Primary outcomes

Table 3 shows the parent ratings on the ACS, ARS and the SPI for both the intervention group and the control group (1) at the start of the trial, (2) after the baseline diet, and (3) at the end of the trial. The mean scores at the start of the trial and after the baseline diet was greater than 22.7 points (ACS) and 13.7 points (ARS Number of ADHD criteria, 18 at the most) in both the intervention and the control groups. There was no significant difference in the scores of both measurement points. At the end of the trial the mean scores in the intervention group showed a 62.6% improvement on the ACS and a 70.3% improvement on

Table 3 Parent ratings, last observation carried forward, at entrance of the trial (Start), after baseline (Base), and at endpoint (End)

	Intervention group					Control group					Control group versus intervention group, End rating	
	N=15					N=12					N=27	
	Start	Base	End	difference (95% CI Base-End)	p * (% SR)	Start	Base	End	difference (95% CI Base-End)	p * (% SR)	mean difference (95% CI)	p * (%SR)
	mean (SD)					Mean (SD)						
ACS	23.7 (3.7)	22.7 (4.1)	8.5 (7.5)	14.2 (9.7-18.7)	<.001 *2.3 (62.6)	24.9 (4.5)	24.9 (4.2)	26.0 (4.6)	-1.1 (-2.4-0.2)	<0.09 *-0.2 (-4.4)	17.6 (12.5-22.6)	<.001 *2.8 (67.3)
ARS Number of ADHD criteria	14.3 (1.9)	13.8 (2.3)	4.1 (4.8)	9.7 (6.8-12.6)	<.001 *2.6 (70.3)	13.7 (2.0)	13.7 (3.5)	13.4 (3.9)	0.3 (-0.4-0.9)	<0.43 *0.1 (2.2)	9.4 (5.9-12.8)	<.001 *2.1 (69.4)
ARS 9 items inattention	19.9 (4.5)	18.7 (4.8)	6.5 (5.7)	12.1 (8.0-16.3)	<.001 *3.2 (65.2)	18.6 (4.5)	17.6 (6.1)	18.3 (5.3)	-0.8 (-1.7-0.2)	<0.10 *-0.1 (-4.0)	11.8 (7.4-16.2)	<.001 *2.3 (64.5)
ARS 9 items hyperactivity/ impulsivity	23.2 (1.4)	20.8 (2.7)	8.7 (6.8)	12.1 (8.2-15.9)	<.001 *2.3 (58.2)	23.2 (3.0)	22.4 (4.5)	22.8 (5.6)	-0.4 (-1.6-0.8)	<0.46 *-0.1 (-1.8)	14.1 (9.1-19.1)	<.001 *2.3 (61.8)
SPI ODD-criteria [a]		6.5 (1.2)	2.9 (2.7)	3.6 (1.7-5.4)	<.001 *1.7 (55.4)		5.4 (1.3)	5.3 (1.3)	0.1 (-0.9-1.1)	<0.83 *0.1 (1.9)	2.4 (0.4-4.3)	<.02 *1.1 (45.3)

SR = Scale Reduction; [a] ODD: N=12 in intervention group, N=10 in control group; * Effect size Base-End, Cohen's *d*

the ARS Number of ADHD criteria ($P < 0.001$). In the waiting-list group the scores increased by 4.4% (ACS) and decreased by 2.2% (ARS Number of ADHD criteria). Children in the intervention group showed a significantly greater decrease in behaviour problems than children in the control group, with a treatment effect—i.e. the difference in improvement between the intervention and control group—of 17.6 (95% Confidence Interval (CI) 12.5–22.6, $P < 0.001$, Student's *t* test) on the ACS and 9.4 (95% CI 5.9–12.8, $P < 0.001$) on the ARS Number of ADHD criteria. The treatment effect on the ARS included both inattention symptoms (mean difference 11.8, $P < 0.001$) and hyperactivity/impulsivity symptoms (mean difference 14.1, $P < 0.001$). The effect size (Cohen's *d*) was 2.8 (67.3% scale reduction) on the ACS and 2.1 (69.4% scale reduction) on the ARS Number of ADHD criteria. According to the parent ratings 11/13 children (85%) in the intervention group who completed the study showed an improvement of 50% or more, (mean difference on the Number of ADHD criteria 11.2 (95% CI 9.0–13.5, $P < 0.001$). None of the children in the control group (0/11) showed an improvement of 50% or more (mean difference on the Number of ADHD criteria 0.3 (95% CI -0.4 to 0.9, $P < 0.43$).

Table 4 shows the teacher ratings on the ACS and the ARS for both the intervention group and the control group (1) after the baseline diet, and (2) at the end of the trial. The parents' conclusions in **table 3** were confirmed by the teachers. The treatment effect was 13.3 on the ACS (95% CI 7.5–19.1, $P < 0.001$) and 8.4 on the ARS Number of ADHD criteria (95% CI 4.8–11.9, $P < 0.001$), including both inattention symptoms (mean difference 8.3, $P < 0.011$) and hyperactivity/impulsivity symptoms (mean difference 12.8, $P < 0.002$). The effect size (Cohen's *d*) was 2.4 (64.3% scale reduction) on the ACS and 2.5 (70.6% scale reduction) on the ARS Number of ADHD criteria.

According to the parent ratings, 11 out of the 15 children in the intervention group (73%) could be classified as responders, defined as showing behavioural improvement of at least 50% on both the ACS and the ARS. All responders did not meet the DSM-IV criteria for ADHD anymore. In the control group, none of the 12 children (0%) were classified as responders (two-tailed Fisher's exact test, $P < 0.001$). According to the teacher ratings ($N = 17$) 7/10 children in the intervention group were responders (70%), versus 0/7 children (0%) in the control group (two-tailed Fisher's exact test, $P < 0.01$).

Table 4 Teacher ratings after baseline (Base) and at endpoint (End)

	Intervention group N=10				Control group N=7				Control group versus intervention group End rating	
	Base	End	Base-End		Base	End	Base-End			
	mean (SD)		difference (95% CI)	p * (% SR)	mean (SD)		difference (95% CI)	p * (% SR)	mean difference (95% CI)	p * (% SR)
ACS	19.1 (5.6)	7.4 (5.3)	11.7 (8.0-15.4)	<.001 *2.1 (61.3)	21.1 (6.7)	20.7 (5.9)	0.4 (-1.9-2.8)	<0.667 *0.1 (1.9)	13.3 (7.5-19.1)	< .001 *2.4 (64.3)
ARS Number of ADHD criteria	12.0 (2.9)	3.5 (3.4)	8.5 (6.4-10.7)	<.001 *2.7 (70.8)	10.9 (4.3)	11.9 (3.3)	-1.0 (-3.2-1.2)	<0.309 *-0.3 (-9.2)	8.4 (4.8-11.9)	<.001 *2.5 (70.6)
ARS 9 items inattention	16.4 (7.4)	7.0 (6.1)	9.4 (5.9-12.9)	<.001 *1.4 (57.3)	13.6 (6.8)	15.3 (4.3)	-1.7 (-6.2-2.8)	<0.389 *-0.3 (-12.5)	8.3 (2.6-14.0)	<.011 *1.6 (54.2)
ARS 9 items hyperactivity/ impulsivity	20.1 (5.3)	7.3 (4.8)	12.8 (8.6-17.0)	<.001 *2.5 (63.7)	20.6 (7.4)	20.1 (7.7)	0.4 (-1.3-2.2)	<0.573 *0.1 (2.4)	12.8 (6.4-19.3)	<.002 *2.0 (63.7)

* Effect size Base-End, Cohen's *d;* SR = Scale Reduction

Secondary outcomes

At the entrance of the trial, 12/15 children in the intervention group (80%) and 10/12 children in the control group (83%) met the DSM-IV criteria for ODD according to the SPI (see **table 3**). The mean number of ODD symptoms was 6.5 in the intervention group (the DSM-IV-diagnostic criteria for ODD are met if the child complies with four or more out of eight symptoms) and 5.4 in the control group. At the end of the trial, 4/15 children in the intervention group (27%) and 10/12 children in the control group (83%) still met the ODD-criteria, the mean number of ODD symptoms now being 2.9 in the intervention group and 5.3 in the control group. The difference between the measure points at the beginning and at the end of the trial was 3.6 (95% CI 1.7–5.4, $P < 0.001$) in the intervention group and 0.1 (95% CI -0.9 to 1.1, $P < 0.83$) in the control group, with a mean difference of 2.4 (95% CI 0.4–4.3, $P < 0.02$). The effect size (Cohen's *d*) was 1.1 (45.3% scale reduction).

Discussion

Our results show that a carefully supervised few foods diet in young children with ADHD, followed for 5 weeks at the most, can exhibit substantial changes in behaviour. Seventy percent of the children showed behavioural improvements of 50% or more according to the ratings of parents and teachers and did not meet the DSM-IV criteria for ADHD anymore. The results of this randomised controlled study do not differ from the results of equivalent studies [7, 8, 14, 17, 25, 26]. All controlled trials on ADHD and foods using a few foods diet show a more or less beneficial effect on the behaviour of the subjects. The extent of restriction of the elimination diet seems important and may affect the degree of the behavioural improvements: a diet including too many foods may reduce the number of responders [25]. Consequently, a diet excluding just one or a limited number of foods, like sugar or additives, would be of little benefit to children with ADHD [8, 10, 15]. Recent additive trials have shown that some degree of hyperactivity, when exposed to artificial food colours and benzoate preservatives, may be applied to all 3-year old children, not exclusively to hyperactive children [4, 20]. This might imply that there is a general adverse effect of additives or preservatives on the behaviour of all young children, with a small effect size (0.18).

As we wanted to investigate the influence of foods on ADHD, we excluded children with potentially predisposing environmental risk factors for ADHD, like prematurity, dysmaturity and foetal exposure to maternal alcohol or cigarettes [31]. Efforts were made to obtain an unbiased sample, the children were not preselected for affinity with dietary intervention.

At the entrance of the study, 22/27 children also met the criteria for ODD, 80% of the children in the intervention group and 83% of the children in the control group. Co-existence of ODD is very common in ADHD [31]. At the end of the trial, all children in the control group still met the criteria, but in the intervention group the number of children meeting the ODD-criteria had diminished by 66%. We expected the children in the intervention group to show deterioration of their ODD behaviour, opposing the dietary restrictions which they surely would not like.

It appears as if the elimination diet triggers a significant change in both ADHD symptoms and ODD symptoms. This is important, as ADHD-children with co-morbid ODD/CD are at risk for long-term maladjustment [3]. It is tempting to speculate that the appliance of an elimination diet in young children might reduce this risk.

Study limitations

This study is an open-label controlled trial, without placebo. The elimination diet used in this study was very restricted, only a few foods were allowed, thus making it impossible to compose a reliable placebo diet. The fact that even a small change in the diet of a child, like removing additives, may have a beneficial effect on the behaviour of children [4, 20], illustrates the difficulties of constructing a placebo diet. Parents and teachers were aware of the intervention, which is a limitation that needs to be acknowledged. Although open randomised controlled trials are commonly used when blinding is difficult [6, 11, 24, 27, 28, 30, 33, 34], we recommend replication of this trial with blinded measurements by an independent observer [6]. Also the incorporation in future studies of objective tests of attentional performance and executive functioning should be considered.

It is conceivable that the increased attention for the child during the elimination diet contributes to the behavioural improvements. In order to measure the effects of increased attention during this trial, all parents had to keep an extended diary during the baseline diet, having to watch their child carefully. The second assessment took place at the end of the baseline diet. There were no significant

differences between the scores at the entrance of the trial and after baseline. Still the placebo effects of expectation and intense caregiver involvement have to be considered.

The adherence to a restricted elimination diet can be considered as burdensome, dietary management is difficult and puts a considerable strain on the family [8], so this method will not be applicable to all children with ADHD. Still dietary investigation can be an option for some children, and parents who are interested should be offered the possibility to follow a few foods diet with their child, provided that a trained dietician is available to supervise the intervention [15]. If the diet has a beneficial effect on the behaviour, challenge tests with specific foods should be exhibited to identify the incriminated foods and to make the diet more manageable. Further research could focus on the follow up of dietary interventions in children with ADHD and on the feasibility of long-term dietary restrictions.

The mechanisms in which foods exerts its effects remain unclear. Toxic, pharmacological, or immunologic mechanisms could be involved and the physiological effects of different foods may vary [8]. More research on this topic is needed.

In conclusion, this study confirms the results of earlier studies [7, 8, 14, 17, 25, 26], that a strictly supervised and restricted elimination diet can affect the behaviour of some children with ADHD and may be a valuable instrument in testing young children with ADHD on whether dietary factors may contribute to the manifestation of the disorder.

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Chapter 4

Effects of food on physical and sleep complaints in children with ADHD: a randomised controlled pilot study

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Abstract

Attention deficit/hyperactivity disorder (ADHD), a common behavioural disorder in children, may be associated with comorbid physical and sleep complaints. Dietary intervention studies have shown convincing evidence of efficacy in reducing ADHD symptoms in children. In this pilot study, we investigated the effects of an elimination diet on physical and sleep complaints in children with ADHD.

A group of 27 children (3.8–8.5 years old), who all met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for ADHD, were assigned randomly to either a diet group (15/27) or a control group (12/27). The diet group followed a 5-week elimination diet; the control group adhered to their normal diet. Parents of both groups had to keep an extended diary and had to monitor the behaviour and the physical and sleep complaints of their child conscientiously. The primary endpoint was the clinical response, i.e. a decrease of physical and sleep complaints, at the end of the trial, based on parent ratings on a Physical Complaints Questionnaire.

The number of physical and sleep complaints was significantly decreased in the diet group compared to the control group ($p<0.001$), with a reduction in the diet group of 77% ($p<0.001$, effect size=2.0) and in the control group of 17% ($p=0.08$, effect size=0.2). Specific complaints that were significantly reduced were in three domains: headaches or bellyaches, unusual thirst or unusual perspiration, and sleep complaints. The reduction of complaints seemed to occur independently of the behavioural changes ($p=0.1$). However, the power of this comparison was low. A positive correlation existed between the reduction of physical and behavioural symptoms ($p<0.01$). The reduction did not differ between children with or without an atopic constitution ($p=0.7$).

An elimination diet may be an effective instrument to reduce physical complaints in children with ADHD, but more research is needed to determine the effects of food on (functional) somatic symptoms in children with and without ADHD. This trial was registered as an International Standard Randomised Controlled Trial, ISRCTN47247160.

Introduction

Attention deficit/hyperactivity disorder (ADHD) [1], one of the most common behavioural disorders in childhood, with symptoms of inattention, hyperactivity and impulsivity [18], often coexists with other problems, like oppositional defiant disorder, depression, anxiety, physical complaints (e.g. headache, eczema and diarrhoea) and sleep complaints [9–11, 13, 14, 16, 21, 22, 27, 29, 35, 39]. The exact aetiological pathways of ADHD are still unknown: genetic risk factors including multiple genes (some of which are involved in the regulation of the immune system [30]) and environmental factors are involved.

To date, pharmacotherapy, combined with behavioural management, is the most effective treatment of ADHD [20]. Despite initial symptom improvement during this treatment, the follow-up study of the Multimodal Treatment Study of children with combined-type ADHD [24] showed that these children exhibit significant impairment in adolescence, implicating that innovative treatment approaches are needed [24]. Moreover, as treatment with psychostimulants like methylphenidate, with a duration of action of between 3 and 12 h [39], neither leads to resolve the behavioural problems in the early morning and in the evening nor resolves the comorbid physical complaints, it is worthwhile to investigate other treatments of ADHD and their effects on comorbid complaints.

One of these alternative treatment methods for ADHD may be an elimination diet. The effects of an elimination diet on ADHD have been investigated in several controlled studies [5, 9, 13, 22, 31, 34, 36], showing a significant effect of a restricted elimination diet on symptoms of ADHD and establishing that there clearly is a diet behaviour connection [2, 6]. Considering the comorbidity between ADHD and physical complaints (in one study, 20 out of 31 children with ADHD were reported to have at least two physical complaints [29]), one may speculate about a connection between food, ADHD and physical complaints. Given that (1) an elimination diet can significantly reduce ADHD symptoms [5, 9, 13, 22, 31, 34, 36], (2) the vast majority of children with ADHD suffers from co-occurring physical complaints [9, 13, 22, 29], (3) children with ADHD and extensive physical problems tend to respond less favourably to medication [3], (4) medication treatment does not solve the physical complaints or even causes some of these complaints [39] and (5) that a diet can have a positive effect on physical complaints in children and adults without ADHD [4, 41], it is timely to study the potentially beneficial

effects an elimination diet may have on physical and sleep complaints in children with ADHD.

In four previous studies, the effect of an elimination diet on comorbid physical symptoms in children with ADHD has already been investigated, resulting both in a reduction of the behavioural as well as of the physical complaints [9, 13, 22, 29]. Most of the children participating in these studies were diagnosed with allergy or had an atopic constitution (being defined as having at least one parent or sibling with an allergic disease like asthma, eczema, hay fever or allergic rhinitis), thus limiting the extrapolation of findings to children with ADHD without allergies or an atopic constitution. Another limitation of these previous studies is that they did not report on whether or not the improvement of physical complaints coincided with improvements in ADHD symptoms. It is important for clinical health care, i.e. to predict the effects of an elimination diet, and for scientific reasons, i.e. to increase our knowledge about the aetiology of ADHD and physical complaints, to investigate whether reduction in ADHD symptoms and physical complaints go hand in hand when applying an elimination diet.

The current study aimed to examine these issues. We previously reported that an elimination diet had a statistically significant and clinically relevant effect on ADHD symptoms as reported by both parents and teachers, with effect sizes of 2.1 and 2.5, respectively [31]. The results on the endpoints concerning physical and sleep complaints will be presented in this paper. More specifically, we aimed to (1) examine whether physical and sleep complaints in children with ADHD could be diminished using an elimination diet, (2) investigate whether the effect of an elimination diet on physical and sleep complaints was limited to those children who clearly showed behavioural improvements to the elimination diet, and (3) investigate whether the effect of an elimination diet on physical and sleep complaints was restricted to children with an atopic constitution.

Subjects and methods

Subjects

Participants were selected from a sample of 79 Dutch children who were referred to the Dutch ADHD Research Centre in Eindhoven, specialised in scientific research on food and ADHD. Children were included if (1) they were between 3

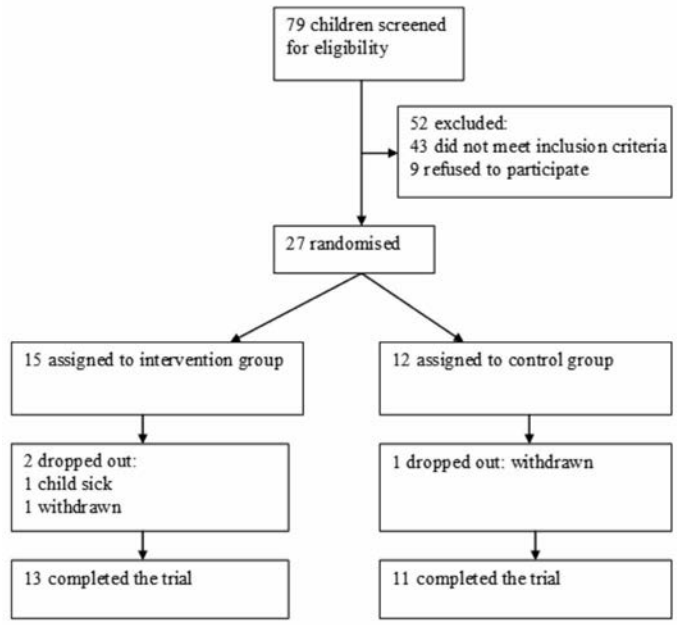
and 8 years old; (2) they met the criteria for ADHD, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition for ADHD Combined Type or Predominantly Hyperactive-Impulsive Type [1]; (3) their behavioural problems were present before the age of 4 or (4) they were medication naïve. Children were excluded if (1) they were diagnosed with Autism Spectrum Disorder or with ADHD Predominantly Inattentive Type [28], (2) they were pre- or dysmature at birth [30, 40] or (3) the mother had been smoking during pregnancy. A total of 43 children of the 79 failed to meet the criteria, and nine refused to participate. As a result, 27 children entered the study between January and July 2006 and were randomly allocated to the diet group (15) or the control group (12), see **figure 1**. Twenty-four children, 13 in the diet group and 11 in the control group, completed the study. At the start of the trial, there was no difference between the number of physical complaints or the severity of ADHD symptoms in diet group and control group (**table 1**).

Table 1 Baseline characteristics of the 24 children who completed the interventions

Characteristic	Diet group, N=13	Control group, N=11	Fisher exact *p* value (two-sided)
	mean (% or SD)	mean (% or SD)	
Boys	10/13 (76.9%)	9/11 (81.8%)	>0.99
Mean age (SD)	6.3 (1.6)	6.2 (1.7)	0.91[a]
Mean number of ADHD			
Criteria (SD)	14.4 (2.0)	13.7 (2.1)	0.44[a]
Co-morbid ODD	12/13 (80.0%)	10/11 (83.3%)	0.60
Atopic constitution family	9/13 (69.2%)	8/11 (72.7%)	0.99
Allergy diagnosed in child	1/13 (7.7%)	2/11 (18.2%)	0.58
On dietary restriction	0/13 (0%)	1/11 (9.1%)	0.46
Mean number of physical			
Problems (SD)	3.0 (1.4)	2.8 (2.2)	0.81[a]
Sleep complaints	5/13 (38.5%)	5/11 (45.5%)	>0.99

N number of participants, [a] Student's *t* test

Figure 1 Flow diagram of subject participation throughout the study



Protocol

The efficacy of an elimination diet on the reduction of physical and sleep complaints in children with ADHD was tested in this randomised controlled trial (RCT) by comparing outcomes within diet and control group, before and after intervention and between groups. Subjects were randomly allocated to one of the two groups by means of a sequence of numbered cards in sealed unmarked envelopes that were prepared by an independent paediatrician. Each card contained a reference to the group to which the child would be allocated, and for each allocation, an equal number of cards (20) were available. The envelopes were picked and opened by the parents in the presence of the researcher, and treatment was then dispensed in accordance to the allocation on the card.

All children started with a 2-week baseline diet in which they adhered to their normal diet; no foods were eliminated. Children who were already on a diet had to

cease this diet at least 2 weeks before the start of the trial. During the baseline diet, the parents kept an extended diary and had to observe their child carefully, in order to assess the child's normal diet, his/her behaviour, physical complaints, sleep complaints and activities. There were two measurement points: at the end of the baseline diet and at the end of the elimination diet (diet group) or the control period (control group).

The diet group started, after the baseline diet and the first assessment, with the elimination diet, which had to be followed for a period of 5 weeks. The elimination diet was based on a few foods diet, as described by Hill and Taylor in their basic algorithm for treatment of ADHD [19]. The rationale behind the few foods diet was the assumption that children might present with ADHD symptoms after eating any kind of foods. Therefore, the diet consisted only of a limited number of hypo-allergenic foods, like rice, turkey, lamb, a range of vegetables (lettuce, carrots, cauliflower, cabbage and beet), pears and water. All other foods were prohibited, but vegetables, fruits, rice and meat were allowed every day, in normal doses. Calcium was supplied daily via non-dairy rice drink with added calcium; children were not at risk for nutrient deficiencies. This few foods diet was complemented with specific foods like potatoes, fruits, corn and wheat, to be eaten on days and in doses stated in advance according to a compulsory intake schedule [9, 29, 31]. As a result of this strategy, an elimination diet as comprehensive as possible could be composed for each individual child, thus making the intervention less incriminating for child and parents. If there was no improvement by the end of the second week, the diet was restricted and gradually limited to the few foods diet [9, 29, 31]. The second measurement point occurred at the end of the elimination diet.

The control group continued, after the first assessment, their baseline diet, i.e. their normal diet in which no foods were excluded, for a period of 5 weeks. Unfortunately, in dietary studies using a very restricted diet, it is not possible to create a reliable placebo diet, thus impeding a placebo-controlled trial. Therefore, this study is an RCT, which is often used in studies when no placebo is available, such as studies into the effects of cognitive behaviour therapy, eczema or other medical intervention trials [32, 37, 38, 41, 43, 45]. As it is conceivable that the child's behaviour and somatic complaints might improve because of the special attention which parents have to give to their child in order to fill in the diary correctly, parents of children in the control group also had to keep an extended

diary and had to monitor the behaviour and the physical and sleep complaints of their child conscientiously. The second measurement point was at the end of the control period.

At the start of the trial, the parents of the control group were informed that they could start with the elimination diet immediately after the last assessment, if they wished so. Parents were given verbal and written information about the study, and written informed parental consent was obtained before randomisation.

Measures

Physical and sleep complaints were measured using the Physical Complaints Questionnaire (PCQ) [28, 29]. This questionnaire consisted of 36 questions, of which 18 items were relevant with respect to specific physical and sleep complaints. Items were rated on a four-point scale, concerning the problems during the past week: problems which occurred every day (3), several times a week (2), once a week (1) or less than once a week (0). The questionnaire had to be filled in by the parents twice, e.g. before and after the elimination diet or control period. The physical complaints concerned 16 items and were subtyped into seven domains: (1) pain (headaches, abdominal pains and growing pains), (2) unusual thirst or unusual perspiration, (3) eczema, (4) asthma or persisting cold (rhinitis), (5) skin problems (blotches in the face, red ears, red-edged mouth or bags under the eyes), (6) tiredness and (7) gastrointestinal problems (diarrhoea, constipation and flatulence). Two of the 18 questions concerned sleep complaints, i.e. problems with sleeping in (sleep initiation or sleep onset) and sleeping on (sleep maintenance). A domain was considered to be present when rated 2 (several times a week) or 3 (every day) for at least one of the items within that domain. A problem was considered to be absent when the score was 0 or 1 for all items within that domain.

Statistical analysis

Main endpoints were the parent ratings on the PCQ at the end of the RCT to establish the effect of the intervention on physical and sleep complaints. Differences in averages within groups (effect size), before and after the trial, were tested by Student's t test and expressed by Cohen's d, a standardised measure of the effect size with an effect size of 0.2 indicative of a small effect and 0.8 of a large effect. Differences in average number of complaints between groups, at the

end of the trial, were analysed using linear regression, including the number of complaints at the start of the trial as covariate.

Differences in presence/absence of complaints between groups, at the end of the trial, were analysed using exact logistic regression, because the endpoints were binary. PCQ ratings at the start of the study were included as covariate. Here, the effect of intervention was expressed in terms of odds ratios (OR) and their *p* values.

After finishing the RCT, all children in the control group (N=11) also completed the elimination diet, resulting in 24 children in total who underwent the elimination diet, i.e. 13 children from the diet group, during the RCT, and 11 children from the control group, following the RCT. The secondary endpoints, analysed using linear and exact logistic regression, and calculated in all 24 children who completed the diet, were (1) the effects of the elimination diet on physical and sleep complaints in children who showed ADHD symptom reduction of 50% or more after following the elimination diet, i.e. responders, and in children who showed less than 50% ADHD symptom reduction, the nonresponders [31] and (2) the effects of the elimination diet on physical and sleep complaints in children with and without an atopic constitution.

Spearman rank correlation coefficients were calculated to study the improvement of physical complaints and ADHD core symptoms after having followed the diet. STATA 10 was used for all statistical analyses. Effects were tested at $p=0.05$.

Results

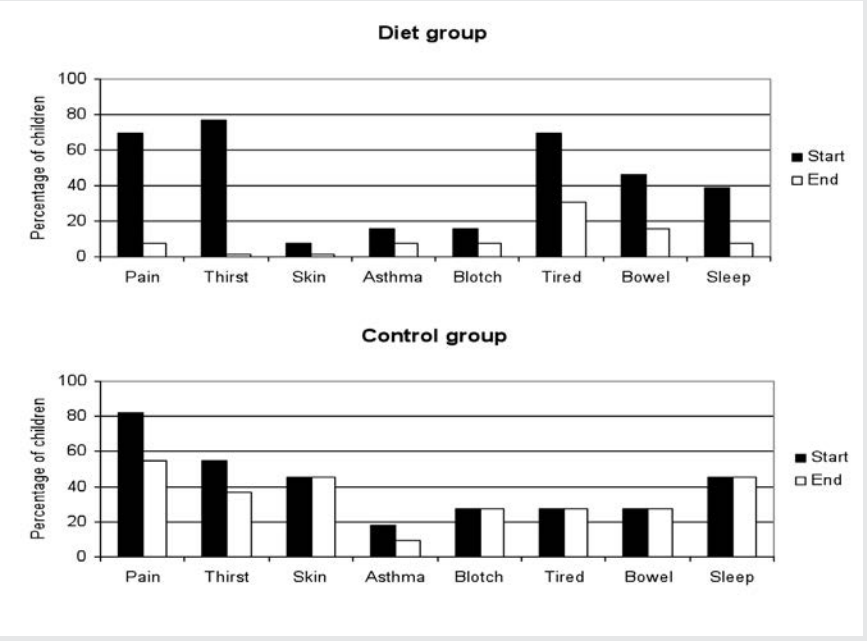
Effect of the intervention on physical and sleep complaints in diet group and control group

The results of the intervention on physical and sleep complaints in both groups are shown in **table 2** and **figure 2**. The total number of complaints in the diet group was 44 (average, 3.4 per child) at the start of the trial and ten complaints (average, 0.8) at the end of the trial, a reduction of 77% ($p<0.001$), with a standardised effect size (Cohen's *d*) of 2.0 (**table 3**). In the control group, 36 complaints (average, 3.3) were reported at the start of the trial and 30 (average, 2.7) at the end of the trial, a reduction of 17% ($p=0.08$), with an effect size of 0.2.

Using linear regression and taking the initial number of complaints into account, the difference in average number of complaints at the end of the trial between the diet and control group equalled 2.04 (95% confidence interval (CI) 1.14–2.94, $p<0.001$, residuals being normally distributed, p value of Shapiro–Wilk test equals 0.55).

In three domains [(1) headaches or bellyaches (OR= 13.25), (2) unusual thirst or unusual perspiration (OR= 10.04) and (3) sleep complaints (OR=11.77)], the complaints were significantly less reduced in the control group than in the diet group ($p<0.05$).

Figure 2 Physical and sleep complaints in the diet group and the control group at start and at endpoint



Pain: headaches, abdominal pains, growing pains
Thirst: unusual thirst or unusual perspiration
Skin: eczema
Asthma: asthma or persisting cold (rhinitis)
Blotch: blotches in the face, red ears, red-edged mouth or bags under the eyes
Tired: tiredness
Bowel: diarrhoea, constipation, flatulence
Sleep: sleeping in or sleeping on

Table 2 Effect of the interventions on physical and sleep complaints

	Diet group, N=13		Control group, N=11		Exact OR	*p* value OR
	Start trial N children % children	End trial N children % children	Start trial N children % children	End trial N children % children		
Headaches, abdominal pains, growing pains	9 (69%)	1 (8%)	9 (82%)	6 (54%)	13.25[a]	0.05
Unusual thirst, unusual perspiration	10(77%)	0 (0%)	6 (54%)	4 (27%)	10.04	0.05
Eczema	1 (8%)	0 (0%)	5 (45%)	5 (45%)	5.00	0.33
Asthma, rhinitis	2 (15%)	1 (8%)	2 (18%)	1 (9%)	1.00	0.99
Blotches in face, red ears, red-edged mouth, bags under eyes	2 (15%)	1 (8%)	3 (27%)	3 (27%)	1.50	0.80
Tiredness	9 (69%)	4 (31%)	3 (27%)	3 (27%)	3.58	0.32
Diarrhoea, constipation, flatulence	6 (46%)	2 (15%)	3 (27%)	3 (27%)	4.66	0.24
Problems with sleeping in or sleeping on	5 (38%)	1 (8%)	5 (45%)	5 (45%)	11.77	0.05
Total number of complaints, including sleep complaints	44	10	36	30	16.20[b]	0.001

[a] The odds of having complaints at the end of the trial is 13.25-fold higher in the control group compared to the diet group; [b] Based on 80 initial complaints

Table 3 Average number of physical complaints, including sleep complaints, per child per intervention group at start and at endpoint

	Average no. of complaints			
	Start	End	Start minus end	
			Difference (95% CI) *p* value	Effect size[a] (% SR)
Diet group (N=13)	3.4[b]	0.8	2.6 (1.8 to 3.4)	2.0 (77.3) p=0.001
Control group (N=11)	3.3[b]	2.7	0.6 (−0.1 to 1.2)	0.2 (16.7) p=0.08

SR scale reduction; [a] Effect size start–end, Cohen's *d*; [b] Difference at start $p=0.89$ (Student's *t* test)

Effect of the elimination diet on physical and sleep complaints in children with and without ADHD symptom reduction

This effect was calculated in all 24 children who followed the elimination diet, 13 children of the diet group and 11 children of the control group following the RCT. Of these children, 20/24 belonged to the responders, 11/13 children of the diet group and 9/11 children of the control group. The responders, having to show a minimal ADHD symptom reduction of 50%, showed an average reduction on the ADHD rating scale of 69.4% (effect size, 2.1), according to the parent ratings, and an ADHD symptom reduction of 70.6% (effect size, 2.5), according to the teacher ratings.

Before following the diet, there was an average of 3.2 physical and sleep complaints per child in the responder group and 2.5 in the nonresponder group. After the diet, these averages were 0.9 and 1.5, respectively. In the responder group, there was a significant reduction of physical complaints ($p<0.001$); in the nonresponder group, the reduction was not significant ($p=0.35$), with standardised effect sizes of 1.4 and 0.8, respectively.

Linear regression, including the initial number of complaints as covariate, revealed a difference in average number of complaints between the responder and nonresponder group of 0.82 (*p* value 0.10, residuals normally distributed, *p* value of Shapiro–Wilk test equals 0.62). The correlation between the total number of physical and sleep complaints and the total number of ADHD criteria on the ADHD rating scale, before and after the diet, was calculated using Spearman rank correlation coefficients. Spearman's rho was 0.54 ($p<0.01$), indicating there

was a positive correlation between the reduction of the physical and the behavioural symptoms. Statistical analyses to investigate the difference in effect of the elimination diet on the specific physical domains in responders and nonresponders could not be performed as there were only four nonresponders.

Effect of the elimination diet on physical and sleep complaints in children with and without an atopic constitution

This effect was calculated in all 24 children who followed the elimination diet. An atopic constitution, i.e. having at least one parent or sibling with allergic complaints like asthma, eczema, hay fever or allergic rhinitis, was present in 17/24 (70.8%) children, equally divided over the diet group (9/13, 69.2%) and the control group (8/11, 72.7%; Fisher's exact test, $p=0.99$). At the start of the trial, an average of 3.5 complaints per child was observed in the atopic children and an average of 2.0 per child in the non-atopic group. After the diet, these averages were 1.2 and 0.6, respectively. In the atopic as well as in the non-atopic children, there was a significant reduction of physical complaints, (p values <0.001 and 0.04, respectively) with standardised effect sizes of 1.5 and 1.1, respectively.

Although the reduction within both groups was significant, linear regression did not show a significant difference between the atopic and non-atopic group at the end of the diet while adjusting for the initial number of complaints (difference equals 0.18 complaints, $p=0.70$, residuals normally distributed, p value of Shapiro–Wilk test equals 0.73).

Complaint specific analyses could not be performed due to the low number of non-atopic children (n=7).

Discussion

Physical complaints, such as headache, bellyache, tiredness, eczema and sleep complaints, are common comorbid problems in children with ADHD [10, 11, 16, 21, 27, 35, 39], with a prevalence of sleep complaints up to 50% [39]. In contrast to comorbid psychiatric conditions, relatively little is known on the comorbidity of ADHD and physical complaints. In this study, we examined whether physical and sleep complaints in 24 children with ADHD were improved by an elimination diet using a randomised controlled design. We previously described that the diet

significantly reduced the ADHD symptoms in this group of patients [31]. In the current study, in which the subjects were not preselected for somatic symptoms, 23/24 (96%) children had one or more physical complaints, indicating that comorbidity between ADHD and physical complaints is high, thus underlining the importance of studying physical complaints in ADHD.

The results of this pilot study should be interpreted in the light of several limitations. First, in this study, a very restricted elimination diet was used, thus making it impossible to compose a reliable placebo diet. Furthermore, parents had to be aware of the intervention and had to pay attention to what the child should eat. Therefore, we had to choose for an open RCT. Although a blinded RCT should be given preference to, open RCTs are commonly used and accepted when blinding is difficult and when no placebo is available, e.g. in studies into the effects of cognitive behaviour therapy, eczema, obesity, autism or other medical intervention trials [7, 12, 15, 32, 37, 38, 41, 43, 45]. Also, the well known and highly cited Multimodal Treatment Study of Children with ADHD, the MTA-study, was not blinded [26]. To compensate for the absence of a placebo diet, the parents in the control group, like the parents in the diet group, had to monitor and to observe their child intensively, writing down the behaviour and the physical and sleep complaints of their child conscientiously in a diary. It is conceivable that the child's behaviour and somatic complaints might improve because of the special attention which parents had to pay to their child. In our study, the reduction of the total numbers of complaints in the diet group (77%) was 4.6-fold compared to the reduction in the control group (17%; $p=0.001$), indicating that the effect of an increase of attention may be small, when compared to the effect of an elimination diet. Second, the trial lasted only 5 weeks, which is a short period of time. Follow-up studies should include a follow-up period of at least 1 year. Finally, the sample size of the study was relatively small; consequently, the data reported here should be considered exploratory. Nevertheless, due to the considerable effect sizes in this study, statistically significant differences between diet and control were obtained.

The effect of the intervention on physical and sleep complaints did not differ significantly between children who did or did not show ADHD symptom reduction after following the diet. The adjusted difference between both groups amounted to 0.82 ($p=0.10$), suggesting the diet is equally effective in reducing physical complaints in responders and nonresponders. However, the power of this analysis

is low (0.26), as the nonresponder group consisted of four children only. Correlation analyses revealed that ADHD symptom reduction and the reduction of physical complaints were correlated significantly. We hypothesise, considering the effect size of an elimination diet on both ADHD and physical complaints, that there may be a common underlying mechanism for both conditions. This mechanism may be a hypersensitivity reaction to food, which could be an etiological factor of both conditions [30]. This hypersensitivity mechanism might either be allergic, i.e. related to the induction of IgE or IgG antibodies or of a cell-mediated response [30], or not allergic, i.e. related to a toxic or pharmacologic mechanism. When there is no effect of an elimination diet on one or more of the complaints, other etiological mechanisms are likely and should be considered.

In this study, 71% of the ADHD children had an atopic constitution. This high prevalence may be related to the possibility that parents acquainted with allergic disorders are more willing to let their child follow an elimination diet than parents unfamiliar with allergies. On the other hand, atopy is a widespread condition, found in many children. A UK study reported that 39% of children in the UK had been diagnosed with one or more atopic conditions [17], and positive skin prick tests to at least one allergen was found in 63.7% of urban children [23]. Our study shows that in atopic and in non-atopic children, the number of physical and sleep complaints did not differ significantly before (p= 0.081) as well as after (p=0.32) the elimination diet. We did find, although not statistically significant, that at the start of the trial more physical complaints were reported in atopic children (average, 3.5 per child) than in non-atopic children (average, 2.0 per child). The results of this study indicate that the presence of an atopic constitution is not a moderator of the effect of an elimination diet on physical complaints and sleep complaints in children with ADHD, but do suggest atopy is an important condition co-occurring with ADHD.

The subjects in our study were young, but children of 4 years and older are generally expected to be able to tell that it hurts and where it hurts. Therefore, headache, abdominal pains and pain in the legs or arms (growing pains) are probably reliably reported. However, restless legs or breathing difficulties may be more difficult for a child to describe, so it may be conceivable that the number of physical complaints is underestimated. We would like to emphasise that the sleep complaints were reported by the parents, not by the child. These complaints are generally well visible to the parents and have a large impact on family life. As

ADHD has an increased association with sleep-related movement disorders such as restless legs syndrome [44], the relationship between food, ADHD and sleep complaints should be investigated more thoroughly in follow-up studies.

Although we do not know the mechanisms in which an elimination diet exerts its effects on physical and sleep complaints in ADHD, our findings indicate that the results of this study may be important for children with physical complaints or sleep complaints and ADHD. They even may be important for children with physical conditions without ADHD [4, 8, 25, 42] and for children with functional somatic symptoms, as these are common health complaints in 5–7-year-old children [33].

More research on the effects of foods and on the underlying mechanism is advised to investigate whether children with ADHD and co-occurring physical complaints may represent a specific ADHD subgroup. We hypothesise that there may be a common underlying genetic mechanism contributing to both medical conditions, comparable to the mechanism found by Campbell et al., in children with co-occurring autism and gastrointestinal conditions [8]. Consequently, the further unravelling of the genetic architecture of ADHD is very important to identify a common genetic pattern or genetic vulnerability in children with ADHD and physical complaints. Also, it is important to segregate between non-allergic or allergic mechanisms involved. This includes analysis of the role of IgE and IgG antibodies being specific for the food and the possible involvement of T cell-mediated hypersensitivity.

In studies specifically asking for physical complaints in children with ADHD, it turns out that comorbidity is high [9, 13, 22, 29]. This high comorbidity between physical symptoms and ADHD does not reflect clinical practice, which may be due to the fact that in children with ADHD, it is not current practice to ask for physical complaints specifically. A general question like ‘are there any physical complaints’ may not be sufficient, generating too little information. Many of the physical symptoms investigated in this trial would not have been mentioned by the parents if we had not asked for them.

Because diets are not without its limitations (socially handicapping, putting a strain on the whole family), they should only be applied after responsiveness has been individually and carefully tested by means of an elimination diet, supervised and administered by trained staff [34]. If a child following the diet shows beneficial behavioural or physical effects, sequential introduction of foods is necessary to

identify the incriminated foods [9, 13], so that the eventual diet of the child will be as comprehensive as possible. If a child who responds favourably to the diet will not proceed with this provocation period and returns to its usual diet, consequently, the problems are likely to return.

Further controlled studies are needed to verify the efficacy of an elimination diet in children with physical complaints and to provide a feasible algorithm for treatment, especially for children with behavioural or physical complaints triggered by foods. We will pursue this issue in a large (N=100) sample of ADHD children using an RCT (the Impact of Nutrition on Children with ADHD study) currently underway, the protocol of which can be found on the website of *The Lancet* (http://www.thelancet.com/ protocol-reviews/06PRT-7719).

Clinical implications and conclusion

Our study shows that hypersensitivity to food may play an etiologic role in physical and sleep complaints in children with ADHD and suggests that an elimination diet may be a valuable tool to manage these problems in ADHD children. As functional somatic symptoms are common health complaints in 5–7-year-old children [33], the results of this study may be important for all children. Still, the sample size was small, and we cannot rule out expectation effects. Therefore, more research is needed to determine the effects of food on physical and sleep complaints in children with and without ADHD.

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Chapter 5

ADHD as a (non-)allergic hypersensitivity disorder: a hypothesis

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Pelsser LM, Buitelaar JK, Savelkoul HF.

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Abstract

Research data concerning the causal association between attention deficit hyperactivity disorder (ADHD) and allergies are conflicting. Allergic disorders, like asthma and eczema are clinical syndromes in which both genetic predisposition and environmental factors (pets, pollen and foods) contribute to its development. The hypothesis of ADHD, in some children also being an allergic disorder, is postulated based on comparison of the mechanisms underlying the development of ADHD and allergic disorders. According to the accepted terminology, ADHD may comply with the criteria of hypersensitivity, allergy and atopy.

This hypothesis has to be thoroughly tested by randomized controlled trials using environmental triggers and immunologic research. As genes related to the immune system may be associated with ADHD, further genetic research is compulsory. Immunotherapeutic approaches, using immunotherapy and probiotics, can subsequently be implicated in the treatment of ADHD. If hypersensitivity to environmental stimuli like foods contributes to the development of ADHD, the assessment and treatment of ADHD will have to be reconsidered, thereby improving the quality of care for these patients.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly heritable psychiatric disorder that affects 2–12% of children worldwide (1, 2). It is as yet unknown whether the prevalence of children with ADHD is increasing. Several environmental influences are known that raise the risk for ADHD development (1), but the exact aetiological pathways are still largely unknown (3). Medication and psychosocial intervention are the most frequently used methods of treatment (4). As our knowledge about the cause(s) of ADHD remains speculative (5), it is important not only to unravel the genetic architecture of ADHD, but also to determine to what extent environmental factors can be regarded as risk factors for developing the disorder. Psychosocial and biological environmental influences like foetal distress, hypoxia and family dysfunction are considered to have aetiological importance (1), and a complete assessment needs to take account of all these influences (6).

To date, clinicians do not consider environmental factors such as exposure to foods or inhalants of much importance and do not pay much attention to them in the current diagnostic process of ADHD. These environmental factors, however, do play a major role in other complex genetic diseases, like asthma and eczema (7, 8). Here we argue that exposure to foods and inhalants and subsequent hypersensitive mechanisms can be important in the multifactorial causation of ADHD and this should have consequences for diagnosis and treatment of this disorder.

The old hypothesis: ADHD being engendered by allergic disorders

Eventually ADHD was hypothesized being a side effect of allergic disorders: allergic reactions engendering cholinergic/adrenergic activity imbalances in the central nervous system, leading to ADHD symptoms in some children (9). Other studies suggested the possibility of a causal relationship between allergies and ADHD (10, 11), based on a surprisingly high proportion of children with ADHD having associated symptoms of allergic disorders. Recently, children with ADHD were found to display skin prick test results to common aeroallergens consistent

with allergic rhinitis (12). However, there is increasing evidence that neither asthma nor its treatment are causing behavioural or school problems in school-age children, yet lingering concerns regarding this issue persist (2, 13). When comparing atopic and non-atopic children for the prevalence of ADHD no association between immunoglobulin E (IgE)-mediated atopic responsiveness and ADHD was found (14–16). Biederman et al. (13) found no substantial aetiological or pathophysiological relationship between asthma and ADHD. The risk for asthma did not meaningfully differ between ADHD and control children (13). Despite the range of diverse studies that attempt to understand the co-morbidity of asthma and psychiatric diagnoses (17), the controversy whether or not ADHD and asthma are causally linked still exists in the literature.

Asthma is a leading cause of childhood chronic medical illness, affecting 7–15% of children and the prevalence rates have dramatically increased by 74% between 1980 and 1994 (2). In addition, a rising prevalence of food hypersensitivity and of severe allergic reactions to food has been reported the last decade (18). Thirty-nine per cent of all children in the United Kingdom have been diagnosed with one or more atopic conditions and 11% with more than one atopic disorder (19). These data imply that there is a significant chance that asthma and ADHD can occur in the same individual, so co-morbidity of ADHD and allergic disorders should not be very surprising (20). Furthermore, from various studies it is concluded that asthma and ADHD show an independent transmission within families (2, 13, 16). This is consistent with the notion that although ADHD and asthma or eczema might occur simultaneously, these disorders need not be causally related with each other (2, 13, 16). Therefore we reject the old hypothesis, ADHD being caused by allergic disorders, replacing it by a new hypothesis, ADHD being a (non-)allergic hypersensitivity disorder itself.

The new hypothesis: ADHD being an (non-)allergic hypersensitivity disorder

The lack of a causal correlation between asthma and ADHD does not exclude the presence of a common pathophysiological mechanism underlying the development of asthma and/or ADHD when exposed to similar environmental triggers. Such a mechanism can exist without a direct causal relationship between both diseases.

According to the nomenclature of allergy, allergic disorders are clinical syndromes each defined by a group of symptoms and signs in target organs, in which genetic predisposition and exposure to environmental factors (dust mites, pets, tobacco smoke, foods) both contribute to its development (21).

ADHD and asthma are both highly hereditary diseases. Polymorphic variants in several genes involved in regulation of the dopamine and related neurotransmitter pathways are reported to be associated with ADHD (22). Not only the dopaminergic system, but also the noradrenergic and histaminergic systems can be involved with ADHD (23).

The term 'hypersensitivity' should be used for allergic and non-allergic reactions for which environmental triggers are held responsible (21). Hypersensitivity is an "umbrella" term to cover for allergic hypersensitivity, i.e. with a defined or strongly suspected immunological mechanism, and for non-allergic hypersensitivity, i.e. with an immunological mechanism excluded. Eighty per cent of childhood asthma has been reported to be allergic, resulting from immunological reactions, being IgE- (extrinsic) or non-IgE-mediated (intrinsic) (21). It has been suggested that eczema can be differentiated into an atopic and nonatopic eczema form. Only atopic eczema might follow the distribution and risk pattern that have been ascribed to asthma and hay fever. As the immunological mechanism underlying the development of eczema and the role of IgE antibodies in the aetiology of the disease are less well known, the term IgE-associated is used, the word 'associated' being provisional (24).

From this, it is clear that the different types of allergic diseases are heterogeneous with respect to the role of the immunopathology underlying the cause of these diseases. Although ADHD has never been postulated as an allergic disorder itself, we are of the opinion that ADHD symptoms may be caused or "triggered" by several heterogeneous factors, reflecting different mechanisms underlying the disorder, as has been stated before (25). Some of these mechanisms may represent allergic immunopathology.

Strengthening the new hypothesis

According to the revised and widely accepted terminology of allergies, ADHD meets the criteria of hypersensitivity. Displaying asthma symptoms after exposure

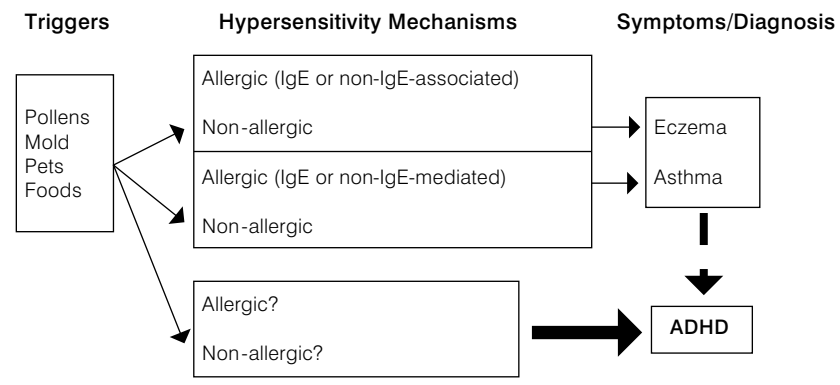
to dust mites reflects a hypersensitive reaction in which the dust mite is the defined stimulus. Equally, showing ADHD symptoms after eating normal amounts of certain foods (10, 15, 26–30), or after pollen exposure (31), can be a matter of hypersensitivity, in which the foods and pollen reflect the defined stimulus which is tolerated by normal subjects (see figure). More research is needed to determine whether such a hypersensitivity reaction is allergic or non-allergic with respect to its underlying cause. Recent research has shown that the effect of food additives on behaviour may occur independently of the presence of an atopic status or the presence of hyperactive behaviour, probably via a non-IgE-dependent histamine release from mast cells and basophilic granulocytes (32). Some children can react to food components, including additives, with the development of atopic symptoms (33), or ADHD-like symptoms (34), while only seldom children will react to an isolated additive component alone (26). Some degree of hyperactivity when exposed to food additives and benzoate preservatives may be applied to all children, not exclusively to hyperactive or atopic subgroups (32, 35). Recently, it has been described using outgrowth of murine neuroblastoma cells in vitro that specific combinations of common food additives show synergistic effects to inhibit neuronal cell differentiation (36). These food additives show their effect at concentrations theoretically achievable in plasma by ingestion of foods or drinks that are typically consumed by children.

When ADHD symptoms develop in response to food components, and when an immunological mechanism can be defined which underlies this development, then ADHD is a consequence of an allergic response. The immune mechanism can be related to the induction of IgE antibodies or be a consequence of other mechanisms. This is in accordance with the revised allergy nomenclature. Subsequently, if the child has the atopic constitution, it may be called ‘atopic’ ADHD. As yet, we do not know to what extent these mechanisms take place, whether they are limited to a subgroup or affect the majority of children with ADHD.

When stepping beyond the borders of the brain we find preliminary studies on the effects of pollen and foods (defined stimuli) on ADHD symptoms which are in line with our hypothesis, and support the existence of a hypersensitive mechanism (10, 15, 25–31). All dietary studies, following the food dye-challenge research in the 1970s and unlike the challenge studies using an individually constructed elimination (few foods) diet (10, 15, 26–30), show evidence of efficacy for a

properly selected subgroup (37, 38). In a nasal pollen challenge study (31), significant neurobehavioural regression was induced in children with ADHD. This regression occurred in both allergic and non-allergic children, and was not associated with the presence of respiratory symptoms. The results of these studies are consistent with our hypothesis, but far more research is needed to accept or reject our hypothesis.

Figure Triggers and mechanisms of asthma, eczema and attention deficit hyperactivity disorder (ADHD) according to the old hypothesis (dashed arrow) and the new hypothesis (solid arrow)



The underlying mechanisms of asthma, eczema and ADHD can be based on allergic sensitization, resulting in immunoglobulin E (IgE) or non-IgE-mediated mechanisms, or upon non-allergic mechanisms. Determining the underlying mechanism may have consequences for diagnosis and treatment of the disorder.

Testing the hypothesis

This hypothesis has to be thoroughly tested by randomized controlled trials in unselected subjects by the following.

1. Genetic research: ADHD is a genetically complex disorder, including among others the involvement of multiple genes, gene-environment correlation, gene-environment interaction and importance of developmental factors (39). Several

genes are able to regulate the immune system and may be associated with development of the symptoms of ADHD (40, 41). Consequently the further unravelling of the genetic architecture of ADHD is very important.

2. Immunological research: dopamine transporters are causally implicated in ADHD, and are targets for drugs like methylphenidate. These receptors are abundantly expressed on human T-cells, and trigger the selective secretion of immune-regulatory cytokines, like interleukin (IL)-10 (42). Furthermore, these receptors react by activating STAT6, a pivotal transcription factor in Th2 cells of the immune system (43).
3. Blood tests: these tests are used to segregate between non-allergic or allergic mechanisms involved. This includes analysis of the role of IgE and IgG antibodies being specific for the food and inhalant components and the possible involvement of cell-mediated hypersensitivity (24). This enables us to understand the processes that initiate and regulate these responses. As a result of the poor prognostic value and reliability of food-specific IgE (44), a true allergy to a foodstuff is revealed by oral provocation tests or by improvement during an avoidance diet, being an essential tool in the diagnostic procedure (45).
4. The development of immunotherapeutic treatments: when allergic triggers are involved in ADHD, these will necessitate the development of new treatment strategies. Recently, children suffering from eczema symptoms, whether or not linked to a food allergy, are efficiently treated by the use of probiotics (46, 47). Moreover, when inhalant components are implicated in the development of ADHD symptoms, also allergen-specific immunotherapy might be useful. The potential use of these new anti-allergic strategies needs to be evaluated with children suffering from ADHD symptoms.
5. By determining the effects of environmental influences, using few foods diets (10, 15, 26–30) and inhalant challenges, e.g. pollen (31), the number and features of children with ADHD in which a hypersensitive mechanism may be involved can be identified.

Implications for clinical practice

According to our hypothesis, hypersensitivity to environmental stimuli like foods and inhalants contributes to the development of ADHD, and thus the assessment and treatment of ADHD will have to be reconsidered. As allergic and non-allergic conditions may present with similar symptoms, an accurate allergy diagnosis is important in order to treat the patient most appropriately (48). Confirmation of this hypothesis will result in considering ADHD as two different entities: hypersensitive and non-hypersensitive ADHD, in accordance with the two variants of eczema depending on the determination of the effects of attributable risks (49). Determining and avoiding such triggers will reduce the predisposition to ADHD, and consequently reduce the use of medication. This new insight will improve the quality of care for ADHD patients in the future.

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Chapter 6

Effects of a restricted elimination diet (RED) on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial

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Abstract

Background The effects of a restricted elimination diet in children with attention-deficit hyperactivity disorder (ADHD) have mainly been investigated in selected subgroups of patients. We aimed to investigate whether there is a connection between diet and behaviour in an unselected group of children.

Methods The Impact of Nutrition on Children with ADHD (INCA) study was a randomised controlled trial that consisted of an open-label phase with masked measurements followed by a double-blind crossover phase. Patients in the Netherlands and Belgium were enrolled via announcements in medical health centres and through media announcements. Randomisation in both phases was individually done by random sampling.

In the open-label phase (first phase), children aged 4–8 years who were diagnosed with ADHD were randomly assigned to 5 weeks of a restricted elimination diet (diet group) or to instructions for a healthy diet (control group). Thereafter, the clinical responders (those with an improvement of at least 40% on the ADHD rating scale [ARS]) from the diet group proceeded with a 4-week double-blind crossover food challenge phase (second phase), in which high-IgG or low-IgG foods (classified on the basis of every child's individual IgG blood test results) were added to the diet.

During the first phase, only the assessing paediatrician was masked to group allocation. During the second phase (challenge phase), all persons involved were masked to challenge allocation. Primary endpoints were the change in ARS score between baseline and the end of the first phase (masked paediatrician) and between the end of the first phase and the second phase (double-blind), and the abbreviated Conners' scale (ACS) score (unmasked) between the same timepoints. Secondary endpoints included food-specific IgG levels at baseline related to the behaviour of the diet group responders after IgG-based food challenges.

The primary analyses were intention to treat for the first phase and per protocol for the second phase. INCA is registered as an International Standard Randomised Controlled Trial, number ISRCTN 76063113.

Findings Between Nov 4, 2008, and Sept 29, 2009, 100 children were enrolled and randomly assigned to the control group (n=50) or the diet group (n=50). Between baseline and the end of the first phase, the difference between the diet

group and the control group in the mean ARS total score was 23·7 (95% CI 18·6–28·8; p<0·0001) according to the masked ratings. The difference between groups in the mean ACS score between the same timepoints was 11·8 (95% CI 9·2–14·5; p<0·0001). The ARS total score increased in clinical responders after the challenge by 20·8 (95% CI 14·3–27·3; p<0·0001) and the ACS score increased by 11·6 (7·7–15·4; p<0·0001). In the challenge phase, after challenges with either high-IgG or low-IgG foods, relapse of ADHD symptoms occurred in 19 of 30 (63%) children, independent of the IgG blood levels. There were no harms or adverse events reported in both phases.

Interpretation A strictly supervised restricted elimination diet is a valuable instrument to assess whether ADHD is induced by food. The prescription of diets on the basis of IgG blood tests should be discouraged.

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Introduction

Attention-deficit hyperactivity disorder (ADHD) affects 5% of children worldwide and is characterised by excessive and impairing inattentive, hyperactive, and impulsive behaviour [1]. Genetic and environmental factors are involved [2], and ADHD is often accompanied by oppositional defiant disorder [3]. Children with ADHD and comorbid oppositional defiant disorder are difficult for parents, guardians, and teachers to handle, give rise to substantial parenting stress, and have a worse prognosis for adverse outcomes (ie, an increased risk of developing conduct disorder and antisocial personality disorder) than have children without comorbidity [4]. At present, ADHD is treated with psychoeducation, parent training, child behavioural interventions, and drugs [5] but follow-up studies have reported limited long-term effects of multimodal treatment [6,7].

One of the risk factors for ADHD that could be targeted for intervention is food [8]. Reports of adverse physical reactions to foods (eg, eczema, asthma, and gastrointestinal problems) that affect various organ systems [9] have led to the suggestion that foods might also affect the brain, resulting in adverse behavioural effects [10]. Colourings and preservatives might have some effect on the behaviour of children with or without ADHD, but additives do not cause ADHD [2,5,11,12]. An individually constructed restricted elimination diet, which consists of some hypo-allergenic foods, might be effective for treatment of ADHD [8,11]. The rationale of this diet for children with ADHD is to investigate whether ADHD is triggered by foods—ie, to identify a hypersensitivity reaction to foods. In a small randomised controlled trial that investigated the effects of a restricted elimination diet [13], we reported statistically significant and clinically relevant effects on ADHD and oppositional defiant disorder.

In children with ADHD that is triggered by foods, ADHD meets the criteria of hypersensitivity according to allergy nomenclature [14]. Accordingly, we postulated that ADHD might be an allergic or non-allergic hypersensitivity disorder in some children [15]. IgE is implicated in typical food allergies. In reactions to food that are not mediated by IgE, assessment of IgG levels might be useful [16], and IgG blood tests are offered—especially in complementary care [17]—with the aim of establishing a relation between foods and ADHD. According to this theory, eating foods that induce high IgG levels would lead to a substantial behavioural relapse whereas eating those that induce low IgG levels would not.

However, there is no evidence for the effectiveness of these tests [18].

The primary aim of the Impact of Nutrition on Children with ADHD (INCA) study was to investigate the effects of a restricted elimination diet on behaviour in children with ADHD. The secondary aim was to differentiate between non-allergic and allergic mechanisms in food-induced ADHD.

Methods

Participants

Children were recruited at medical health centres and through media announcements in the Netherlands and Belgium. Interested parents or guardians (hereafter called parents) were provided with verbal and written information about the study. Eligible children were assessed for ADHD and comorbid disorders by a senior paediatrician (JT) using a structured psychiatric interview (SPI). Children were included if they had been diagnosed with ADHD of any subtype [1]. Further inclusion criteria were children's age 4–8 years (sufficiently young to maximise dietary compliance), and parents with adequate knowledge of Dutch and who were motivated to follow a 5-week restricted elimination diet. Exclusion criteria were children receiving drugs or behavioural therapy for ADHD, children already following a diet, or family circumstances that were likely to prevent completion of the study. The presence of comorbid psychiatric disorders was not a reason for exclusion.

The INCA study was approved by the medical ethics committee of Wageningen University and by the executive board and ethics committee of Catharina Hospital Eindhoven. The parents of children who participated in the trial provided written informed consent before week 1 of the study.

Randomisation and masking

INCA consisted of two phases. The first phase was an open-label phase with masked paediatrician measurements. After the baseline assessment, eligible children were randomly assigned to either a diet group or a control group. Randomisation was individually done by random sampling. Ten blocks of ten identical, sealed envelopes containing concealed treatment codes were made by a masked epidemiologist (KF) to prevent unbalanced assignment of treatment

over time. Parents randomly picked and opened an envelope. Staff who recruited and assessed patients were not involved in the procedure used to generate group allocations.

Because the diet was individually tailored and restricted, a reliable placebo diet was not possible, thus parents and teachers could not be masked to group allocation. Also, the researcher (LP) who provided expert advice to parents and teachers during the diet period could not be masked. Parents were instructed not to reveal dietary information to the paediatrician (JT) who did masked assessments [19].

The second phase was a double-blind crossover food challenge phase in the diet group. Eligible children from the diet group were randomly assigned, by simple sampling, to one of two challenge groups. Each group was offered either three foods that induce low IgG levels or three that induce high IgG levels in a crossover design. The three foods within each group were selected by an independent dietician who was masked to group assignment. The researcher, paediatrician, parents, and teachers were masked to IgG allocation. KF did the data entry for both phases and was masked to the assigned treatment.

Procedures

During the trial we used four questionnaires to assess outcome: the 18-item ADHD rating scale (ARS) [20], ten-item abbreviated Conners' scale (ACS) [21], strengths and difficulties questionnaire (SDQ) [22], and SPI [23]. The ARS, which is based on the diagnostic and statistical manual of mental disorders part IV (DSM-IV) criteria for ADHD, consists of nine inattention and nine hyperactivity and impulsivity criteria, with a four-point scale (0=never [less than once a week], 1=sometimes [several times a week], 2=often [once a day], and 3=very often [several times a day]). Three measures were taken from the ARS: total score (0–54), inattention score (0–27), and hyperactivity and impulsivity score (0–27). The ACS, also a four-point rating scale, covers hyperactivity, impulsivity, attention, mood, and temper tantrums. The DSM-IV-based SPI was used to assess oppositional defiant disorder (with the eight DSM-IV oppositional defiant disorder criteria) and conduct disorder (with seven of the 15 DSM-IV conduct disorder criteria relevant to this young group of patients, ie, criteria 1–5, 9, and 11). The SDQ provides a total difficulties score on the basis of the results of four problem subscales: emotional symptoms, and conduct, hyperactivity–inattention, and

peer problems. Unmasked parent and teacher assessments (ACS, ARS, and SPI) and masked paediatrician assessments (ARS and SPI) were done at baseline and at the end of the first phase (week 9 in the diet group and week 13 in the control group; **table 1**). The masked paediatrician based his ratings on information obtained from the parents as well as on his own observation and assessment of the child's behaviour and presentation. The masked measurements were used for all analyses in the first phase, apart from the ACS score and the week 9 measurements in the control group. Blood samples were taken at the start and end of the first phase.

After the baseline assessments, randomisation was done, and parents started a 2-week baseline period during which they did not exclude any foods from their child's diet. Parents kept extended diaries (containing information on the child's diet, behaviour, activities, physical complaints, and medications; **webappendix page 1**) and closely monitored their child's behaviour. After the baseline period (in week 3), the second unmasked parent assessment took place (ACS and ARS) and parents and teachers filled in the SDQ.

During week 4 (start of the first phase), the diet group started a 5-week individually designed restricted elimination diet, which has been described elsewhere [24] (**webappendix page 2**). Briefly, the diet consisted of the few-foods diet (ie, rice, meat, vegetables, pears, and water) [8,24] complemented with specific foods such as potatoes, fruits, and wheat. The aim was to create an elimination diet as comprehensive as possible for each individual child, to make the intervention easy for children and their parents to follow [10,13]. If the parents reported no behavioural changes by the end of the second diet week, the diet was gradually restricted to the few-foods diet only [10]. At the end of the first phase, all children were assessed by the masked paediatrician (ARS and SPI), unmasked parent and teacher ratings (ACS, ARS, and SPI) were done, the SDQ was completed by all parents and teachers, and blood samples were taken. Children in the diet group who had behavioural improvement of at least 40% on the ARS—ie, clinical responders—entered the challenge phase; the non-responders left the trial.

IgE and IgG levels were analysed from the blood samples taken at week 1. Total IgE, food-specific IgE (to chicken egg, peanut, soy, milk, fish, and wheat), and food-specific total IgG levels to 270 different foods were assessed with ELISA. Based on the levels of IgG (μg/mL) in serum, measured with a certified

IgG-specific food screening test (ImuPro test), each analysed food was categorised as a low-IgG food or a high-IgG food.

In the diet group responders, in the second phase (double-blind crossover challenge phase; weeks 10–13), two groups of foods consisting of either three high-IgG or three low-IgG foods were consecutively added to the restricted elimination diet, each for 2 weeks. For every child, the composition of the food challenge groups was tailored by the dietician on the basis of total IgG levels to 270 different foods, which were assessed in the first blood samples. Any of the 270 foods could be chosen by the dietician, except for foods that caused increased IgE levels (to preclude an anaphylactic reaction), were disliked by the child, or were already part of the diet. Thus, the foods added in the challenge phase were individually chosen and differed per child. All children were to complete both challenges, and each challenge food group had to be eaten every day in equal amounts during the 2-week period or until behavioural changes occurred.

All behavioural measurements in the challenge phase were double-blind. Parent ACS and ARS assessments were done after each challenge; the other measurements were done at week 13 or at week 11 if there was a relapse in behaviour during the first challenge (**table 1**). If the child's behaviour showed no relapse (according to the double-blind parent ARS score) during the first challenge period (weeks 10–11), the child proceeded with the second challenge (weeks 12–13), and a third blood sample was taken at week 13. Conversely, if the ADHD problems returned during the first challenge, the third blood sampling was brought forward, after which the challenge foods were eliminated again. After a washout period, the length of which depended on the remission of the behavioural problems, the second challenge would start, after which the randomised controlled trial ended.

After the baseline period, the control group followed the first phase until week 13 and received healthy food advice according to the guidelines of the Dutch Nutrition Centre. Parents continued to keep an extended diary until the end of the trial (week 13). Measurements took place at comparable times to the measurements in the diet group (**table 1**). At week 13, the second blood sample was taken, after which all parents of children who did not show behavioural improvements were offered the possibility of starting the diet.

Table 1 Measurement points during baseline, and the first and second phases

	Diet group	Control group
Baseline period		
Weeks 1–3	No foods excluded	No foods excluded
Week 1	ACS, ARS, SPI (LP: P, T) ARS, SPI (JT) Blood samples taken	ACS, ARS, SPI (LP: P, T) ARS, SPI (JT) Blood samples taken
End of week 1	Randomisation	Randomisation
During week 3	ACS, ARS (LP: P) SDQ (P, T)	ACS, ARS (LP: P) SDQ (P, T)
First phase		
Weeks 4–9	Restricted elimination diet	Healthy food advice
During week 9	ACS, ARS, SPI (LP: P, T) ARS, SPI (JT) SDQ (P, T) Blood samples taken	ACS, ARS, SPI (LP: P) SDQ (P)
Second phase*		
Weeks 10–11	First double-blind challenge	Healthy food advice
Week 11	ACS, ARS, SPI† (LP: P, T) ARS†, SPI† (JT) SDQ† (P, T) Blood samples taken†	ACS, ARS (LP: P)
Weeks 12–13	Second double-blind challenge	Healthy food advice
End of week 13	ACS, ARS, SPI‡ (LP: P, T) ARS‡, SPI‡ (JT) SDQ‡ (P, T) Blood samples taken‡	ACS, ARS, SPI (LP: P, T) ARS, SPI (JT) SDQ (P, T) Blood samples taken

Masking (paediatrician only) during the first phase (diet group and control group) is for group assignment, masking (paediatrician, researcher, parent, and teacher) during the second phase (diet group only) is for challenge assignment. ACS=abbreviated Conners' scale. ARS=attention-deficit hyperactivity disorder rating scale. SPI=structured psychiatric interview. LP=researcher assessor. P=parent. T=teacher. JT=paediatrician assessor. SDQ=strengths and difficulties questionnaire. *Diet group responders only. †Responders who relapsed only. ‡Those who had not relapsed at 11 weeks.

The first phase primary endpoints were the difference in ARS (masked paediatrician assessment) and ACS scores (parent; unmasked assessment) between baseline and the end of the first phase. The challenge phase primary endpoints, in the clinical responders, were the change in ARS and ACS score from the end of the first phase to week 11 (after the first challenge) and week 13 (after the second challenge). A relapse in ADHD behaviour was defined as an ARS increase of at least 40% of the ARS score at the end of the first phase, and up to at least 60% of the ARS baseline score.

The first phase secondary endpoints were the IgE blood levels at the start of the trial associated with the behavioural changes at the end of the first phase, and the child's comorbid behavioural problems, assessed by the change in SPI-scores

(masked paediatrician) from week 1 and SDQ-scores (parent) from week 3 to the end of the first phase. The challenge phase secondary endpoints were the food-specific IgG levels at baseline related to the behaviour of the diet group responders after IgG-based food challenges. The other secondary endpoints of physical and sleep problems assessed with the other complaints questionnaire [24], and other blood tests, as specified in the INCA protocol, will be assessed in a separate paper.

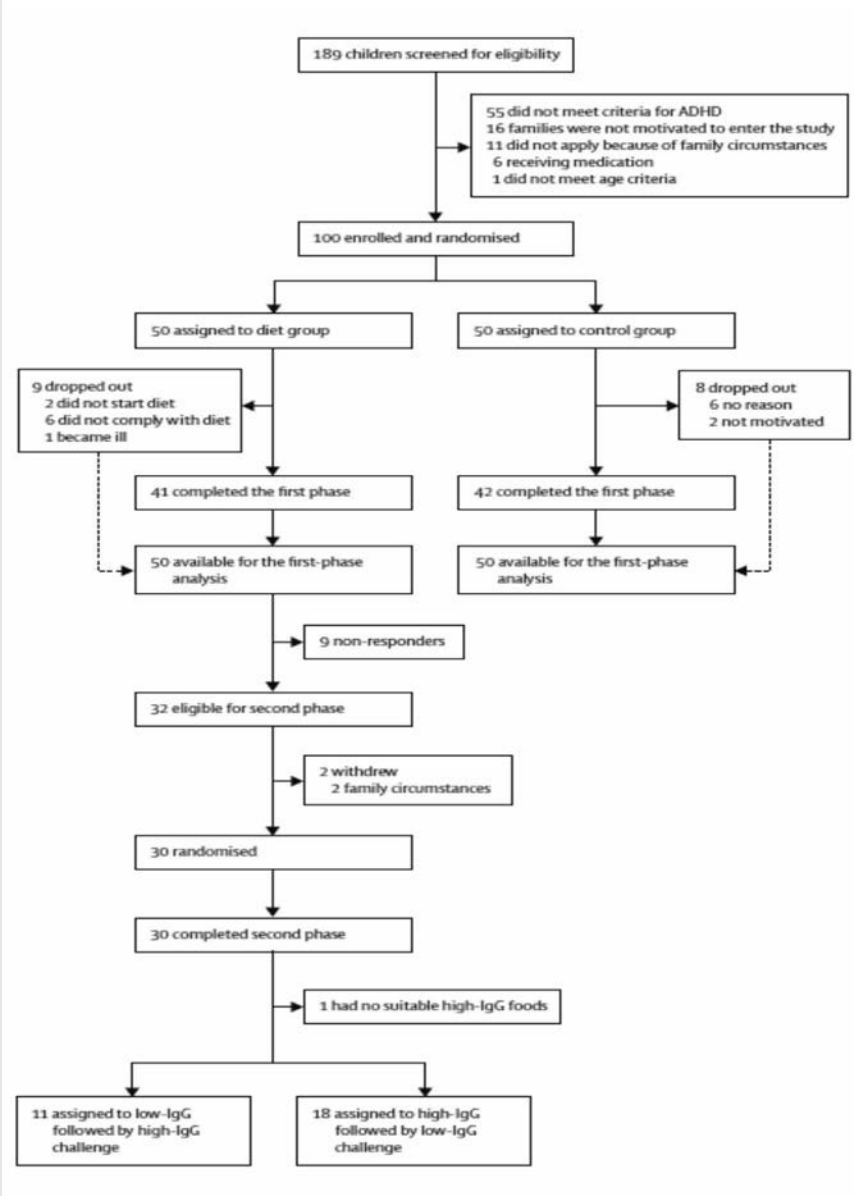
Statistical analysis

In our previous randomised controlled trial [13], 11 of 15 children in the diet group and none of 12 children in the control group showed behavioural improvements of 40% or more. We therefore assumed that a behavioural improvement of at least 40% would occur in 60% of children in the diet group and in 20% of those in the control group in this study. To achieve 80% power (α=0.05, two sided test), taking into account a potential block effect and 10% dropouts, we calculated that 40 children per group were needed. To allow for a potentially higher percentage of dropouts, we included ten extra children per group.

We did statistical analyses with Stata (version 10) and SPSS (version 15). In the first phase, masked measurements were done at Catharina Hospital Eindhoven by JT and unmasked measurements were done at the ADHD Research Centre Eindhoven by LP. In the second phase, double-blind measurements were done by JT and LP. The first phase ARS and SPI analyses were done with the masked measurements and were by intention to treat, last observation carried forward. The challenge phase analyses were per protocol. To assess the agreement between the unmasked (parent) and masked paediatrician measurements for ARS and SPI, we calculated kappa values [25], and intra-cluster correlation coefficients (ICCs) [26] for categorical and continuous parameters, respectively. Kappa values greater than 0.75 (ICC >0.80) were taken to represent excellent agreement beyond chance; values below 0.40 (ICC <0.40) suggested poor agreement.

Behavioural endpoint scores were analysed by a general linear model with treatment (diet group *vs* control group), block, and their interaction as independent variables and baseline scores as covariates. The most reduced model was selected but treatment and block were forced in each model. We assessed the fit of the models with the link test command of Stata. The association between

Figure 1 Trial profile



clinical response (yes or no) and treatment, and its association with IgE blood levels was calculated with Fisher's exact test. We analysed the effect of the crossover challenges (low-IgG or high-IgG) on the child's behaviour with the Mainland-Gart procedure [27]. We did a second analysis that also included those children who responded equally to both challenges with the Prescott test [27]. The effect of the challenges (low-IgG, high-IgG) was expressed as odds ratios (ORs) and estimated by generalised estimated equations (binomial distribution, logit link), with adjustment for challenge period and intra-patient correlation.

INCA is registered as an International Standard Randomised Controlled Trial, number ISRCTN 76063113. The protocol for this study was peer reviewed and accepted by *The Lancet*; a summary of the protocol was published on the journal's website, and the journal then made a commitment to peer review the primary clinical manuscript.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or in the decision to submit for publication. All authors had full access to the data in the study and LMP, NNR, and JKB had final responsibility for the decision to submit for publication.

Results

Between Nov 4, 2008, and Sept 29, 2009, 100 children were enrolled and randomly assigned to the control group (n=50) or the diet group (n=50; **figure 1**). Most children were boys and the mean age was 6.9 years (SD 1.3; **table 2**). Of the 41 children in the diet group who completed the first phase, the diet of 17 was restricted to the few-foods diet only.

Table 3 and **figure 2** show the ARS results from the first phase. Of the 41 (82%) of 50 children in the diet group who completed the first phase, nine (22%) of 41 did not and 32 (78%) of 41 did respond to the diet (**figure 1**). The mean difference in ARS score between baseline and the end of the first phase was significantly higher in the diet group than in the control group for both the masked paediatrician ($p<0.0001$) and unmasked teacher ratings ($p<0.0001$; **table 3**). When comparing the unmasked (parent; LP) with the masked (JT) ARS and SPI

measurements from the first phase, both kappa and ICC of inter-rater agreement were greater than 0.40 (mean 0.90 [SD 0.07] for ICC and 0.83 [0.20] for kappa). The ACS score difference between baseline and the first phase was also significantly higher in the diet group than in the control group for both parent ($p<0.0001$) and teacher ($p<0.0001$) ratings (**table 3**).

The difference between groups on the oppositional defiant disorder criteria measured by the SPI at the end of the first phase was also significant for both the masked paediatrician ($p<0.0001$) and teacher ratings ($p=0.0320$; **table 3**; **figure 2**). Because only three children in the diet group met the criteria for conduct disorder, we did not analyse these results. The decrease in hyperactivity–inattention problems, measured on the SDQ, was similar to the decrease on the ARS (**webappendix page 3**).

Pre-specified IgE immunological analyses in responders (32 of 41) and nonresponders (nine of 41) in the diet group showed no association between clinical response and increased IgE blood levels. Total IgE was increased in six of 30 responders (data missing for two children) and two of nine nonresponders ($p=1.0$, Fisher's exact test). Food-specific IgE levels were increased in one of 31 responders (data missing for one child) and one of nine nonresponders ($p=0.41$, Fisher's exact test).

Of the 32 children who were clinical responders, 30 proceeded to the challenge phase (**figure 1**). 19 of 30 showed a behavioural relapse after one or both challenges. The ACS (unmasked parent) and ARS (masked paediatrician) results in the children in the diet group who were included in the challenge phase ($n=30$) were compared with the results of the children in the control group who completed the trial ($n=42$; **figure 3**). The decrease in ARS total score in the clinical responders from baseline to the end of the first phase was 35.9 (95% CI 33.2–38.6; $p<0.0001$), which subsequently increased after the challenge by 20.8 (14.3–27.3; $p<0.0001$). The decrease in ACS score in the clinical responders from baseline to the end of the first phase was 18.3 (95% CI 16.7–19.9; $p<0.0001$), which increased after the challenge by 11.6 (7.7–15.4; $p<0.0001$). In the control group, the ARS score did not differ between the measurements at week 1 and week 9 (0.8, 95% CI −0.4 to 2.0; $p=0.21$) and week 9 and week 13 (0.8, −0.4 to 2.0; $p=0.17$). In the control group, the ACS score did not differ between week 1 and week 9 (0.2, 95% CI −0.8 to 0.4; $p=0.5$) and between week 9 and week 13 (0.2, −0.5 to 1.0; $p=0.57$). SDQ measurements showed similar results (**webappendix page 4**). Because

Table 2 Demographics and characteristics during week 1

	Diet group (n=50)	Control group (n=50)
Boys	44 (88%)	42 (84%)
Age (years)	6·8 (1·3)	7·0 (1·3)
Pregnancy and birth*		
Mother smoked during pregnancy	5 (10%)	2 (4%)
Pregnancy ≤36 weeks	4 (8%)	4 (8%)
Problems at birth (hypoxia, incubated)	5 (10%)	4 (8%)
Parental data		
Non-native parent(s)	5 (10%)	7 (14%)
1 parent or co-parenting	3 (6%)	3 (6%)
Adopted or foster child	3 (6%)	1 (2%)
Age of onset of behavioural problems		
<2 years	33 (66%)	38 (76%)
2–4 years	16 (32%)	11 (22%)
>4 years	1 (2%)	1 (2%)
Psychiatric history		
Referred because of ADHD symptoms	40 (80%)	44 (88%)
On ADHD drugs before start of trial	6 (12%)	8 (16%)
Allergy data at start of trial		
Increased total IgE level	8 (16%)	6 (12%)
Increased food-specific IgE level	5 (10%)	9 (18%)
ADHD diagnoses at start of trial		
Combined type	41 (82%)	44 (88%)
Inattentive type	3 (6%)	3 (6%)
Hyperactive type	6 (12%)	3 (6%)
Other psychiatric diagnoses at start of trial		
Oppositional defiant disorder	20 (40%)	27 (54%)
Conduct disorder	3 (6%)	5 (10%)

Data are number (%) or mean (SD). ADHD=attention-deficit hyperactivity disorder. *Data missing for two adopted children in the diet group and one in the control group.

only six of 30 teacher data were available at the end of the second phase, we did not analyse these results.

29 of 30 children were included in the IgG assessments (no suitable high-IgG foods were available for one responder; **figure 1**). 11 of 29 children were randomly assigned to start with the low-IgG challenge and 18 to the high-IgG challenge. Each challenge was followed by the other challenge. 13 of 29 low-IgG challenges and 13 of 29 high-IgG challenges resulted in a relapse of ADHD behaviour. No relapse was reported in 11 of 29 children, eight had relapses after both challenges, 15 had relapses after the first challenge, and 11 after the second challenge. The sequence of the challenges (low-IgG then high-IgG or high-IgG then low-IgG) was not significantly associated with the relapse of ADHD symptoms

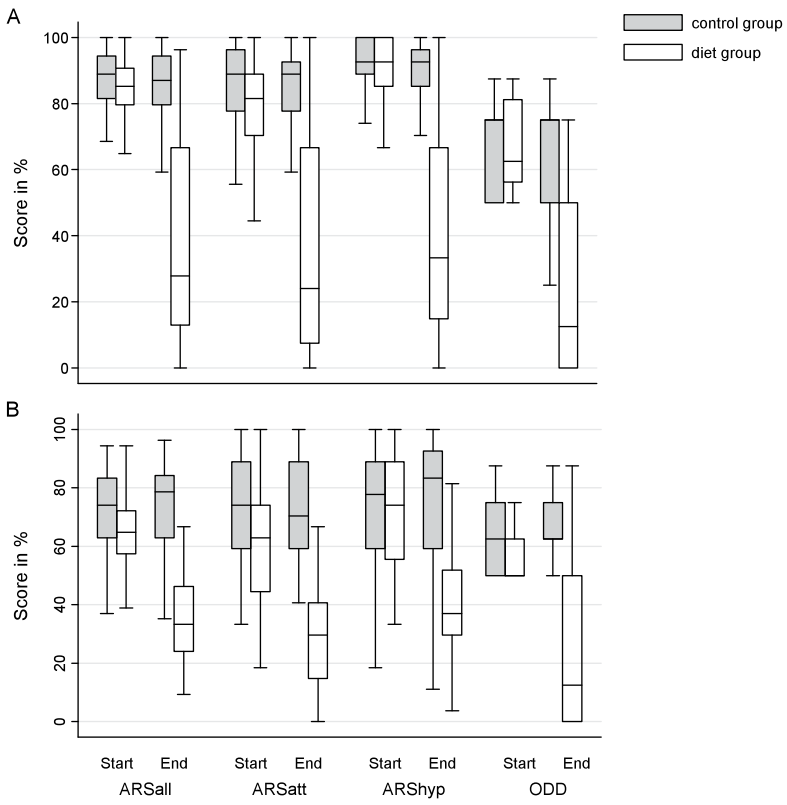
Table 3 ADHD rating scale, abbreviated Conner's scale, and structured psychiatric interview scores at start and end of the first phase

	Diet group (parent n=50; teacher n=37)						Control group (parent n=50; teacher n=40)						End rating*	
	Start	End (week 9)	Difference (95% CI)	p value†	Scale reduction (%)	Cohen's d	Start	End (week 13)	Difference (95% CI)	p value†	Scale reduction (%)	Cohen's d	Difference (95% CI)	p value†
ADHD rating scale														
Parent total score (JT; 0–54)	45·3 (4·7)	21·1 (16·8)	24·2 (19·5–29·0)	<0·0001	53·4	2·0	47·6 (4·1)	46·2 (5·8)	1·3 (0·2 to 2·5)	0·023	2·7	0·28	23·7 (18·6–28·8)	<0·0001
Teacher total score (LP; 0–54)	34·4 (6·7)	20·1 (10·1)	14·3 (11·6–17·1)	<0·0001	41·6	1·67	39·2 (7·8)	39·6 (8·6)	−0·4 (−1·7 to 1·0)	0·580	−1·0	−0·05	15·3 (12·0–18·6)	<0·0001
Parent inattention score (JT; 0–27)	21·2 (4·1)	9·9 (9·0)	11·3 (8·9–13·8)	<0·0001	53·3	1·62	23·2 (3·5)	22·9 (3·6)	0·2 (−0·4 to 0·8)	0·433	0·9	0·09	11·8 (9·1–14·4)	<0·0001
Teacher inattention score (LP; 0–27)	15·1 (5·7)	8·6 (6·1)	6·5 (4·9–8·2)	<0·0001	43·0	1·10	19·5 (5·2)	19·3 (5·2)	0·3 (−0·6 to 1·1)	0·587	1·5	0·04	7·4 (5·4–9·4)	<0·0001
Parent hyperactivity and impulsivity score (JT; 0–27)	24·1 (3·5)	11·2 (8·6)	12·9 (10·5–15·3)	<0·0001	53·5	1·96	24·4 (3·1)	23·3 (4·5)	1·1 (0·2 to 2·0)	0·012	4·5	0·28	11·9 (9·3–14·5)	<0·0001
Teacher hyperactivity and impulsivity score (LP; 0–27)	19·3 (5·0)	11·5 (6·0)	7·8 (6·2–9·5)	<0·0001	40·4	1·41	19·7 (6·6)	20·3 (6·3)	−0·6 (−1·4 to 0·2)	0·128	−3·0	−0·09	8·5 (6·8–10·3)	<0·0001
Abbreviated Conners' scale														
Parent (LP; 0–30)	23·7 (3·4)	11·7 (8·7)	12·0 (9·4–14·6)	<0·0001	50·7	1·82	23·5 (3·9)	23·4 (4·7)	0·1 (−0·7 to 0·8)	0·828	0·3	0·02	11·8 (9·2–14·5)	<0·0001
Teacher (LP; 0–30)	18·5 (3·8)	11·9 (6·7)	6·6 (4·9–8·4)	<0·0001	35·9	1·22	19·1 (4·5)	19·9 (4·6)	−0·8 (−1·4 to −0·3)	0·003	−4·3	−0·18	7·5 (5·9–9·2)	<0·0001
Structured psychiatric interview														
Parent ODD score (JT; 0–8)‡	5·5 (1·1)	1·9 (2·3)	3·6 (2·5–4·6)	<0·0001	65·4	2·00	5·5 (1·2)	5·3 (1·4)	0·2 (−0·3 to 0·7)	0·488	3·6	0·15	3·6 (2·5–4·8)	<0·0001
Teacher ODD score (LP; 0–8)§	4·9 (1·1)	2·1 (2·9)	2·8 (1·5–4·0)	<0·0001	57·1	1·28	5·2 (1·1)	5·0 (1·7)	0·2 (−0·4 to 0·9)	0·501	3·8	0·14	2·0 (0·2–3·9)	0·0320

Data are mean (SD). All data are masked, except for the teacher ratings and the abbreviated Conners' scale ratings. ADHD=attention-deficit hyperactivity disorder. JT=masked paediatrician. LP=unmasked researcher. ODD=oppositional defiant disorder. *Adjusted for score at start and block. The interaction between block and group was not significant (generalised linear model) and the link test showed sufficient fit in all analyses. †Generalised linear model. ‡Diet group n=20, control group n=27. §Diet group n=8, control group n=13.

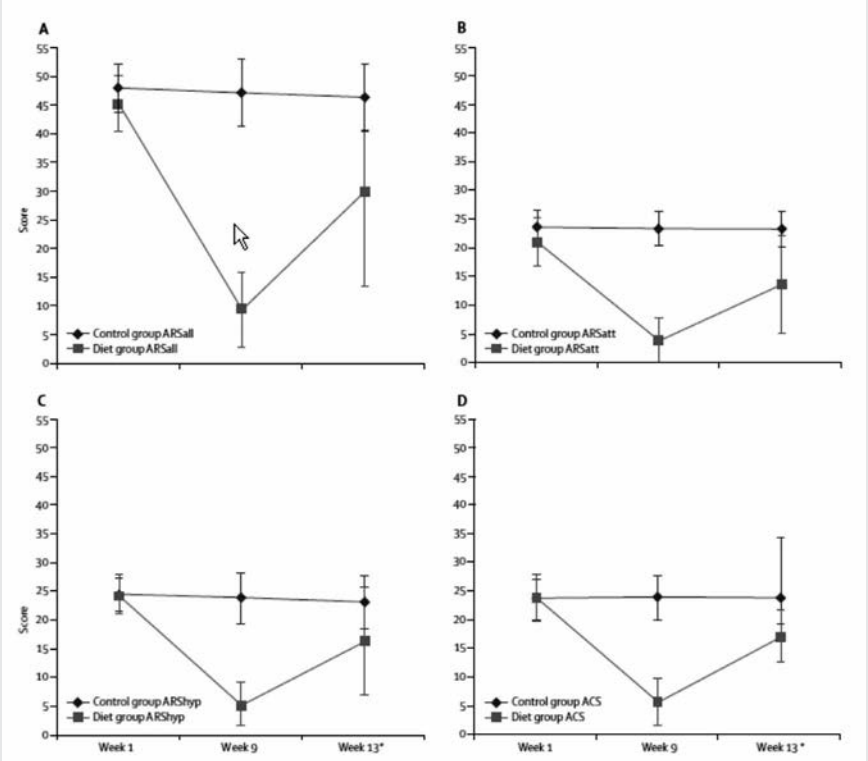
(Mainland-Gart p=1.0; Prescott p=0.38). The generalised estimated equations model showed no significant effects of IgG type (high-IgG *vs* low-IgG OR 0.86, 95% CI 0.36–2.09; p=0.75) or challenge period (first challenge *vs* second challenge 0.55, 0.23–1.33; p=0.26). Parents, teachers, and children reported no harms or adverse events in the first or second phase.

Figure 2 Distribution (Box-Whisker plots) of behaviour scores (%) at start and end of the first phase



Scores according to masked paediatrician (A) and unmasked teacher (B) ratings of control group (in grey) and diet group (in white). To facilitate comparison between the various measures, scores have been standardised as percentages of the maximum score per measures. ARS = ADHD Rating Scale; ARStot = total score, maximum score 54 (100%); ARSatt = inattention score, maximum score 27 (100%); ARShyp = hyperactivity /impulsivity score, maximum score 27 (100%); ODD = Oppositional Defiant Disorder, maximum score 8 (100%). Bars = maximum and minimum score. Shaded boxes = interquartile range. Horizontal bars within boxes = median.

Figure 3 Behaviour scores at week 1, week 9, and week 13*



ARS total (A), inattention (B), and hyperactivity and impulsivity scores (C), and ACS scores (D) for the diet (n=30) and control (n=42) groups at week 1 (start), week 9 (end of the first phase in the diet group and during the first phase in the control group), and week 13 (end of the second phase in the diet group and end of the first phase in the control group). All ARS scores were masked paediatrician ratings except for the week 9 control group scores. All ACS scores were unmasked, except for the scores in the diet group at the end of the second phase. Error bars=SD. ADHD=attention-deficit hyperactivity disorder. ACS=abbreviated Conners' scale. ARSall=ADHD rating scale total score (maximum score 54). ARSatt=ADHD rating scale inattention score (maximum score 27). ARShyp=ADHD rating scale hyperactivity and impulsivity score (maximum score 27). *Week 11 in case of behavioural relapse in the diet group.

Discussion

In the INCA study, the restricted elimination diet had a significant beneficial effect on ADHD symptoms in 32 (64%) of 50 children, and reintroducing foods led to a significant behavioural relapse in clinical responders. Blood tests assessing IgG levels against foods did not predict which foods might have a deleterious behavioural effect. The effect of the diet was consistent and had a similar effect in reducing both ADHD and oppositional defiant disorder symptoms. Because of

the worse prognosis of children with comorbid oppositional defiant disorder compared with those without comorbid disease, interventions that reduce oppositional defiant disorder symptoms have great clinical potential. The number of children with conduct disorder was, in accordance with the young age of the patients, too small to draw conclusions.

Total IgE levels were increased only in a few children, equally in responders and nonresponders, suggesting that the underlying mechanism of food sensitivity in ADHD (which could be related to genetic factors [28]) is non-allergic, although we cannot rule out the involvement of a cell-mediated allergic response. In the second phase, some eliminated foods were added to the diet of the responders. Although the challenges consisted of only two groups of three different individually selected foods, there was a substantial relapse in behaviour in 63% of children. We recorded no difference in behavioural effects after challenge with high-IgG or low-IgG foods. These results suggest that use of IgG blood tests to identify which foods are triggering ADHD is not advisable. However, IgG blood tests might be useful in other diseases [29,30].

Our results must be viewed in light of some limitations. First, in the first phase, we did an open-label randomised controlled trial with masked measurements by an independent paediatrician because parents, teachers, and researchers could not be masked. This method is generally accepted and applied when a double-blind randomised controlled trial cannot be done [31–37]. Nevertheless, expectations of the parents cannot be fully ruled out as a possible cause of the behavioural improvements. Theoretically, the fact that the second assessment was done by the paediatrician after 9 weeks in the diet group compared with after 13 weeks in the control group might have led to unmasking of the paediatrician. To prevent this from happening, the paediatrician was not informed about any previous assessments. Because of the number of children included, with new children starting every week, and some children from the diet and control groups returning every week for their second assessments, the paediatrician was unlikely to remember whether he had seen a particular child 9 or 13 weeks earlier. Parents were also instructed not to reveal any information about group assignment. Second, we cannot rule out that the behavioural improvements during the first phase might have been caused by increased attention for the child in the diet group. However, to avoid differences between groups the control group received healthy food advice and parents kept an extended diary of their child's behaviour

during the trial. Furthermore, the relapse in behaviour during the second phase, which required comparable parental attention as in the first phase, might be regarded as an internal replication of the effects of the diet. Third, we applied a tailor-made diet for each child to minimise the burden of the diet. In 24 (59%) of 41 children this individually composed diet proved to be sufficient.

Research in context

Systematic review

We first searched PubMed and the Cochrane Library with no date limits set (search terms "ADHD AND diet", "ADHD AND elimination diet" and "ADHD AND food") and then screened the references of relevant articles. Our search identified seven published randomised controlled trials [10,13,38–42], that applied some form of restricted elimination diet (ie, a diet that did not just focus on single foods such as additives or sugar) in children with ADHD.

Interpretation

The total number of children involved in these trials was 188 (age 2–15 years), and all trials showed evidence for the efficacy of a restricted elimination diet on ADHD. The overall weighted effect size of this group of heterogeneous studies was 1.6, but treatment groups were either small or only patients who had an allergic constitution were included, which thus impeded extrapolation of the results to the general population. Our study shows comparable effect sizes in patients who are representative of the general ADHD population, supporting the implementation of a dietary intervention in the standard of care for all children with ADHD.

A strength of the INCA study was its design, which included multiple ratings, its large sample size, and blood tests to investigate the existence of an immunological mechanism of action. Furthermore, the heterogeneous sample is representative of the general population of children with ADHD, and thus the results of our study are applicable to young children with ADHD whose parents are motivated to follow a 5-week dietary investigation period (**panel**). Another strength is the investigation of the effects of the diet on comorbid disorders such as oppositional defiant disorder. The results of the multiple ratings are consistent, which provides evidence for the clinically relevant beneficial effects of a restricted elimination diet on ADHD and oppositional defiant disorder.

The mechanisms and effects of food need to be investigated—eg, at a functional and structural brain level and in relation to genetic factors that increase the susceptibility to ADHD. Also, the challenge procedure, which is done to identify the incriminated foods in clinical responders, should be made as easy as possible to follow, to increase the feasibility of the diet. Furthermore, the long-term effects of foods should be investigated; children might outgrow the sensitivity to the incriminating foods when they are avoided for a long period of time.

Our study shows considerable effects of a restricted elimination diet in an unselected group of children with ADHD, with equal effects on ADHD and oppositional defiant disorder. Therefore, we think that dietary intervention should be considered in all children with ADHD, provided parents are willing to follow a diagnostic restricted elimination diet for a 5-week period, and provided expert supervision is available. Children who react favourably to this diet should be diagnosed with food-induced ADHD and should enter a challenge procedure, to define which foods each child reacts to, and to increase the feasibility and to minimise the burden of the diet. In children who do not show behavioural improvements after following the diet, standard treatments such as drugs, behavioural treatments, or both should be considered.

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Webappendix page 1

INCA diary (compressed format)

RED-dairy of: …… …..……day, ……-…… – 2011				
	Medication	Food and drinks	Activities*	Physical complaints and behaviour
Night				
Breakfast				
Snack				
Lunch				
Snack				
Dinner				
Evening				
Night				

* Register all activities: at home, at school, breaks at school, at sports, at day care, when playing, going to hair dresser, at day trips, swimming, visits, etc.

Webappendix page 2

The INCA Restricted Elimination Diet

This individually composed Restricted Elimination Diet (RED), which had to be followed for 5 weeks at the most, was based on the few foods diet as described by Hill and Taylor [1]. Assuming that children might show ADHD symptoms after eating any kind of foods, the few foods diet consisted only of a limited number of hypo-allergenic foods, like rice, turkey, lamb, a range of vegetables (lettuce, carrots, cauliflower, cabbage, beet), pears and water [2]. In our study the RED was complemented with specific foods like potatoes, fruits, and wheat, to be eaten according to a compulsory intake schedule, in order to compose an elimination diet as comprehensive as possible for each individual child, thus making the intervention less incriminating for child and parents [3,4]. If the parents reported no behavioural changes by the end of the second week, the RED was further restricted and gradually limited to the few foods diet: all other foods were prohibited, but vegetables, rice and meat were allowed every day, in unlimited amounts. Calcium was supplied daily via non-dairy rice drink with added calcium, ensuring that children were not at risk for nutrient deficiencies.

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Webappendix page 3

Web-table 1 SDQ measurements according to parent and teacher ratings, at start and at end phase 1

	Diet group (Parent: n=50 resp 41* for start and end measurement) (Teacher: n=50 resp 33* for start and end measurement)						
	Start	End	Mean difference (95% CI) start-end	p value[a]	%SR[b]	Cohen's d	
	Mean (SD)						
Parent emotion	3·7 (2·7)	1·9 (2·0)	1·8 (1·2–2·5)	<0·0001	49·2	0·8	
Teacher emotion	2·5 (2·7)	1·9 (2·0)	0·6 (0·0–1·3)	0·044	26·0	0·3	
Parent conduct	3·6 (2·0)	1·7 (1·6)	2·1 (1·3–2·8)	<0·0001	57·2	1·1	
Teacher conduct	2·7 (2·0)	2·2 (2·1)	0·5 (-0·1–1·2)	0·10	19·8	0·3	
Parent Hyper	8·9 (1·2)	4·1 (2·6)	4·7 (3·8–5·6)	<0·0001	52·8	2·4	
Teacher Hyper	8·6 (1·7)	6·6 (2·5)	2·3 (1·5–3·1)	<0·0001	22·8	1·2	
Parent Peer	2·9 (2·4)	2·1 (2·4)	0·9 (0·5–1·3)	<0·0001	30·6	0·3	
Teacher Peer	2·6 (2·2)	2·2 (2·0)	0·5 (-0·1–1·2)	0·10	15·0	0·2	
Parent total diff	19·1 (5·1)	9·8 (6·1)	9·5 (7·5–11·5)	<0·0001	49·6	1·7	
Teacher total diff	16·4 (4·9)	12·8 (5·7)	4·3 (2·3–6·3)	<0·0001	21·6	0·7	
Parent impact	3·8 (1·8)	1·0 (1·7)	2·9 (1·2–3·6)	<0·0001	76·6	1·6	
Teacher impact	2·2 (1·5)	1·6 (1·6)	0·9 (0·3–1·4)	0·004	28·1	0·4	

SDQ=Strengths and Difficulties Questionnaire: emotion=emotional symptoms scale, conduct=conduct problems scale, hyper=hyperactivity-inattention scale, peer=peer problems scale, total diff=total difficulties score [the sum of all scales], impact=impact score [the sum of items on overall distress and social impairment, interfering with home life, peer relationships, leisure activities and

	Control group (Parent: n=48* resp 42* for start and end measurement) (Teacher: n=47* resp 42* for start and end measurement)						End rating control versus diet group, adjusted for scores at start and block†	
	Start	End	Mean difference (95% CI) start-end	p value[a]	%SR[b]	Cohen's d	Mean difference (95% CI)	p value[a]
	Mean (SD)							
	3·1 (2·4)	3·0 (2·5)	0·2 (-0.4–0·8)	0·48	6·7	0·1	-1·4 (-2·2– -0·6)	0·001
	2·7 (2·4)	2·0 (2·2)	0·7 (0·0–1·4)	0·052	26·9	0·3	0·1 (-0·7–0·8)	0·88
	3·7 (2·5)	3·5 (2·3)	0·3 (-0·3–0·9)	0·31	7·9	0·1	-1·8 (-2·5– -1·0)	<0·0001
	3·2 (2·2)	3·0 (2·4)	0·0 (-0·4–0·4)	1·00	3·8	0·1	-0·5 (-0·4–1·5)	0·28
	9·5 (0·8)	9·1 (1·3)	0·3 (-0·1–0·8)	0·15	3·5	0·3	-4·9 (-5·9– -4·0)	<0·0001
	8·7 (1·7)	8·6 (1·7)	0·2 (-0·4–0·5)	0·75	1·5	0·1	-2·1 (-3·0– -1·3)	<0·0001
	2·4 (1·9)	2·4 (2·3)	0·0 (-0·5–0·5)	1·00	0·0	0·0	-0·8 (-1·4– -0·16)	0·014
	2·9 (2·1)	2·9 (1·9)	0·0 (-0·5–0·5)	1·00	1·4	0·0	0·5 (0·1–1·2)	0·13
	18·7 (5·1)	18·0 (6·1)	0·8 (-0·5-2·1)	0·20	4·4	0·1	-8·3 (-10·1– -6·1)	<0·0001
	17·5 (5·6)	16·5 (6·0)	1·1 (-0·5–2·6)	0·17	5·8	0·2	-3·0 (-5·2– -0·7)	0·009
	3·9 (2·2)	2·9 (2·0)	1·0 (0·5–1·5)	<0·0001	25·0	0·5	-1·9 (-2·7– -1·2)	<0·0001
	2·7 (1·5)	2·4 (2·0)	0·4 (-0·1–0·8)	0·09	11·8	0·2	-0·5 (-1·1–0·2)	0·17

classroom learning]. *The number of forms included in the computations depended on the number of forms received eventually [the forms had to be filled in at home (parent) or at school (teacher) and had to be returned per post]. [a] Based on GLM. [b] %SR=% scale reduction. † The interaction between block and group was insignificant (GLM) and the link test showed sufficient fit in all analyses.

Webappendix page 4

Web-table 2 SDQ measurements according to parent* ratings in diet responders (n=30), at start and at end phase 2

	Diet group Responders Return behavioural problems after challenge n=19						
	Start phase 2	End phase 2	Mean difference (95% CI) start-end	p value[a]	%SR[b]	Cohen's d	
	Mean (SD)						
Emotion	1·5 (1·5)	3·3 (2·4)	-1·8 (-2·9– -0·7)	0·002	-120·0	-0·9	
Conduct	1·3 (1·0)	3·8 (1·7)	-2·5 (-3·4– -1·6)	<0·0001	-192·3	-1·8	
Hyper	3·2 (1·8)	7·7 (1·9)	-4·5 (-5·6– -3·5)	<0·0001	-140·6	-2·4	
Peer	1·4 (1·6)	2·1 (2·1)	-0·7 (-1·2– -0·2)	0·005	-50·0	-0·4	
Total diff	7·3 (3·7)	16·8 (5·0)	-9·5 (-12·1– -6·9)	<0·0001	-130·1	-2·2	
Impact	0·5 (1·0)	3·7 (1·9)	-3·2 (-4·2– -2·1)	<0·0001	-640·0	-2·1	

SDQ=Strengths and Difficulties Questionnaire: emotion=emotional symptoms scale, conduct= conduct problems scale, hyper=hyperactivity-inattention scale, peer=peer problems scale, total diff=total difficulties score [the sum of all scales], impact=impact score [the sum of items on overall distress and social impairment, interfering with home life, peer relationships, leisure activities and classroom learning]. *Teacher data were not analysed, as only 6/30 teachers returned the forms. [a] Based on GLM. [b] %SR=% scale reduction.

	Diet group Responders No return behavioural problems after challenge n=11					
	Start phase 2	End phase 2	Mean difference (95% CI) start-end	p value[a]	%SR[b]	Cohen's d
	Mean (SD)					
	1·7 (2·1)	1·5 (1·8)	0·2 (-1·1–1·5)	0·79	11·8	0·1
	1·1 (1·0)	0·9 (0·9)	0·2 (-0·7–1·1)	0·68	18·2	0·2
	3·1 (1·1)	3·5 (1·6)	-0·5 (-1·7–0·8)	0·49	-12·9	-0·3
	1·7 (2·0)	1·9 (2·2)	-0·2 (-0·8–0·5)	0·58	-11·8	-0·1
	7·6 (4·4)	7·9 (4·9)	-0·3 (-3·7-3·1)	0·88	-3·9	-0·1
	0·3 (0·6)	0·6 (1·3)	-0·4 (-1·1-0·4)	0·35	-133·3	-0·3

Chapter 7

Are the effects of a restricted elimination diet on ADHD and ODD mediated by changes in family structure: a further analysis of the INCA study

Submitted as:

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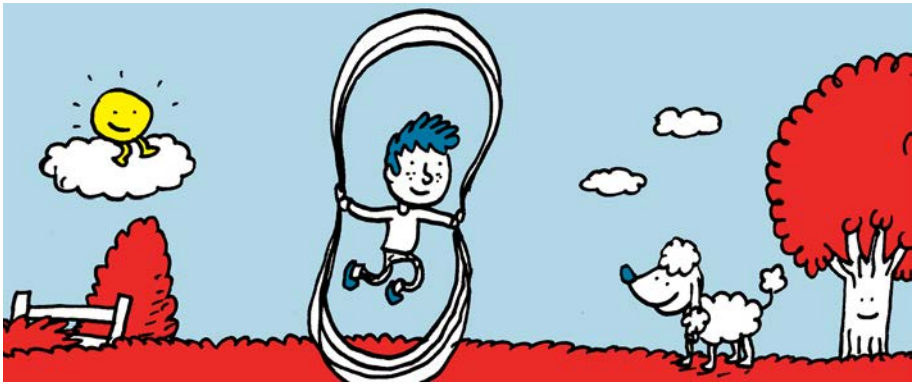


Abstract

Objectives Research has shown conclusive evidence for the effects of a Restricted Elimination Diet (RED) on Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD) in young children. However, behavioural improvements may also be mediated by changes in family environment following an RED. We aimed to investigate whether changes of family environment contributed to the positive behavioural effects of an RED in children with ADHD.

Method Twenty-four children with ADHD, a subsample of the Impact of Nutrition on Children with ADHD (INCA) study investigating the effects of an RED on ADHD and ODD[1], were randomised to either a 5-week RED intervention (n = 11), or a control intervention(n = 13). An additional No-ADHD control group did not receive any intervention (n = 23). Blinded (ADHD groups) and open assessments (No-ADHD control group) at start and end of the trial concerned the children's behaviour (assessed by the ADHD Rating Scale and a Structured Psychiatric Interview) and family structure and relationships (assessed by the Family Environment Scale [FES]).

Results When compared to the norm, significantly higher FES scores were found in both ADHD groups and in the No-ADHD control group at baseline. Both ADHD groups showed significantly higher scores for conflicts than the No-ADHD control group. When comparing start and end measurements, no differences in family environment were found in both ADHD groups.

Conclusions The effects of an RED on ADHD and ODD symptoms are not mediated by improvement of family environment.

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD), characterized by problems in attention, impulse control and activity regulation[2], is one of the most common psychiatric disorders, with a strong genetic disposition.[3] Both biological as well as psychosocial environmental factors are related to ADHD, including prenatal maternal smoking, prematurity, low birth weight, foetal distress, foster placing and disturbed parent-child relationships.[4-6] An important, albeit controversial, environmental factor that may trigger ADHD is food[7]. Research investigating the effects of additives like colourings and preservatives on ADHD, has shown that, although additives may have some effects on the behaviour of all children (effect size 0.3), additives do not cause ADHD.[8] Conversely, recent research investigating the effects of a Restricted Elimination Diet (RED), i.e. eliminating many kinds of foods from the child's diet, has shown statistically significant and clinically relevant results, with effect sizes on the ADHD DSM-IV Rating Scale varying from 1.7 according to the open teacher measurements to 2.0 according to the blinded paediatrician measurements.[1] These results confirm the outcomes of seven previous randomised controlled trials, investigating the effects of an RED on ADHD, with an overall effect size of 1.6.[1]

One could argue that the children's behavioural changes might be due to concomitant improvement of parental behavioural strategies, caused by the strict parental supervision necessary to comply with the RED. Research has shown that ADHD is associated with disruptive parent-child relationships and poor parenting structure[9-12], even more when children are suffering from comorbid oppositional defiant disorder (ODD).[6] Conversely, consistent parenting and positive parent-child interactions are associated with improvements of child behaviour.[13] This suggests the possibility that behavioural improvements assessed in the RED trials might be mediated by the strict parenting structure necessary to follow the RED, rather than be a direct result of the diet.

The present study uses a subsample of the Impact of Nutrition on Children with ADHD (INCA) study and investigated whether the effects of an RED on ADHD and ODD symptoms as previously reported[1], can be explained by changes in family structure during the intervention. A group of No-ADHD control children was included as a comparison group, to investigate changes in family structure over time. Our study is the first study investigating the effects of following an RED on parenting abilities.

Methods

Participants

Children with ADHD were recruited as part of the INCA study (n = 100), investigating the effects of an RED on ADHD and ODD in children, the results of which have been reported elsewhere.[1] All parents of children entering the INCA study in September 2009 (ADHD RED group n = 11, ADHD control group n = 13), took part in this study. INCA inclusion criteria were 1) the children were diagnosed with ADHD any subtype[2], 2) children were age 4-8, 3) their parents had sufficient command of the Dutch language and 4) parents were motivated to follow an RED during a 5-week period. Exclusion criteria were children taking medication for ADHD or receiving behavioural therapy, children already following a diet, or family circumstances which were likely to impede completion of the study. The INCA study was approved by the Medical Ethics Committee of Wageningen University and by the executive board and ethics committee of Catharina-Hospital Eindhoven.

A control group (n = 23) consisting of children without ADHD, aged 4-8 years, was recruited through the teachers of the participating INCA-children. All teachers were contacted by phone and were asked to distribute an information leaflet, concerning a request to participate in this study, to parents of children without any behavioural problems at school. Interested parents filled in the ADHD DSM-IV Rating Scale (ARS) and subsequently were contacted by phone. Parents of all children participating in this trial gave written informed consent before the start of the study.

Measures

Three questionnaires were used to assess outcome: 1) the Dutch version of the Family Environment Scale (FES)[14], to assess family relationships and parenting structure; 2) the 18-item ADHD DSM-IV Rating Scale (ARS)[15] to assess ADHD, and 3) a semi-structured, DSM-IV-based, psychiatric interview ([SPI][16], to assess ODD. The FES consists of 77 yes/no questions related to 7 subscales: 1) cohesion (family commitment and support), 2) expressiveness (expression of feelings), 3) conflict (expression of anger and aggression), 4) organization (structure and planning of family life), 5) control (rules used in family life), 6) family values (opinion about norms and behaviour) and 7) social orientation (involvement in the social environment). Each subscale consists of 11 questions and scores range

from 0 to 11, higher scores indicating a more positive environment, with the exception of the conflict scale. In this study two index scores were used: the Family Relationships Index (FRI), based on three subscales (i.e. cohesion, expressiveness and conflict) and the Family Structure Index (FSI), based on two subscales (i.e. organization and control). Higher scores indicate better family relationship and parental structure.[17] Both FES subscales and FES indices have shown good reliability and adequate validity.[14] The two subscales which are not linked to the two indices i.e. family values and social orientation are not included in this article.

The ARS, based on the DSM-IV criteria for ADHD, was used to assess ADHD, and consists of 18 criteria, nine inattention and nine hyperactivity/impulsivity criteria, using a 4-point scale (0 = never [less than once a week], 1 = sometimes [several times a week], 2 = often [once a day], and 3 = very often [several times a day]), with a maximum of 54 points.

Comorbid ODD was assessed by the SPI, based on the eight DSM-IV-ODD-criteria, with a maximum of 8 points. A detailed description of the behavioural questionnaires has been published elsewhere.[1]

Procedures

The study design is shown in **figure 1**. The assessment points of all questionnaires, in both ADHD groups and in the No-ADHD control group, were at baseline and at the end of the trial, and data were collected in all children participating in the study (n = 47). After the baseline assessments the ADHD group (n = 24) was randomised to the ADHD RED group (n = 11) or the ADHD control group (n = 13). The ADHD control group received healthy food advices according to the guidelines of the Dutch Nutrition Centre, the ADHD RED group followed a 5-week individually composed RED. The RED, of which the details are described elsewhere[18], was based on the few foods diet, consisting of rice, meat, vegetables, pears, and water. This diet was complemented with specific foods such as potatoes, fruits, and wheat, in order to create an elimination diet as comprehensive as possible for each individual child, thus making the diet easier for children and their parents to follow. If the parents reported no behavioural changes by the end of the second diet week, the diet was gradually restricted to the few foods diet only. After the baseline assessments the control group without ADHD (n = 23) did not receive any intervention.

The FES was filled in by the parents in both ADHD groups and the No-ADHD control group. The ADHD and ODD behavioural ratings in both ADHD groups were executed by a paediatrician blinded for treatment assignment[1], whereas the behavioural ratings in the No-ADHD control group were unmasked parent assessments.

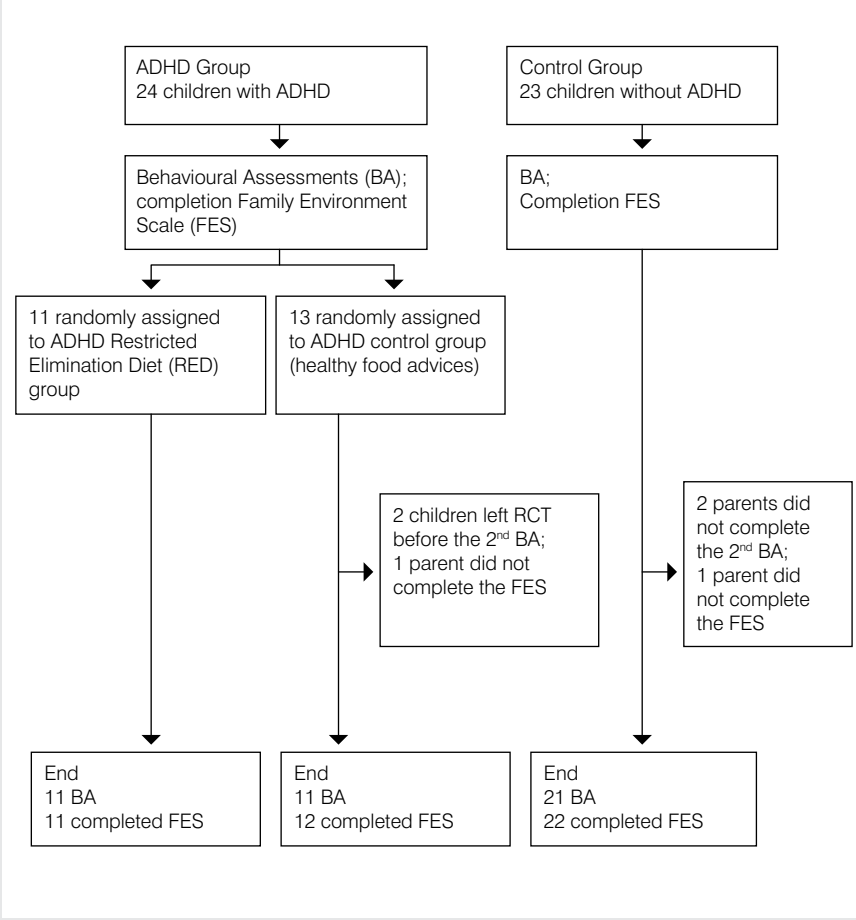
Statistics

Statistical analyses were done with STATA version 10 and SPSS version 15. Statistical significance was based on $\alpha = 0.05$, two sided, and clinical relevance was expressed by means of effect sizes (ES), with ES ≥ 0.5 indicating a clinically significant effect.[19] FES-outcomes at baseline before randomisation were compared between ADHD group, No-ADHD control group and norm score provided by the FES manual, based on 941 mother reports.[14] P-values for differences between groups were obtained using General Linear Model (GLM) and additionally Cohen's d was calculated as effect size estimate. P-values for comparisons with the norm were obtained by the Welch-Satterthwaite equation.

To assess any mediating effects of FES on the behaviour of the children, the FES-outcomes at the end of the study were analysed by GLM, using group (ADHD RED, ADHD control, No-ADHD control) as independent variable and the scores at start of the trial as covariate to adjust for differences that were potentially present at start already.

ADHD and ODD analyses were by intention-to-treat, last observation carried forward, and based on the blinded measurements in both ADHD groups. A detailed description has been published elsewhere.[1] Repeated measurement models were used to separately analyse the moderating role of the two FES indices (Relationship and Structure) on the effect of the RED on ADHD and ODD scores. Independent variables were 1) group (ADHD RED or ADHD control), 2) measurement point (start or end), and FES indices (FRI of FSI). Child was added as repeated effect to adjust for potential intra-child correlation (Generalized Estimated Equations, Gaussian distribution, exchangeable covariance structure). Dependent variables were ADHD and ODD scores. All 2-way interactions (FRI and FSI x group, FRI and FSI x measurement point, group x measurement point), and 3-way interactions (FRI and FSI x group x measurement point) were evaluated.

Figure 1 Study design



Results

In both the ADHD control group and the No-ADHD control group two families left the study prematurely and one family did not complete the second FES-questionnaire. None of the families in the ADHD RED group left the trial. Most FES questionnaires were completed by the mother (43 / 47), and most children were boys (38 / 47). No significant differences regarding age, family size, number of

siblings and single parent families were found between the ADHD groups and No-ADHD control group (see **table 1**). In the ADHD group 11 / 24 children (46%) were also diagnosed with comorbid ODD (6 / 11 children in de ADHD RED group, 5 / 13 in the ADHD control group). In the No-ADHD control group one child met the criteria for ODD, none of them meeting the criteria for ADHD.

Table 1 Baseline characteristics of study participants

	ADHD RED n = 11	ADHD control n = 13	No-ADHD control n = 23	P-value Fisher exact
Boys	10 (91%)	10 (77%)	18 (78%)	0.708
Age in years (mean (SD))	7.7 (0.9)	7.2 (1.2)	6.8 (1.4)	0.115[1,2]
Parental / sibling data				
Step/single parent family	0.1 (0%)	1 (8%)	2 (9%)	1.000
FES completed by mother	11 (100%)	11 (85%)	21 (91%)	0.668
Family size, number of siblings				0.073[2]
Only child	0 (0%)	3 (23%)	0 (0%)	0.028[3]
1 sibling	5 (45%)	8 (63%)	16 (70%)	0.431[3]
2 siblings	4 (36%)	2 (15%)	6 (26%)	0.562[3]
3 siblings	2 (18%)	0 (0%)	1 (4%)	0.203[3]
Meeting criteria ADHD / ODD				
ADHD	11[4] (100%)	13[4] (100%)	0[4] (0%)	
ODD	6 (55%)	5 (38%)	1 (4%)	0.001

[1] ANOVA; [2] overall p-value; [3] tested against other categories; [4] frequency equals 100% or 0% by definition

Baseline comparison of family relationships index (FRI) and family structure index (FSI) in ADHD and No-ADHD control families

At baseline the FRI and the FSI scores of the ADHD group preceding randomisation (n = 24) were similar to the scores of the No-ADHD control group (n = 23) (see **table 2**). Also no differences were found between the ADHD RED group (n = 11) and the ADHD control group (n = 13). Both ADHD groups showed significantly more conflicts on the conflict subscale than the No-ADHD control group, whereas

on the other subscales no significant differences were found. When compared to the norm scores provided by the FES-manual, significantly higher scores of FRI and FSI were found in both ADHD groups and in the No-ADHD control group at baseline.

Effects of RED on family relationships index (FRI) and family structure index (FSI)

The FRI and FSI baseline and endpoint scores of the ADHD RED group and ADHD control group are presented in **table 3**. No intervention effect was found on the FRI and FSI, neither in the ADHD RED group nor in the ADHD control group.

Effects of RED on ADHD and ODD symptoms taking into account any effects of family relationships and family structure

The effects of the diet intervention on ADHD and ODD are shown in **table 3**. The analysis of the ADHD score using a repeated measurement design showed that FRI was significantly associated with the ADHD score (i.e. a higher FRI was related to less ADHD symptoms), independent of ADHD group and measurement moment (estimate -0.8, 95% CI = -1.5 - -0.1, p = 0.024, see **figure 2.1A and B**). The 2-way and 3-way interactions with group and measurement point were non-significant. No effect of FSI on ADHD score was found, (estimate 0.8, 95% CI = -0.2 - 1.8, p = 0.134), and the 2-way and 3-way interactions were non-significant, suggesting that changes in both FRI and FSI did neither mediate nor moderate the results of the RED on ADHD symptoms.

A similar analysis for ODD score equally showed a significant association for FRI, independent of ADHD group and measurement moment (estimate -0.2, 95% CI = -0.4 - -0.03, p = 0.022), indicating that a higher FRI was related to less ODD symptoms (see **figure 2.2A and B**). No effect of FSI on ODD score was found (estimate 0.2, 95% CI = -0.1 - 0.5, p = 0.238). Again 2-way and 3-way interactions were non-significant, suggesting that changes in both FRI and FSI did neither mediate nor moderate the results of the RED on ODD symptoms.

Table 2 FES ratings in ADHD group, No-ADHD control group and the FES-manual norm, at start trial

	1 n=24	2 n=23	3 n=941	Difference 1-2[1]			Difference 1-3[2]			Difference 2-3[2]		
	ADHD group	No-ADHD Control group	Norm	Mean difference	p value	Cohen's d	Mean difference	p value	Cohen's d	Mean difference	p value	Cohen's d
	Mean (SD)											
Cohesion	8.9 (1.7)	9.1 (0.9)	8.5 (2.0)	-0.2 (-1.0-0.4)	0.59	-0.2	0.4	0.134	0.2	0.6	0.003	0.4
Expressiveness	10.1 (1.3)	9.7 (1.2)	8.3 (2.2)	0.3 (-0.4-1.1)	0.352	0.3	1.8	<0.0001	1.0	1.4	<0.0001	0.8
Conflict	4.7 (2.2)	3.0 (2.1)	5.0 (2.5)	1.7 (0.5-2.9)	0.007	0.8	-0.3	0.256	-0.1	-2.0	<0.0001	-0.9
Organization	8.3 (1.5)	8.7 (1.0)	8.0 (2.3)	-0.4 (-1.2-0.3)	0.230	-0.3	0.3	0.175	0.2	0.7	0.002	0.4
Control	9.5 (1.3)	9.5 (1.2)	8.5 (2.1)	0.0 (-0.7-0.7)	0.951	0.0	1.0	0.001	0.6	1.0	<0.0001	0.6
FRI	25.3 (3.8)	26.8 (2.9)	22.9 (3.4)	-1.5 (-3.5-0.4)	0.123	-0.4	2.4	0.003	0.7	3.9	<0.0001	1.2
FSI	17.8 (2.1)	18.3 (1.7)	16.5 (3.8)	-0.5 (-1.6-0.7)	0.429	-0.3	1.3	0.003	0.4	1.8	<0.0001	0.6

FES: Family Environment Scale; SD Standard Deviation; FRI: Family Relationships Index (consisting of cohesion, expressiveness and conflict); FSI: Family Structure Index (consisting of organization and control); [1]Based on GLM; [2]Based on Welch-Satterthwaite equation

Table 3 Comparison of ADHD score, ODD score and FES ratings within and between ADHD RED group and ADHD Control group at start and at end of trial

	ADHD RED N=11					ADHD Control N=12					End rating ADHD Control versus ADHD RED group, adjusted for score at start	
	Start	End	Mean difference (95% CI) start-end	p value	Cohen's d	Start	End	Mean difference (95% CI) start-end	p value	Cohen's d	Mean difference (95% CI)	p value
	Mean (SD)					Mean (SD)						
ADHD*	44.6 (4.1)	18.1 (12.9)	26.5 (18.2-34.9)	<0.0001	2.8	46.0 (4.2)	43.7 (7.1)	2.3 (-0.-5.6)	0.156	0.4	25.1 (16.4-33.8)	<0.0001
ODD*	3.3 (2.0)	2.0 (2.0)	1.3 (-0.2-2.8)	0.101	0.7	3.2 (2.3)	2.9 (2.6)	0.2 (-0.3-0.8)	0.411	0.1	1.0 (-0.5-2.5)	0.201
Cohesion	8.7 (1.4)	8.9 (1.1)	-0.2 (-0.9-0.5)	0.606	-0.2	8.9 (2.0)	9.0 (1.6)	-0.2 (-0.7.-0.4)	0.575	-0.1	-0.1 (-0.8-0.7)	0.883
Expressiveness	10.1 (1.2)	10.0 (1.6)	0.1 (-0.2-0.4)	0.576	0.1	10.2 (1.5)	10.0 (1.1)	0.2 (-0.4-0.7)	0.538	0.2	0.1 (-0.6-0.7)	0.840
Conflict	5.6 (2.2)	4.7 (2.2)	0.8 (0.0-1.6)	0.041	0.4	4.3 (1.6)	3.8 (1.5)	0.5 (-0.1-1.1)	0.083	0.3	-0.1 (-1.0-0.9)	0.904
Organization	8.4 (1.4)	8.6 (0.7)	-0.2 (-0.8-0.5)	0.606	-0.2	8.1 (1.6)	8.0 (1.6)	0.1 (-0.6-0.7)	0.804	0.1	0.4 (-0.4-1.2)	0.332
Control	9.4 (1.0)	9.8 (1.0)	-0.5 (-0.8- 0.1)	0.004	-0.4	9.5 (1.4)	9.6 (1.5)	-0.1 (-0.6-0.5)	0.772	-0.1	0.3 (-0.3-1.0)	0.295
FRI	24.3 (3.2)	25.2 (3.2)	-0.9 (-2.1-0.3)	0.136	-0.3	25.8 (4.0)	26.3 (2.8)	-0.5 (-1.8-0.8)	0.455	-0.1	-0.1 (-1.6-1.4)	0.882
FSI	17.7 (1.7)	18.4 (1.0)	-0.6 (-1.4-0.2)	0.121	-0.5	17.6 (2.7)	17.6 (2.8)	0.0 (-1.1-1.1)	1.000	0.0	0.7 (-0.6-1.9)	0.282

ADHD: Attention-Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; FES: Family Environment Scale; SD Standard Deviation; FRI: Family Relationships Index (consisting of cohesion, expressiveness and conflict); FSI: Family Structure Index (consisting of organization and control); * last observation carried forward

Figure 2.1 Family Relationship Index (A), Family Structure Index (B) and Predicted ADHD total score for ADHD control and ADHD RED group at start and end. Prediction based on the final GEE model

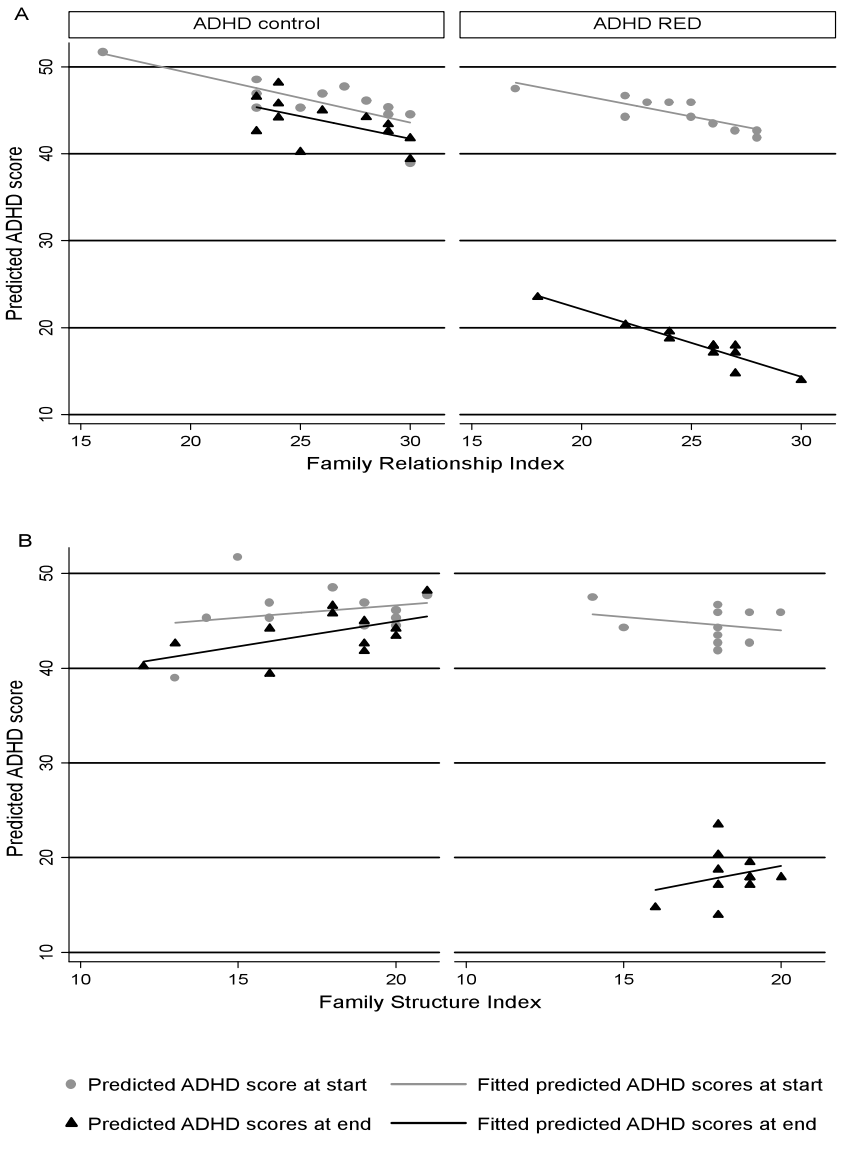
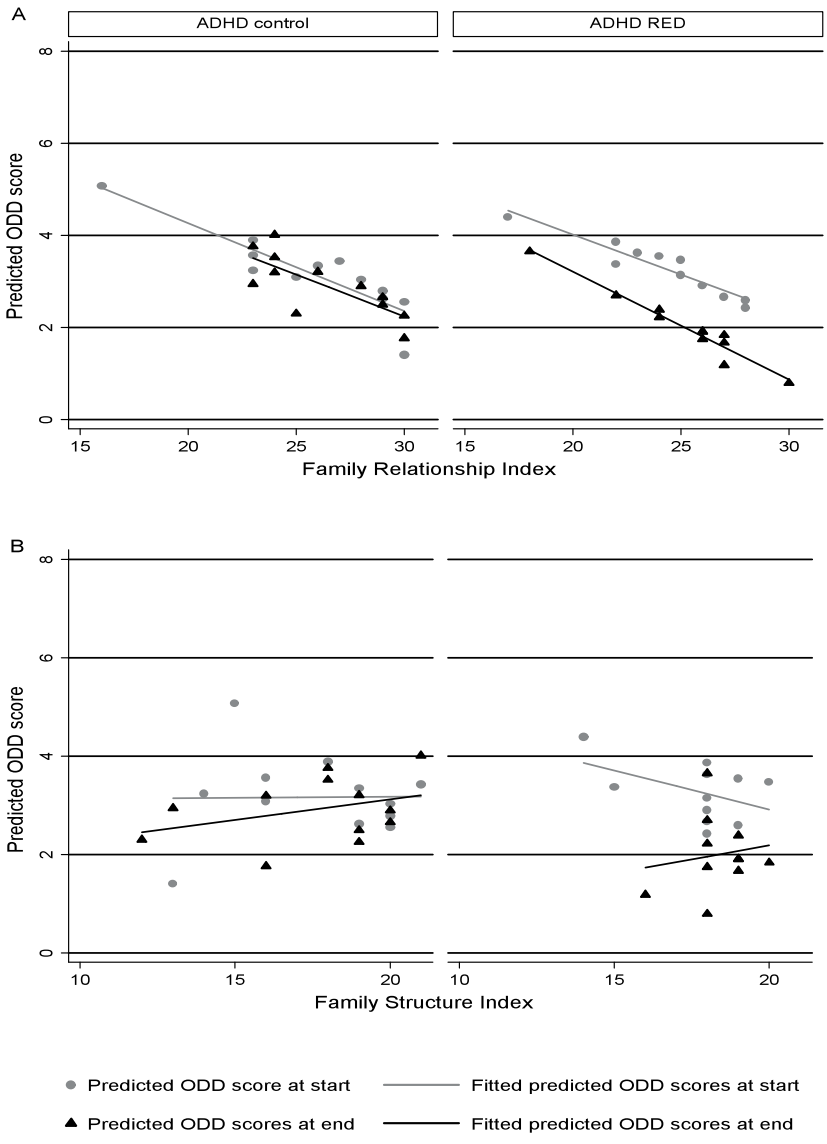


Figure 2.2 Family Relationship Index (A), Family Structure Index (B) and Predicted ODD total score for ADHD control and ADHD RED group at start and end. Prediction based on the final GEE model



Discussion

The main aim of this study was to investigate whether the beneficial behavioural effects in children with ADHD following an RED[1], may be explained by an improvement of family environment, i.e. family relationships and family structure. Our findings indicate that 1) family environment in families of children with ADHD, motivated to follow a 5-week RED, is similar to the family environment of a No-ADHD control group and better than the FES-manual norm; 2) family relationships and structure are not affected by following a 5-week RED; 3) the effects of an RED on ADHD and ODD symptoms are not mediated by changes in family relationships and structure (in fact, there were no changes); 4) family relationships but not family structure are inversely associated with ADHD and ODD.

At baseline we did not find any significant differences in family environment between the ADHD group (n = 24) and the No-ADHD control group (n = 23), nor between the ADHD RED group (n = 11) and the ADHD control group (n = 13). All groups, however, showed a better family environment compared to the norms. Consequently, relationships and structure of ADHD families taking part in this study were (more than) adequate. These findings are consistent with the findings of Pimentel at al[20], who found that parental practices of mothers of children with ADHD were similar to those of a validation sample. Conversely, our results are contrary to the findings of Kepley & Ostrander[21] who found that families with ADHD were less cohesive and expressive than families without ADHD. It is conceivable that this discrepancy may be caused by the fact that, in advance, parents were adequately informed about the stringency of the diet. It is conceivable that parents who dreaded this challenge would decide not to participate, and that only parents who were confident of their parenting capacities, would decide to participate. Consequently, our sample may have consisted of families with an above average family environment only.

We found no differences in family relationships and structure when comparing the start and end measurements of both ADHD groups. Consequently, in our sample the RED did not affect family environment. Considering that all families in the ADHD RED group completed the study, we could not investigate the parenting capacities of parents not complying with the diet.

The results of the RED on the behavioural outcomes of the ADHD group, i.e. statistically significant and clinically relevant improvements of ADHD and ODD in

64% of the children, have been discussed elsewhere.[1] The analyses of two-way and three-way interactions of the family relationships and structure indices and behaviour, with group and measurement point as independent variables, showed that family relationships and structure did not mediate the effect of the RED on ADHD and ODD symptoms. However, we found an inverse correlation between family relationship and both ADHD and ODD symptoms, i.e. a higher family relationships index score co-occurred with less ADHD and ODD symptoms. These findings are consistent with the findings of Deault[6], showing that ADHD is associated with conflicted parent-child relationships. We found no significant association between family structure and both ADHD and ODD symptoms.

Limitations of this study should be noted. First, the ADHD-group only consisted of families with good family environment. It is conceivable that families with less adequate family environments were deterred from following an RED, which may have led to a sample bias. Consequently, our study shows that in families with an average family environment an RED is a feasible intervention in children with ADHD. Second, it is conceivable that parenting problems might impede the compliance to and the completion of the RED, but this aspect could not be investigated because all families assigned to the ADHD RED group completed the diet. Concluding, behavioural improvements of children with ADHD and ODD following an RED are not mediated by improvements of family relationships and structure. The results of our study are applicable to those families of young children with ADHD motivated to follow a 5-week RED.

Key points

- At baseline family environment scores of the ADHD group were similar to those of a control group without ADHD and better than those of the norm group
- The ADHD group reported significantly more conflicts than the control group without ADHD at baseline
- In families of children with ADHD, with or without ODD, family relationships and family structure did not change during a 5 week Restricted Elimination Diet (RED)
- Behavioural improvements of children with ADHD, with or without ODD, were not mediated by changes in family environment during the RED
- ADHD and ODD were negatively associated with family relationships but not with family structure

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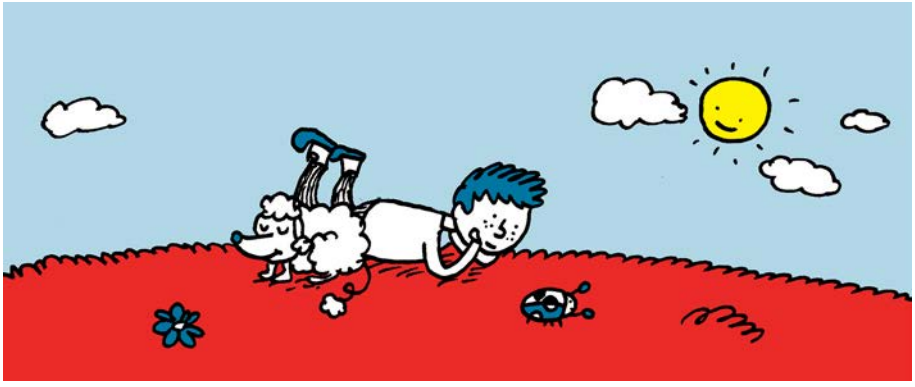
Chapter 8

Summary



8.1. General introduction

Chapter 1 of this thesis is a general introduction that provides an overview of the history, diagnosis and aetiology of ADHD. Furthermore, the current assessment and therapy of ADHD is described and food as a specific environmental factor is discussed, considering the results of additive studies, supplement studies and restricted elimination diet (RED) studies in children with ADHD. No relevant effects have been found of additive free diets on ADHD, and the results of studies supplementing omega-3 (fish oil) and/or omega-6 fatty acids are commensurable to the results of additive studies, i.e. no relevant beneficial effects of fatty acids on ADHD have been found. Conversely, there is convincing evidence for the statistically significant and clinically relevant effects of an RED on ADHD. In a meta-analysis including all double-blind placebo controlled RED studies conducted preceding the studies discussed in this thesis, an average effect size of 0.8 was calculated, which is impressive. For comparison, the effect size of methylphenidate, the most used drug in children with ADHD, may vary from 0.6-0.9. Subsequently, in 2001 an RED was included in a UK algorithm for treatment of ADHD. Still, despite the results of the RED studies and the recommendation for application, an RED is not part of the current ADHD assessment or therapy yet.

8.2. Part 1

The overall aim of *Part 1* of this thesis was to investigate the effects of an RED on ADHD in heterogeneous groups of children with ADHD, in order to determine whether the RED results are applicable to the general population of children with ADHD, and to investigate the RED effects on comorbid ODD, physical complaints and sleep problems.

In *Chapter 2* an exploratory pilot study is described in which a group of young children with ADHD, of whom 84% also suffered from comorbid ODD, followed a 2-week RED. Children were not selected for atopic constitution or diet affinity and all children with ADHD whose parents were motivated to follow an RED were included. Conversely, children whose parents reported unfavourable environmental factors associated with ADHD were excluded from participation.

According to parents' and teacher's ADHD measurements 62% of children showed behavioural improvements of at least 50% following the RED. According to the ODD measurements an ODD symptom decrease of 50% or more was shown in 81% of children with comorbid ODD. The diet response did not differ between children with or without an atopic constitution. Physical and sleep complaints were reported in the majority of children, which diminished significantly following the RED.

Chapter 3 reports the results of a randomised controlled trial (RCT) in which children with ADHD were randomised either to an RED group or to a control group. In accordance with the previous study, the children included in this study were not preselected, but children with potentially predisposing environmental factors were excluded. The results shown in Chapter 2 were confirmed in this randomised controlled design: following the RED impressive effect sizes of 2.1 (ADHD) and 1.1 (ODD) were established, according to both parents' and teacher's measurements. The ADHD behaviour improved with an average of 70% in 85% of children. ODD improvements, with an average of 55%, were shown in 73% of children with comorbid ODD. No significant ADHD or ODD improvements were established in the control group.

In *Chapter 6* the INCA study is described, which comprises two parts. Based on the immunological assessments chapter 6 has been incorporated in part 2 of this thesis. Conversely, the first and behavioural part of Chapter 6 is a follow-up study of the RCT discussed in Chapter 3, consequently, this part of the INCA study will be discussed here. The INCA study was an RCT including an unselected and heterogeneous group of children with ADHD; no children were excluded. According to parent, teacher and blinded paediatrician ADHD measurements the majority of children showed striking behavioural improvements following an RED. Sixty-four per cent of children in the diet group showed behavioural improvements of an average of 60%; the average improvements in responders were 89% (see chapter 9.1, figure 1). The average ODD improvements in diet group children with comorbid ODD were 65%, and were found in 70% of children; the average improvements in the ODD responders also amounted to 89% (see chapter 9.2, figure 2). In the control group no significant improvements of ADHD as well as ODD were found.

The responders did not meet the criteria of ADHD and ODD anymore, neither at home nor at school, thus confirming the results of previous studies (see chapter

2 and chapter 3). Considering that the children participating in the INCA study were representative of the general population of children with ADHD, the INCA results are applicable to all young children with ADHD whose parents are motivated to follow a 5-week RED.

In *Chapter 4* the effects of an RED on comorbid physical and sleep complaints in children with ADHD were investigated following an RED. Significant symptom reduction was shown in three domains: headaches or bellyaches, unusual thirst or unusual perspiration, and sleep complaints. The total number of complaints was significantly reduced in the RED group (a reduction of 77%, effect size 2.0) but not in the control group (a reduction of 17%, effect size 0.2). The symptom reduction did not differ between children with or without an atopic constitution and did not differ between children who did or did not show behavioural improvements following the RED. The results of this RCT confirm the findings of the pilot study described in Chapter 2.

Conclusions part 1: An RED may have considerable effects on ADHD and comorbid ODD, physical complaints and sleep problems, thus confirming and strengthening the results of the previous RED studies. The double-blind placebo controlled RED studies have shown that the beneficial effects of an RED on ADHD are not moderated by parental expectations, and all studies investigating the relationship between an RED and ADHD resulted in statistically significant and clinically relevant improvements of behaviour. Therefore, in accordance with the recommendations mentioned in *Chapter 6*, the conclusion is warranted that an RED is beneficial to the majority of young children with ADHD, with an overall effect size of 1.2, and that it is timely for an RED to be implemented. In responders the behavioural problems may diminish to such an extent that they do not meet the ADHD and ODD criteria anymore and show normal behaviour. Considering that children with comorbid ODD have a worse prognosis, interventions that may reduce ODD have great clinical potential. The INCA study, as discussed in *Chapter 6*, used the most pragmatic design including a heterogeneous group of children. Consequently, the results of this study are applicable to all young children with ADHD provided that parents are motivated and able in terms of parenting skills and time resources to follow a 5-week diet.

8.3. Part 2

The overall aim of *Part 2* of this thesis was to investigate the occurrence of an underlying immunological mechanism of food in children with ADHD by means of IgE and IgG blood tests. Furthermore, the effect of an RED on family structure and environment was considered in order to define whether behavioural improvements during an RED were instigated by improvements of parental capabilities.

In *Chapter 5* it is hypothesised that ADHD may be a (non-)allergic hypersensitivity disorder. According to the terminology of allergy the manifestation of ADHD when eating normal amounts of foods which are usually tolerated by the general population, implies that the criteria of a hypersensitivity reaction are met. The hypersensitivity hypothesis in ADHD is in accordance with other hypersensitivity disorders, e.g. the manifestation of asthma when exposed to dust mite or the manifestation of eczema when eating strawberries. The hypersensitivity triggering ADHD may be allergic or non-allergic, depending on whether or not an immunological mechanism will be established.

The occurrence of an immunological mechanism was investigated in the second part of *Chapter 6*. In all children participating in the INCA study immunological parameters (IgE and IgG blood levels) were determined at the start of the trial and following an RED or control period. At the start of the trial only a minority of children showed increased IgE-levels (14%), and no association was found between a behavioural response to the RED and increased IgE blood levels, thus confirming previous findings that IgE or an atopic constitution is not related to a hypersensitivity reaction to foods in children with ADHD. Chapter 6 also focussed on IgG, investigating whether a relationship might exist between IgG blood levels against specific foods and ADHD behaviour. It was shown that IgG blood levels did not predict behavioural changes in RED responders; no differences in behavioural relapses were established after challenges with either high-IgG foods or low-IgG foods. These results suggest that the underlying mechanism of food hypersensitivity in ADHD is non-allergic, although the involvement of a cell- mediated allergic response cannot be ruled out.

The main aim of *Chapter 7* was to investigate whether the children's behavioural improvements following an RED were due to improvement of family structure and environment as a consequence of the strict structure of the diet. The results indicated that family abilities in families motivated to enter an RED trial were

equivalent or even better than those of families without ADHD, and that an RED did not affect family structure or family environment. It is conceivable that only parents confident of their parenting capacities decided to participate in the RED trial, consequently the results of this study are applicable to those families motivated to follow a 5-week RED.

Conclusions part 2: ADHD may, in the majority of children, be considered a hypersensitivity disorder triggered by food. The underlying mechanism of food hypersensitivity in children with ADHD appears not to be IgE or IgG mediated, consequently a non-allergic mechanism or a cell-mediated allergic response may be involved. Furthermore, families motivated to follow an RED have shown excellent parenting capabilities and an RED does not affect family structure or family environment.

8.4. General discussion

Chapter 9 of this thesis is a general discussion in which the results of this thesis are elucidated in coherence with all previous RED results and in light of the current opinions of ADHD. The general discussion concludes with recommendations for further research into this intriguing subject (see chapter 9.6), with a proposal for an Algorithm for Multimodal Diagnosis and Treatment of ADHD in which the results of this thesis are incorporated (see chapter 9.7, figure 4), and with suggestions for the DSM-V which may lead to improvement of our child mental health (see chapter 9.8).

8.5. Conclusions and recommendations

Taking the results of all previous and recent RED studies into account, there is conclusive evidence for the statistically significant and clinically relevant effects of an RED on ADHD and ODD. The RED studies discussed in this thesis have shown that an RED has a beneficial effect on ADHD and comorbid ODD in 60% of children with ADHD, to such an extent that in children responding to an RED the behavioural problems, ADHD as well as comorbid ODD, disappear completely (see chapter 9.1, figure 1 and chapter 9.2, figure 2).

The impact of an RED appears not to be limited to ADHD and ODD, but is also manifest in the frequently occurring comorbid physical and sleep complaints in children. Consequently, an important environmental cause of ADHD, ODD, comorbid physical complaints and sleep problems has now been established; this recognition may lead to a paradigm shift with regard to our knowledge and opinions on the aetiology of ADHD and may have considerable consequences for the current diagnostic procedure and therapy of ADHD.

8.5.1. Implementation of RED research

The most important recommendation is implementation of RED research in young children with ADHD. Right now, the main therapy of children with ADHD is medication, eliminating symptoms during 3-12 hours (the duration depending on the drug), with an effect size of 0.6-0.9 and with disappointing long-term effects. This dissertation has shown that in the majority of young children ADHD may be caused by food and that an RED is an effective treatment of ADHD in children diagnosed FI-ADHD, preventing symptoms 24/7, with an effect size of 1.2 and with promising long-term prospects. The pros of an RED are to such an extent that RED research should be implemented especially in young children with ADHD, consequently, all young children with ADHD should be offered the opportunity to participate in RED research, provided that expert supervision is available. Children with ADHD responding favourably to an RED should be diagnosed with food-induced ADHD (FI-ADHD), considering that in these children food appears to be the predominant cause of ADHD and that elimination of specific foods results in normal, typical behaviour. Children not responding to an RED should be diagnosed with Classic ADHD (C-ADHD); in these children the cause of the disorders remains, for the time being, unknown. These children, just like children of parents not motivated to start or to comply with an RED, should start treatment as usual.

Children diagnosed with FI-ADHD are advised to start a challenge period, as described in the Algorithm for Treatment in chapter 9.7, in order to establish the incriminated foods, at the end of which the therapy consists of dietary advice to avoid a limited number of foods. Offering children with ADHD the opportunity to start RED research may consequently result in prevention of ADHD and in improvement of the children's prospects.

Finally, the concurrent economical effects of every child completing the RED research may be impressive. According to a Dutch report, making a rough inventory of some of the costs of ADHD by comparing the costs including RED research with the current costs of ADHD, implementation of RED research may yield savings of 7.000 euros per year per child starting RED research.

8.5.2. alleviation of the challenge period

Facilitation of the challenge period is another important recommendation. This part of the RED research is the most poignant part for parents, child and school, due to the recurrent behavioural relapses during this period. All efforts should be made to facilitate this period by means of expert coaching and by means of follow-up research in order to define the mechanisms of food in children with FI-ADHD. It must be noted that, until an easier method is available to define the incriminated foods, the current challenge period is crucial to determine the incriminated foods and thereby to 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, which may differ per child. Thus, compared to the RED and the challenge period the final dietary restrictions will be easy to adhere to, and relapses will only occur if the child does not stick to the diet. Concluding, additional expert coaching during the challenge period will increase the compliance and further research should focus on facilitating the challenge period and on defining the mechanisms of food in children with FI-ADHD.

8.5.3. Follow-up research

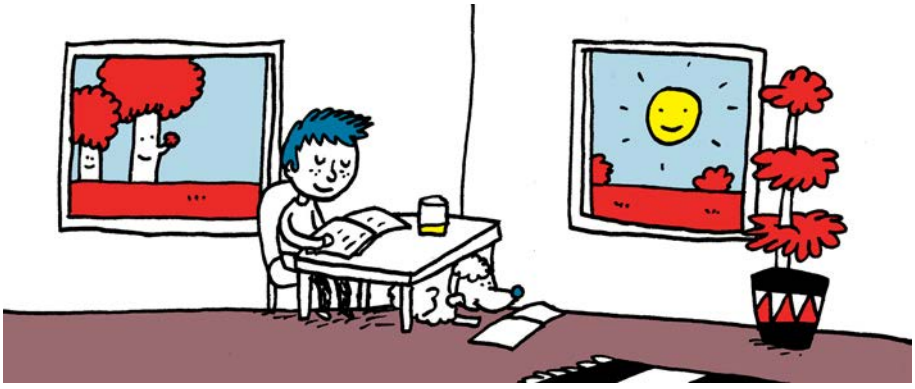
Some RED studies have already shown that the beneficial effects continue unabated during a follow-up period of one year. Also, the preliminary results of the INCA 10-month follow-up study show that the behavioural effects, in children who adhere to their diet, persist. Still, it is important to investigate the effects of an RED during a longer period of time, and to investigate whether children may overgrow the sensitivity to specific foods when avoiding the incriminated foods.

8.6. Acknowledgement and consensus

In 2001 RED research was already advised to be applied in subgroups of children with ADHD. Unfortunately, this advice has been confronted with a striking deficit of attention and has, just like all previous RED research and despite convincing evidence, generally been ignored. Now, in 2011, RED research has repeatedly been conducted in heterogeneous groups of children, thus confirming the results of the previous RED trials in groups of children representative of the general population of children with ADHD. Consequently, this thesis results in the advice to implement RED research in all young children with ADHD. Acknowledgement of the impact of food on ADHD is needed in order to achieve consensus. It would be deplorable, especially for all children suffering from ADHD, if the advices resulting from this thesis would sink into oblivion, commensurable to the 2001 advices.

Chapter 9

General discussion



Introduction

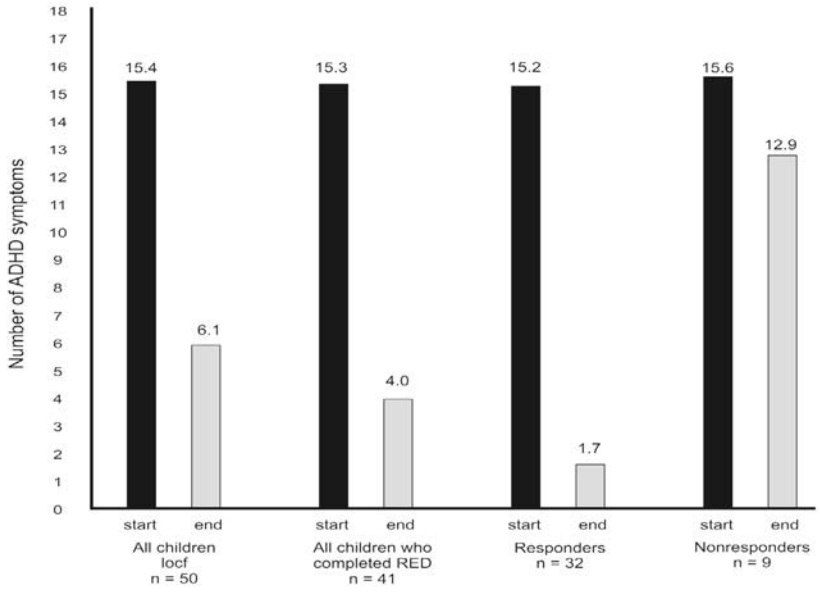
ADHD is an aetiologically complex disorder in which genes and environment play a substantial role. So far, the exact aetiology of ADHD and the extent of the interaction between genes and environment are still unknown. This thesis shows that food has a considerable impact on ADHD, comorbid ODD and physical complaints in the majority of young children with ADHD whose parents are motivated to follow an RED. Consequently, the results of this thesis may be considered an important step forward towards the understanding of the pathogenesis of ADHD, which may lead to improvement of the diagnostic and therapeutic procedures.

Considering that the findings of each separate study included in this thesis have been discussed at the end of each chapter, this general discussion will focus on the overall findings of all RED studies and on the consequences these findings may have on our knowledge of ADHD. Based on the current point of view as described in the introduction of this thesis, the impact of an RED on ADHD, on ODD, on physical complaints and sleep problems, and on our knowledge of the aetiology of ADHD will be discussed. Furthermore the discussion elaborates on the mechanisms in which an RED exerts its effects, on follow-up research, on the practical implications and implementation of the RED findings in general practice, including a proposal for a multimodal algorithm for diagnosis and treatment, and on suggestions for the DSM-V that will be implemented in 2013.

9.1. The Impact of an RED on ADHD

The results of the INCA study (see *Chapter 6*), investigating the effects of an RED on ADHD in an unselected group of young children with ADHD, are impressive.[1] Both the number of children responding favourably to the RED and the extent of the behavioural improvements are remarkable. The average improvement in the responders (32/50 children), based on the measurements by the blinded paediatrician, was 89%, the number of ADHD symptoms decreasing from 15.2 to 1.7, which is an impressive change in behaviour (see **figure 1**). The nonresponders showed an average improvement of 17%, the ADHD symptoms decreasing from 15.6 to 12.9.

Figure 1 Average number of DSM-IV ADHD symptoms (0-18) at start INCA and at end RED



LOCF = last observation carried forward

The INCA results confirm and strengthen the results of preceding randomised controlled RED studies, all showing considerable effects of an RED on ADHD in selected as well as in unselected groups of children,[1-8] with an overall effect size of 1.2 (see **table 1**). This effect size is impressive, taking into account that the effect size of methylphenidate (the most used drug in children with ADHD) may vary from 0.6-0.9.[9,10] The effect sizes of the RED RCTs vary from 0.6-1.8, depending on the study design (see **table 2**). Five out of 8 studies used a double-blind placebo controlled (DBPC) design, of which in three studies a food challenge (FC) design[2,4,5] and in two studies a placebo diet was applied.[3,7] The remaining three studies used an open design,[1,6,8] one of which with blinded measurements.[1] Below the pros and cons of each design will be discussed.

First of all, 5 out of 8 studies used a double-blind placebo controlled (DBPC) design. In a recent meta-analysis concerning these 5 studies an average effect size of 0.8 was calculated,[11] which of course is impressive. Still, two out of 5 DBPC studies, the placebo diet studies, resulted in the lowest effect sizes when compared to the other RED RCTs (see **table 2**).[3,7] This difference may be explained by the fact that, in order to conceal the treatment conditions, these studies had to allow a wide variety of foods, i.e. they applied a more elaborate verum diet. According to the researchers a more stringent diet would have jeopardised the double-blind conditions, although it might have resulted in greater behavioural changes.[3] Furthermore, one placebo diet study used a very short diet period of 8 days only,[7] while the average diet period of the other RCTs was 3.7 weeks (varying from 2-5 weeks); thus an 8 day diet period may be considered too short to effectuate behavioural changes. It is conceivable that if the diet was followed for a longer period of time the results might have been different.

Three out of 5 DBPC studies used a DBPCFC design following the open diet period (in order to identify the responders) and the open challenge period (in order to identify the incriminated foods).[2,4,5] Two of these studies lasted more than 12 months,[2,4] as the challenge period following the RED comprised at least 40 different foods, which were reintroduced at a rate of one a week. If the ADHD symptoms recurred, the challenged food was withdrawn again, conversely, if the behaviour did not change, the challenged food was incorporated in the RED, thus gradually resulting in elaboration of the RED and normalization of the diet. Following the challenge period the DBPCFC was conducted, with foods that could be disguised and which had caused deterioration of the behaviour during the challenge period. These studies have shown that open findings could be confirmed in a double-blind design. A disadvantage of DBPCFC design is that the challenged foods had to be concealed during the DBPC part of the trial. Consequently the amounts of the challenged foods were limited, possibly resulting in smaller behavioural effects[4] than in the open RCTs (see **table 2)**.

Concluding, two out of 3 DBPCFC studies established the long term effect of an RED, that is, at least for a period of one year. All DBPCFC studies showed that most children reacted to more than one food and that the incriminated foods, i.e. the combination of foods the child reacted to, were different for each child. In addition, despite lower effect sizes which are in accordance with the limitations due to the blinded design, the DBPC studies are of paramount importance to

illustrate that behavioural changes following a diet are not attributable to expectations, believes, hopes of parents or changes in family structure.

Three out of 8 RCTs used an open design.[1,6,8] Although an open design is considered second best, it is often used in trials faced with blinding difficulties (see *Chapter 6*). Considering the disadvantages of the DBPC method, i.e. a too elaborate RED in the placebo diet trials and a too small amount of challenged foods in the food challenge trials, in studies applying an RED the open design is a legitimate choice. Furthermore, the results of the DBPCFC trials have shown that parents' findings can be relied upon, as the open parents' results were confirmed in the DBPCFC design. In addition, an open design has two important advantages: 1) the diet may be as stringent as necessary, thus achieving the most optimal behavioural effects; and 2) the diet may be constructed for each child individually, in order to achieve the most optimal diet for each child (see *Chapter 6*). These optimal dietary circumstances may have lead to the open RCTs' higher effect sizes, i.e. an average ES of 1.8. In all open RCTs the parents' results were confirmed by the teacher's findings.[1,6,8] On top of that, the results of one of the open RCTs, the INCA study (see *Chapter 6*), were based on the measurements of a paediatrician blinded for treatment conditions,[1] which were also confirmed by the teacher's measurements. Finally, the INCA study proceeded following the RED with a DBFC, and the relapse in behaviour during the DBFC may be regarded as an internal replication of the effects of the RED.

Concluding, the 3 open RCTs show higher effect sizes than the DBPC studies, which are confirmed by teacher's measurements and blinded measurements, and these studies are of paramount importance to emphasize the magnitude of the effect an RED may have on the behaviour of children with ADHD.

Considering that RCTs are executed to confirm or refute the results of previously conducted pilot studies without a randomised controlled design, and considering that all RED RCTs confirm the results of these pilot studies, additional evidence is provided by two previously performed Dutch open pilot studies.[12,13] One of these open studies is discussed in *Chapter 2*,[13] the other study was published in a peer reviewed Dutch Child and Adolescent Psychology Journal. This study included an unselected group of 64 children, meeting the DSM-IV criteria for ADHD and aged 3-15 (average age 6.7), of which six children left the study prematurely.[12] In this pilot study, 34/58 children (59%) showed behavioural improvements of more than 50% following the RED, according to parents' and

teacher's measurements. To examine whether younger children tend to respond more favourably to the RED, the group was divided into two age categories, children aged 3-7 (n=40) and children aged 8-15 (n=18). 24/40 children aged 3-7 were diet responders (60%), and 10/18 children aged 8-15 were diet responders (56%). Consequently, the age of children participating in RED trials does not predict the response to the diet. Another interesting aspect of this pilot study is the subtype versus responder differentiation: 18/25 children who met the ADHD criteria for the combined type were diet responders (72%), as were 14/24 children who met the predominantly hyperactive/impulsive type criteria (42%) and 2/9 children who met the predominantly inattentive type criteria (22%). In most RED studies the children were not divided in subgroups,[2-7] or the inattentive subgroup was too small to be analysed.[1,8,13] Still, according to these results children who meet the combined type criteria tend to respond most to an RED, while children who meet the inattentive type criteria are likely to respond least. Conversely, all studies analysing the effects of an RED on both groups of ADHD symptoms[1,8,13] showed that both the hyperactive/impulsive symptoms and the inattentive symptoms decreased equally after following the RED.

In sum, the findings of the RED RCTs may be taken seriously. The results of the double-blind placebo controlled RED studies have shown that the results are not caused by parental expectations or by changes in family structure. The RED RCTs confirm the results of previously executed pilot studies, thus providing even more evidence for the effect of an RED on ADHD, and it is important to note that all studies investigating the relationship between an RED and ADHD resulted in statistically significant and clinically relevant improvements of behaviour.

Therefore, in accordance with the recommendations mentioned in *Chapter 6*, the conclusion is warranted that an RED is beneficial to the majority of young children with ADHD, with an overall effect size of 1.2, and that it is timely for an RED to be incorporated in our overall knowledge on ADHD. In responders the behavioural problems may diminish to such an extent that they do not meet the ADHD criteria anymore and show normal behaviour. The INCA study, as discussed in *Chapter 6*, used the most pragmatic design including a heterogeneous group of children. Consequently, the results of this study may be considered representative of the general population of children with ADHD, i.e. the results are applicable to all young children with ADHD provided that parents are motivated and able in terms of parenting skills and time resources to follow a 5-week diet.

Table 1 Summary of all 8 RED RCTs, including effect sizes

Article	RCT type	Age	Diagnosis at start	Methods	Selection	RED period	ES ACS	Weight	Contribution to Weighted ES
1. Egger 1985	DBPCFC	2-15	Hyperkin. syndrome	Open RED n=76, open challenge n=56, dbpcfc^ **n=25**	Selected Group*	4 weeks	1.03	0.11	0.12
2. Kaplan 1989	DBPC diet	3.5-6	DSM-III	RED vs placebo diet dbpc^ **n=24**	Aselected group	4 weeks	0.55	0.11	0.06
3. Carter 1993	DBPCFC	3-12	DSM-III	Open RED n=78, open challenge n=59 dbpcfc^ **n=19**	Selected Groep*	3-4 weeks	0.61	0.09	0.05
4. Boris 1994	DBPCFC	7.5 +- 2.2	DSM-III-R	Open RED n=26 open challenge n=19 dbpcfc **n=16**	Selected Group**	2 weeks	1.60	0.07	0.12
5. Schulte 1996	Open RCT	8.4 +- 2.0	ICD-9	Open RED vs challenge diet^ **n=21**	Aselected group#	3 weeks	1.26	0.10	0.12

6. Schmidt 1997	DBPC diet	6-12	DSM-III	RED vs placebo diet dbpc^ **n=49**	Aselected Group	8 days	0.59	0.22	0.13
7. Pelsser 2009	Open RCT	3-8	DSM-IV	RED **n=15** vs waiting list n=12	Aselected group#	5 weeks	2.35	0.07	0.16
8. Pelsser 2011	Open RCT, blinded measure-ments	4-8	DSM-IV	RED **n=50** vs waiting list n=50 blinded measurements	Aselected group	5 weeks	1.82	0.23	0.42
				Total n RCT 219			Average ES=1.2	Total 1.00	Weighted ES=1.2

ACS = abbreviated ACS = ACS = abbreviated conners scale; RCT = Randomised Controlled trial; DBPCFC = double-blind placebo controlled food challenge; ES = effect size; ^ = crossover; *subjects selected via diet clinics; **subject selected via allergy clinic; #exclusion of children with risk factors for ADHD (e.g. premature, dysmature, foster child, IQ<70)

Table 2 Effect size per RED RCT design

RCT	Average ES	Weighted average ES
DB placebo diet design n=2	0.57	0.58
DBPCFC design n=3	1.08	1.05
Open design n=3	1.81	1.78

RCT = Randomised Controlled trial; DB = double-blind; DBPCFC = double-blind placebo controlled food challenge; ES = effect size

The weighted average ES has been calculated by weighting the average ES by the number of children in each study relative to the total number of children in the particular design. I.e., the weighted average ES of the open design studies (see table 1; study 5, 7 and 8), including 86 children (21+15+50) = 1.26*21/86+2.35*15/86+1.82*50/86 = 1.78.

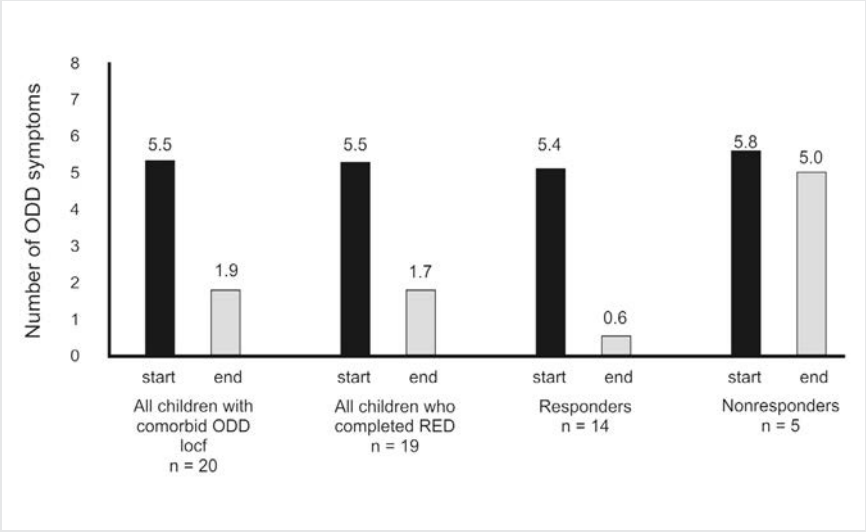
9.2. The Impact of an RED on ODD

The INCA study also investigated the effects of an RED on comorbid ODD in an unselected group of young children with ADHD (see *Chapter 6*).[1] Equally to the effects of the RED on ADHD, both the number of children with ODD responding favourably to the RED and the extent of the behavioural improvements were impressive. In the RED group 14/20 children belonged to the responders, i.e. after following the RED 14/19 children did not meet the ODD criteria anymore and showed behavioural improvements of at least 40%. The average ODD improvement in the responders, based on the measurements by the blinded paediatrician, was 89% and the number of symptoms decreased from 5.4 to 0.6. The nonresponders (5/19) showed behavioural improvements of 14%, the number of symptoms decreasing from 5.8 to 5.0 (see **figure 2**).

The INCA ODD results confirm and strengthen the results of preceding RED studies, i.e. one RCT[8] and one pilot study.[13] In the pilot study, which is discussed in *Chapter 2*,[13] the ODD criteria decreased from 6.0 at the start of the study to 1.3 at the end of the RED. In the RCT, which is discussed in *Chapter 3*,[8] the average number of criteria decreased from 6.5 to 2.9 and the number of children meeting the criteria of ODD decreased by 66%. Furthermore, the teacher's findings confirmed the blinded paediatrician's findings (see *Chapter 6*).

The conclusion is warranted that an RED is beneficial to the majority of children with ADHD and comorbid ODD, with an effect size of 2.0.[1] In responders the behavioural problems diminished to such an extent that at the end of the RED they did not meet the criteria of ODD anymore and showed typical behaviour. As discussed at the end of section 9.1. the INCA study used the most pragmatic design, consequently the heterogeneous group of children participating in this study may be considered representative of the general population of children with ADHD and comorbid ODD, i.e. the results are applicable to all young children with ADHD and ODD, provided that parents are willing and able to follow a 5-week RED.

Figure 2 Average number of ODD symptoms (0-8) at start INCA and at end RED



LOCF = last observation carried forward

9.3. The impact of an RED on physical complaints and sleep problems in children with ADHD

Sleep disorders[14] and physical complaints like eczema, asthma, headache, bellyache, enuresis and encopresis are conditions often reported by parents of children with ADHD.[2-4,15] RED studies including the assessment and analysis of these comorbid problems found evident treatment effects on sleep problems (i.e. sleep latency, getting out of bed and night awakenings)[3] and on headache, unusual thirst and abdominal pains.[2] In *Chapter 2*[13] and *Chapter 4*[16] the effects of an RED on physical and sleep complaints have been discussed, showing significant symptom reduction specifically in the domains of headache and bellyache, unusual thirst and perspiration, and sleep complaints, thus establishing not only a decrease of behavioural problems, but also of physical complaints as a result of an RED. Furthermore, the responders showed significantly more physical complaints than the nonresponders, i.e. 80% of the responders and none of the nonresponders reported 3 or more physical complaints.[13] As discussed in *Chapter 4*, the RED effect on physical and sleep complaints was established both in RED responders and in nonresponders.[16] Also, no differences were found between the number of physical complaints in atopic and non-atopic children.[13,16]

This specific subject, i.e. physical complaints in children with ADHD, belongs to the frontiers of our ADHD knowledge. The high comorbidity found in the RED studies does not reflect clinical practice and may be explained by the fact that the RED researchers specifically inquired after all kinds of physical complaints,[2-4] and applied a physical complaints questionnaire.[13,16] Furthermore, in general practice physicians are not aware of the importance to scrutinize this aspect of ADHD. It is not part of the routine to use a specific physical complaints questionnaire when ADHD is concerned, and they are not accustomed to ask for seemingly vapid complaints like unusual thirst or perspiration or pain in limbs. It may also be conceivable that many of the physical complaints, unless urgent and impairing, will not be reported by parents in a psychiatric or psychological setting, as parents may not be aware of the relevance of these complaints. To illustrate this: many parents participating in the Dutch RED studies reacted amazed and concurrently with recognition when hearing the specific questions, exclaiming “indeed, you’re describing my child, how striking that you ask”.

In conclusion, the relationship between food, psychiatric and somatic disorders is a challenging subject in need of more research. Considering that the current approach of ADHD, i.e. drug treatment, does not affect comorbid physical complaints and may even cause some of these complaints[17] and considering that children with ADHD and physical problems tend to respond less favourably to medication,[18] it is important to underline the impact of an RED. This impact appears not to be limited to ADHD and ODD, but is also manifest in the frequently occurring comorbid physical and sleep complaints in children.

9.4. The implications of the RED findings for our knowledge of ADHD aetiology

9.4.1. ADHD and genes

Despite many efforts made to unravel the ADHD mysteries the exact aetiology of ADHD is still unknown.[19,20] However, it is quite clear that ADHD "runs in families", i.e. it is a highly heritable disorder with a heritability estimate of 75%, established in twin and adoption studies.[21] Consequently, ADHD research has been predominantly focussed on genetics, as a logical consequence of the high heritability results of twin studies, and on the brain, as a result of the dopamine hypothesis of ADHD, strengthened by the effects of medicines like methylphenidate, which enhance the dopamine function.[22] By now bioinformatic analyses have described extensive gene-protein networks that include many genes that may be involved in ADHD.[23] Yet, no genetic markers of major effect have been established[24] and most genes involved in ADHD seem to be of small effect size.[9] Genome wide association studies (GWAS) thus far have shown inconclusive and divergent findings,[25] and the effects of the genes involved in ADHD account for only a small part of the considerable heritability observed in twin studies.[26] Concluding, how exactly genetic factors contribute to the development of ADHD is not quite clear and more research is imperative.

9.4.2. The threshold model: genes and environment

More research might focus on the specific contribution of environmental factors to ADHD, which have been rather under-researched.[27] Some environmental factors are specifically denominated in the threshold model, which implies that

ADHD is a complex disorder, "caused by the confluence of many different types of risk factors (i.e. genetic and environmental factors), with every risk factor having a small effect on the increasing vulnerability to the disorder through their additive and interactive effects".[9] If a threshold is exceeded, then ADHD will become manifest, and according to this model no one causal factor is necessary or sufficient to initiate the disorder.[9] The environmental factors considered relevant in ADHD are perinatal risk factors (e.g. prematurity, prenatal maternal smoking or alcohol consumption, low birth weight and dysmaturity) and psychosocial risk factors (e.g. family or marital conflicts, foster placement, low social class and parental mental disorders).[9,26,28]

9.4.3. Environment: association or causal

Unfortunately, it is not yet quite clear whether the established association between these environmental risk factors and ADHD is causal. In fact, many environmental factors are influenced by genetic factors.[22] For instance, the association between maternal smoking during pregnancy, a well-known risk factor for ADHD, may represent an inherited effect, as the association was significantly higher in biologically related mother-child pairs than in unrelated pairs.[29] Consequently, smoking during pregnancy may be associated with ADHD, but may not be a true causal factor for ADHD.[29] Considering that in practice an established association sows the seed of a causal relationship, it it is important to emphasize that an association found between two factors does not imply that a causal relationship exists: an established association is necessary in order to establish a causal relationship, but an established association alone is not evidential for the existence of a causal relationship.[30] A striking example of an association in ADHD that is not causal, is the often established lower essential fatty acid (EFA) blood levels in children with ADHD. It has been repeatedly proven that supplementation of EFA does not affect ADHD behaviour,[31] although the EFA blood levels do increase following the supplementation.[32] I.e., although low EFA blood levels are often found in children with ADHD, there is no causal relationship between these low blood levels and ADHD. Still, suggestive advertisements and media smelling breaking news report otherwise, and to date, despite inconvincing evidence, there is a surprisingly positive opinion among parents, the media and some professionals about the potential benefits of EFA treatment of ADHD. To prevent this from happening, it is important that physicians and researchers should be careful with causal claims, also when ADHD is concerned.[33]

9.4.4. Food, the missing environmental factor in the threshold model

It is evident that prominent associations between genes and environment have been established in ADHD. Consequently, although it is not quite clear to what extent genes and environment are causal, it is obvious that the current aetiologic perception of ADHD is based on the multifactorial threshold model. However, a query may be raised as to the actual applicability of the threshold model. It is true that there is overwhelming evidence for an association between genetic and environmental risk factors and ADHD, but ambiguities remain concerning the pathophysiologic significance of both risk factors. In addition, the threshold model does not take the results of the RED studies into account. This implies that the threshold model, although it comprises environmental risk factors, does not encompass one important environmental factor, i.e. food.

Food is an environmental factor which has been thoroughly and conclusively investigated in children with ADHD, and which has proven to play an important triggering role in ADHD. Although the impact of food on ADHD may appear a novelty, the first RED RCT was conducted in 1985 and published in *The Lancet*, after which 5 independent RCTs followed, all of them resulting in the same conclusion. In 2001 these 6 RCTs eventually led to the incorporation of an RED in an UK algorithm for ADHD treatment.[34] It is intriguing and disconcerting that, despite the results of these studies and the treatment recommendation, no attention has been paid to this studies and to the effect of the RED in for the most part excellent review studies.[9,26,35,36] Considering the RED evidence available at the time of these reviews, it is amazing that, as explained in the introduction, all RED studies have been overlooked by the reviewers. This incomplete information may result in readers (mainly expecting information to be comprehensive and relying on the data given) who remain ignorant of the facts. Given this ignorance it is once again important to emphasize the following: 1) there is conclusive evidence for the effects of food on ADHD; 2) all RED studies have shown that an RED may normalise the behaviour in the majority of children with ADHD to such an extent that in children responding to an RED the behavioural problems, ADHD as well as comorbid ODD, disappear completely (see **figure 1** and **figure 2**).

In conclusion, an important environmental cause of ADHD and comorbid ODD has now been established (see *Chapter 6*) and this recognition may have considerable consequences and may eventually lead to a paradigm shift with regard to our knowledge and opinions on the aetiology of ADHD.

9.4.5. Food-Induced ADHD (FI-ADHD)

In children with ADHD responding favourably to an RED, the RED responders or children with food-induced ADHD (FI-ADHD), food may be considered a necessary cause of the disorder, and elimination of specific foods will result in normal, typical behaviour. A necessary cause may be defined as a risk factor without which the effect cannot occur, just like a specific infectious agent is a necessary cause for a particular infectious disease.[30,37] To elucidate the point of view that food can be considered a necessary cause of ADHD in children with FI-ADHD, ADHD may be compared to coeliac disease. Coeliac disease is an intestinal condition triggered by gluten in individuals susceptible for gluten and is, like ADHD, a multifactorial disease in which both genetic and environmental factors are involved. Twin studies in coeliac disease have shown heritability estimates of 60-90%,[38] suggesting a genetic role in determining phenotypic differences between individuals. However, despite substantial heritability "elimination of gluten from the diet is a typical example of environmental intervention that, in the case of coeliac disease, can result in total recovery".[38] The aetiologic analogy of ADHD and coeliac disease is striking. In both coeliac disease and ADHD genetic factors play a dominant role, but the environmental factors, in coeliac disease as well as in children with FI-ADHD, are decisive and will determine whether or not the symptoms manifest themselves or disappear. In sum, notwithstanding the substantial contribution of genetic factors, environmental factors and in particular foods are important and decisive in both coeliac disease and FI-ADHD.

9.4.6. Gene-Environment studies

Considering 1) the established genetic component of ADHD, 2) the association between genetic and environmental risk factors, and 3) the finding that food is a necessary cause of ADHD in children with FI-ADHD, further research into both genetic and environmental risk factors for ADHD is of the essence to develop effective strategies that eventually may lead to adequate ADHD treatment and risk reduction and may contribute to the long-term management of ADHD.[39] To date gene-environment (GxE) studies, investigating the interaction between genetic and environmental risk factors in order to find aetiologic clues,[26] are considered increasingly important in ADHD research. GxE research investigates the assumption that genotypic and environmental factors may increase or

decrease each other's effect, resulting in an actual interplay between genes and environment.[26] Unfortunately, until now GxE research did not focus on food, which may be due to the former disregarding of the RED studies, but focuses on the currently recognised perinatal and psychosocial environmental factors only. Considering the information of the RED studies, it would be intriguing to investigate into what extent genetic factors may contribute to FI-ADHD.

9.4.7. Food, a necessary cause of ADHD in children with FI-ADHD

It is a challenging hypothesis that an underlying genetic vulnerability to show ADHD after eating specific foods may be found in all children with FI-ADHD. If so, then both genetic factors as well as food factors are necessary causes, similar to the temperature sensitivity in the Siamese cat (see also *Chapter 1.5*): both the genetic vulnerability and the temperature are causal of the cat's black tips.[40] The combination of both necessary causes designates a sufficient cause: if both causes exist, the effect must occur. In fact, if a genetic vulnerability is underlying the effect of food in children with FI-ADHD, then the combination of both food and genetic constitution may be considered as a sufficient-component cause (i.e. "a sufficient-component cause is made up of a number of components, no one of which is sufficient on its own but which taken together make up a sufficient cause").[37] Metaphorically speaking: the genetic constitution of a child with ADHD may be compared to a loaded gun, and the food the child reacts to may be considered the pulling of the trigger. If the trigger is pulled the results may be a disaster for the person the loaded gun was aimed at, likewise it is a disaster when the child eats foods it should not eat and consequently shows ADHD and/or ODD behaviour again. Conversely, if the necessary genetic constitution, i.e. the genetic vulnerability to show ADHD after eating certain foods, is missing in a child, the metaphoric gun would be unloaded, consequently pulling the trigger (i.e. eating specific foods) would not cause any harm.

On the other hand, although it is seems obvious to assume that genes are involved in FI-ADHD, it is possible that future research will result in the conclusion that genes are not related to FI-ADHD and that FI-ADHD may manifest itself independent of the genetic constitution the child has inherited from his or her parents. In that case, food may be the only necessary cause involved, comparable to infectious diseases, in which the environmental trigger only, i.e. the infectious agent, is considered a necessary cause. Drawing an analogy between food as a

cause of ADHD and infectious agents as a cause of infectious diseases it is self-evident that without the infectious agent in the infectious disease, or without the incriminated foods in FI-ADHD, there is no disease or disorder. In both cases the environmental trigger is a necessary cause. Remarkably, it is intriguing and worth mentioning that in the era before Robert Koch, the founder of bacteriology, infectious diseases were believed to be inherited disorders.[41] This idea was abolished immediately after Koch's discovery of infectious agents, and up to now the infectious agents are considered the necessary cause of infectious diseases. Imagine the amazement that, in the twentieth century, adoption and twin studies confirmed the heritability of susceptibility to several infectious diseases, showing remarkable differences in individuals and at the level of populations.[41] Consequently, despite general consensus that infectious diseases are caused by specific agents, even in these diseases an underlying genetic vulnerability may be part of the cause.

Still, despite the fact that even infectious diseases seem to manifest themselves in genetic vulnerable subject, hypothetically food might be the only necessary cause of FI-ADHD. Considering food as a necessary cause of FI-ADHD is in contrast with the psychopathologic assumption that environmental triggers are considered probabilistic.[26] A probabilistic cause increases the probability or chance of its effect occurring, but may be neither necessary nor sufficient for the disease to occur.[37] This probabilistic concept may indeed be applicable to the current environmental factors (i.e. perinatal and psychosocial factors) believed to play a role in ADHD, but, considering the results of the RED studies, it may now be clear that the probabilistic concept is not applicable to food in children with FI-ADHD.

9.4.8. Reconsidering the threshold model

Whether or not genes are involved in FI-ADHD, the results of the RED studies have convincingly shown that food is a necessary cause of FI-ADHD, and it must be emphasized that FI-ADHD may be applicable to the majority of children with ADHD. Consequently, it is timely for an aetiologic paradigm shift and a revision of the threshold model to be taken into consideration. Above two causal possibilities concerning FI-ADHD have been discussed: one in which both genetic factors and food are necessary causes of FI-ADHD, and another (less likely, but still hypothetically relevant), in which genetic factors are not causally involved in

FI-ADHD. In both scenarios the threshold model does not hold. If genetic factors are involved in FI-ADHD (i.e. if in RED responders but not in RED nonresponders specific genetic factors may be established), then both genetic factors and food are necessary causes and are equally important, each being a component of a sufficient-component cause. The threshold model does not fit in this sufficient-component model, because the threshold model is based on many causal risk factors, each having a small effect and none of them being necessary or sufficient. If genetic factors prove not to be involved in FI-ADHD (e.g. if these genetic factors are equally present in RED nonresponders), then food may be the one and only necessary cause, in which case the threshold model should also be dismissed.

In this light the Bradford Hill considerations on causality are worth mentioning. Although Hill did not intend to write a checklist of criteria to assess causality, his points of view are often used to separate causal from non-causal associations.[42] Still, Bradford Hill seems to apply the counterfactual model, considering his words: "…the decisive question is whether the frequency of the undesirable event B would be influenced by a change in the environmental factor A". Taking food and ADHD into account, the undesirable event ADHD may be influenced by a change in the environmental factor food.

9.4.9. Classic ADHD (C-ADHD)

It must be acknowledged, although many children respond to an RED and consequently may be diagnosed FI-ADHD, that the RED studies have also elucidated that 40% of children with ADHD do not respond favourably to an RED. Consequently in these children other causal factors must be involved, and in order to distinguish both groups of children, these children may be diagnosed with Classic ADHD (C-ADHD). The aetiology of the 40% of children with C-ADHD needs further attention and research, which will be discussed in section 9.6.

Concluding, the RED studies have shed a new and promising light on the aetiology of ADHD. Food has been established as an important environmental factor and a necessary cause of ADHD in children with FI-ADHD, thus offering an important opportunity to improve the quality of care for ADHD patients in the future. Investigating whether a child suffers from FI-ADHD or from C-ADHD and subsequently determining and avoiding the incriminated foods in children with FI-ADHD will lead to prevention of ADHD in children with FI-ADHD. The number of children responding to an RED and the impressive scale of symptom reduction

are to such an extent that a paradigm shift concerning the aetiology and consequently concerning the therapy of ADHD is imperative.

9.5. The mechanism underlying the effects of an RED

As yet the occurrence of FI-ADHD is not widely recognised, consequently research into the mechanisms in which food exerts its effects are limited. Still, in order to improve and facilitate the RED procedures it is important to investigate and ascertain the underlying mechanism of food in children with FI-ADHD. Some mechanisms already have been explored, as discussed in *Chapter 5, 6 and 7*.

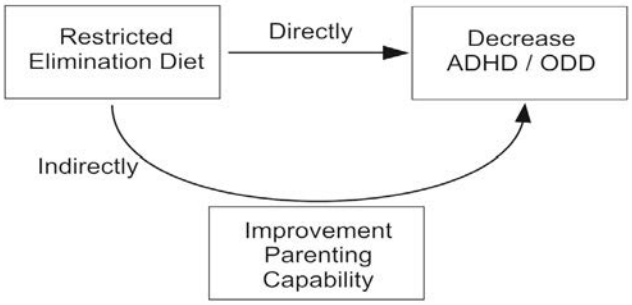
First of all, in *Chapter 5* it is hypothesised that, in children with FI-ADHD, ADHD may be considered a hypersensitivity disorder, commensurate with asthma and eczema.[43] This hypothesis is based on the definition of hypersensitivity according to the revised nomenclature for allergy as discussed in the introduction[44] and has been tested in 8 RCTs and two pilot studies.[1-8,12,13] The remission of ADHD following an RED[1-8,12,13] and the recurrence of ADHD after exposure to normal amounts of foods[1,2,4,5] is evidential for a food hypersensitivity reaction according to the gold standard.[45] No studies have been published negating these findings. In sum, there is convincing evidence that the hypothesis discussed in *Chapter 5*, i.e. ADHD being an hypersensitivity disorder, is accurate in the majority of the young children with ADHD and is in accordance with the results of the RED studies. Consequently, a logical and timely conclusion would be to accept this hypothesis.

Subsequently, an important question to be answered is whether the mechanism of food in ADHD is allergic or non-allergic. Study results have shown that it is unlikely that an allergic mechanism is involved: 1) Two out of 3 RED studies investigating the relationship between an atopic constitution and hypersensitivity to foods in ADHD[2,13] found no differences in atopic constitution between RED responders and nonresponders. One study found a significant higher percentage of atopic children in responders,[5] but it is important to notice that the children participating in this study were selected via allergy clinics, which may have affected the results. 2) None of the RED studies including unselected groups of children and executing IgE blood tests[1,7] found differences in IgE blood levels between responders and nonresponders. 3) As discussed in *Chapter 6* an

IgG-mediated hypersensitivity mechanism has been investigated.[1] Although the provocation of foods following the RED resulted into a considerable and clinically relevant behavioural relapse in the RED responders (with a scale increase of 79% on the ADHD Rating Scale, thus confirming the hypersensitivity reaction in these children), equal behavioural responses were established after challenges with foods against which both high and low IgG levels were found in the blood samples at the start of the trial. In conclusion, considering that no relationship has been established between atopic constitution, IgE- or IgG-levels and FI-ADHD, it is unlikely that an allergic mechanism is involved, although we cannot rule out the involvement of a cell-mediated allergic response. Consequently, further research should focus on both a cell-mediated allergic response and on non-allergic mechanisms, such as mechanisms related to toxic, pharmacologic or epigenetic events, which will be discussed in chapter 9.6.

An indirect non-allergic mechanism of the RED has already been investigated, i.e. the effect of an RED on family structure and family relationship, thus effectuating improvement of the child's behaviour (see **figure 3**). *Chapter 7* showed that the effects of an RED on ADHD and ODD were not mediated by improvement of family structure and family relationship.[46] Indeed, at start of the trial parenting abilities in families with ADHD were equivalent or better than those of families without ADHD. Furthermore, parenting qualities did not change during the RED, which implies that the indirect route as shown in figure 3 did not take place, thus confirming the direct route of an RED on ADHD. Of course it should be emphasised that prior to entering the study as described in *Chapter 7*, all families received information on the challenges they were to expect when following the diet, so it is conceivable that only parents aware of their good parenting qualities may have entered this study. Therefore the conclusion that behavioural improvements of children with ADHD and ODD are not mediated by improvements of family relationships and structure, cannot be extrapolated to families of all children with ADHD, but should be limited to those families motivated to follow an RED.

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 proof 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 regulatation 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 alterations[70] which may affect the offspring. It is tempting to hypothesise that, if epigenetic alterations proof 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 comprensive 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% responders[1] 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 with[78] and without[79-82] 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 air[85]) or may affect the central nervous system (e.g. thinner inhalation in painters[86] or solvents in glue sniffers[87]). 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.

9.7. Practical implications and implementation of the RED in general practice: a proposal for a multi-modal algorithm for diagnosis and treatment

The results of the RED studies, convincingly showing that ADHD may be caused by food in the majority of young children with ADHD, may incite a child psychiatric paradigm shift when ADHD and ODD are concerned. Implementation of RED research in the ADHD diagnostic procedure, as suggested in *Chapter 6*, provides an opportunity to prevent ADHD and ODD in those children responding to the RED. A comparison of the pros and cons of both medication and an RED will elucidate why it is timely to implement an RED in ADHD.

Medication has two advantages: First of all it is a "quick fix": soon after ingesting the tablet the child's behaviour will improve and the improvement will last until the moment the tablet has lost its effect. An RED is the opposite of a quick fix and asks for commitment of parents and child. It takes a year to establish to which foods a child reacts and during that year the child has to comply with a more or less strict diet. Second: medication is easy to apply and thus convenient for all families, while an RED needs a great deal of commitment and is not easy to apply.

An RED also has some advantages. First of all, although medication used to be the most powerful treatment of ADHD with effect sizes varying from 0.6-0.9,[9] to date an RED may be considered the most effective ADHD treatment with a mean effect size of 1.2. Second, psychostimulants like methylphenidate, the most commonly used drug in ADHD, have a duration of action of 3-12 hours. This implicates that this medication does not solve the behavioural problems in the early morning and in the evening. Conversely, the effects of an RED last 24/7. Third, despite initial symptom improvement when treating ADHD with medication, the follow-up study in the Multimodal Treatment Study of children with ADHD (MTA),[89] showed that children who received medication exhibited significant impairment in adolescence, in fact comparable to children who had not received any medication at all. Follow-up research in RED studies, lasting 1 year, has shown beneficial effects throughout the year, but further follow-up studies are necessary. Fortunately, the prospects are promising: the initial RED will, slowely but surely, be expanded to a more or less normal dietary pattern, thus increasing the feasability of diet with a limited number of restrictions. Fourth, almost 60% of children do not continue medication despite initial favourable behavioural effects,

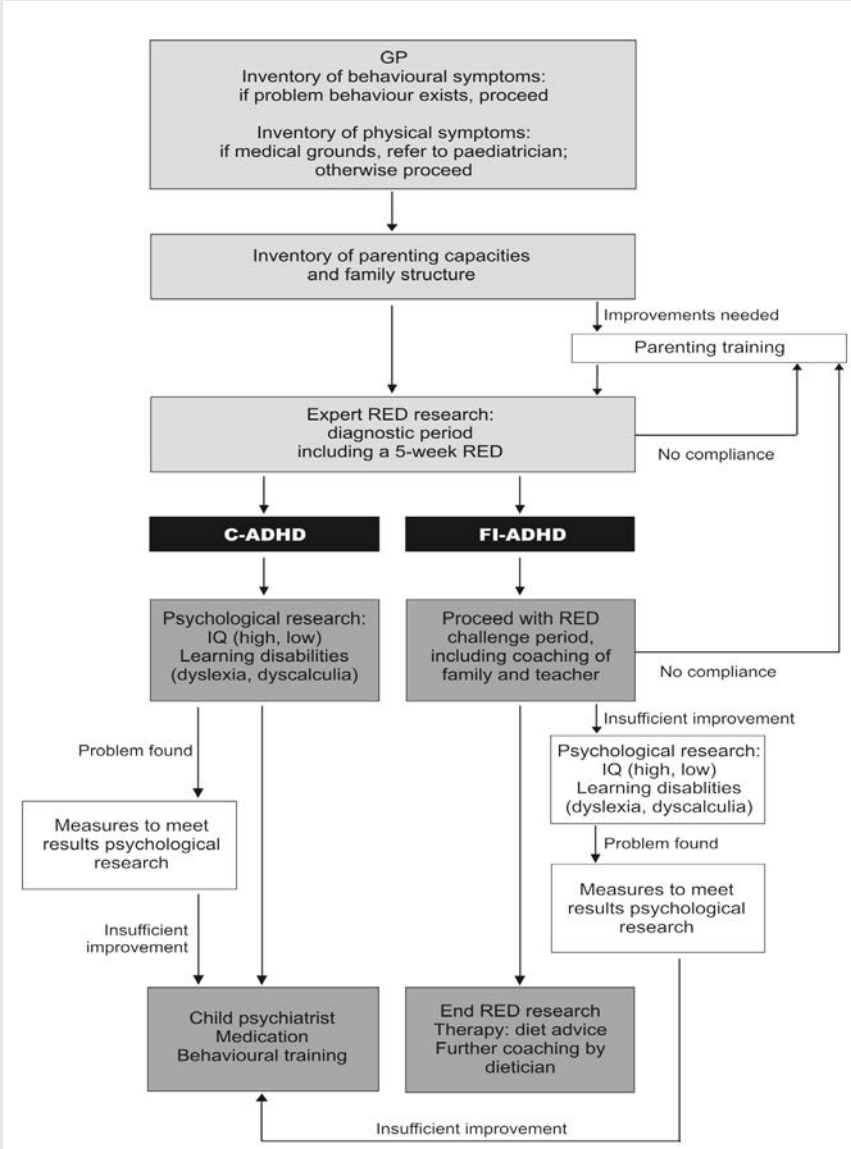
mostly because of adverse side effects like loss of appetite and perceived tolerability.[90] Conversely, an RED has a beneficial effect on somatic and sleep problems. Still, the diet itself, with concurrent limitations when attending parties or celebrations, may especially during the first year be interpreted as an adverse side effect. Fifth, not all children with ADHD respond favourably to medication; children show individual variability in medication response and in duration of effect and for this reason determining the optimal dose and the choice of medication is a matter of trial and error.[91] Of course neither do all children respond to an RED, but in 5 weeks it is clear whether the child suffers from FI-ADHD or C-ADHD.

In sum, medication, the most applied treatment of ADHD, has some disadvantages while the RED has some advantages, accordingly, innovative treatment approaches like the RED would be welcome in ADHD. Therefore it is timely to present a proposal for new ADHD guidelines which include RED research. Once before, in 2001, an RED was included in a basic algorithm for treatment of ADHD, based on the 6 RED RCTs available at that time. Somehow this part of the algorithm has never been put into effect, probably as a result of the false claims that additives were the main cause of ADHD.[20] The negating of the RED trials and of the 2001 algorithm for treatment may ensue from these false claims or may be due to change blindness.[92] Now, ten years later, additional RED RCTs haven been performed, confirming and strengthening the previous study results in unselected groups of children with ADHD, and thus warranting a revised algorithm for multimodal diagnosis and treatment of ADHD (see **figure 4**).

9.7.1. The parenting part of the algorithm

In this algorithm a multidisciplinary and multimodal approach is proposed, including educational therapists, RED experts, psychologists, psychiatrists and dieticians. It goes without saying that communication between these professionals is of the essence to optimise the diagnostic and therapeutic procedure. First, the GP or child health centre physician will make an inventory of the behavioural and physical problems. Subsequently, if applicable, the parenting capacities and family environment and structure may be considered by an educational specialist. If parents show at least average parenting qualities, the RED research may start. Conversely, if improvement of parenting capabilities (e.g. consistency, family interaction, affection and clear communication) seems important, this should first

Figure 4 Algorithm for Multimodal Diagnosis and Treatment of ADHD



be attended to. Still, it is conceivable that parenting incapabilities are consequential and not causal of the child's behavioural problems. Consequently, if the child's behaviour does not improve sufficiently despite parent training, the RED research should start. If a family proofs to be unable to comply with the 5-week diet, it is worthwhile to consider the parenting capacities once more and offer expert educational advice in order to help the family to comply with the RED.

In addition to the inventory of parenting capabilities prior to the RED, it is also important to investigate whether parents are willing and motivated to follow an RED. In families who do not want to start RED research or who repeatedly fail to adhere to the dietary restrictions, treatment as usual is indicated. Still, the results of the RED studies are striking and to such an extent, that no efforts should be spared to grant every child the opportunity to participate in RED research. For this reason it would be in the interest of children whose parents are not motivated to follow an RED to offer all assistance required to help these parents to see the RED through, and it is important to inform all parents in great detail of the pros en cons of participation in RED research and of treatment as usual.

9.7.2. The RED research part of the algoritm

When it has been established that parents are motivated to start an RED and that parenting capabilities are sufficient, the RED research may start. This research needs expert supervision by trained staff, i.e. a physician. There are several reasons why expert supervision is important to meet the conditions required for high quality diagnostic research in accordance with the model as applied in the INCA study (*Chapter 6*). First of all, most children with ADHD suffer from other disorders as well, and comorbidity is rule rather than exception, i.e., the problems involved are complex and in most children not limited to ADHD. This implicates that the RED research covers various areas of health problems and the RED expert must be capable to handle the variety of problems involved. Second, in children starting the RED and already taking medication the RED physician will monitor the reduction of medication which will take place in due course during the RED, consequently the RED expert must be clearly aware of all medical ins and outs of the child. Third, the RED expert will, depending on the child's behaviour during the 5-week RED, not only adapt the medication but also adapt the diet, in order to maximize the behavioural improvements. Unremitting consultation with parents and teacher on the effects of the RED is compulsory in order to maintain

the high quality and the impressive effect sizes achieved in the RED studies. Adapatations are made based on behavioural questionnaires, in accordance with the questionnaires used in the INCA study. It is important to emphasize the disadvantages of unsupervised elimination diets which may be prescribed undeservedly, which may lead to dietary insufficiencies or the results of which may be interpreted incorrectly because of missing reliable information. Finally, children diagnosed FI-ADHD who proceed with the challenge period and who subsequently show a severe behavioural relapse due to one of the challenged foods, may be advised to start or restart medication for a short period of time, i.e. until the effects of the challenged foods have faded away, in order to sooth the effect of the challenged food and to decrease the behavioural problems, especially at school. This is an important aspect of the challenge period which has to be monitored by an expert. At the end of the 5-week RED the diagosis FI-ADHD or C-ADHD will be made, based on the results of the questionnaires and the information of parents and teachers.

9.7.3. Follow-up strategy in children with C-ADHD

Parents need to be informed about the procedure that will take place when their child is diagnosed with C-ADHD. It will be obvious that these children, not responding to an RED, are allowed to eat anything again. They may proceed with psychological research to establish any other problems that may underly ADHD symptoms, e.g. learning disorders or learning problems, including an above average or high IQ. Unrecognised high talented children, similarly to children with unrecognised nonverbal learning disabilitiy (NLD) or dyslexia, may have problems at school, may show inattention problems or become restless and fidgety, may underperfom and may eventually be diagnosed with ADHD because they are showing the symptoms of ADHD. It must be acknowledged that ADHD is a symptomatic disorder, based on the number of symptoms and the concurrent problems in daily life. Consequently, unrecognised learning problems and disorders may lead to the diagnosis ADHD, and it is of the utmost importance to investigate and determine any psychological conditions which may be underlying of C-ADHD. If none of these psychological conditions are present or if an adequate approach of established psychological conditions does not improve the behavioural problems, then referral to a child psychiatrist is imperative, and medication as well as behavioural interventions should be considered.

9.7.4. Follow-up strategy in children with FI-ADHD

Children diagnosed FI-ADHD will proceed with the RED challenge period, in order to define the incriminated foods which may differ per child and per amount of food. This period is considered aggravating for parents and teacher, due to the recurrent behavioural relapses. Consequently, expert coaching of parents and teacher is important to increase the feasibility of the challenge period. Families showing compliance problems may be offered complementary parenting training, including video home training. The results of the RED in children with FI-ADHD is to such an extent, that it is important to strain every nerve in order to help families to see this period through. At the end of the challenge period the child's diet has returned to almost normal, the incriminated foods have been pin-pointed and the individual sensitivity for each incriminated food has been established, resulting in an dietary advice to what extent these foods have to be avoided, i.e. partially or completely, thus preventing ADHD.

If in the course of the RED challenge period a relapse in behaviour occurs or if the behavioural improvements manifest themselves predominantly at home and are less prominent at school, then also in children with FI-ADHD psychological research must be considered. Co-occurrence of ADHD with learning disabilities or learning problems is a conceivable option which might be the reason for less behavioural improvements at school. It is worth mentioning that in this algorithm psychological research consciously has been placed after the RED, to improve the reliability of the test results, because children with ADHD tend to underperfom which may affect the test results. Executing the psychological research following the RED will offer, at least in children with FI-ADHD and provided that the child has complied with the diet preceding the test, more reliable results because in these children the effects of ADHD are ruled out. Still, if in children with FI-ADHD the underlying cause of the relapse in behaviour cannot be established, and if the relapse is causal of malfunctioning at school or at home, then medication needs to be considered.

It has to be acknowledged that the challenge period is the most poignant part of the RED research. Expert monitoring and coaching of family and teachers is of paramount importance, first of all in order to pull everyone through this period; secondly, in order to define to which foods a child reacts; and most of all to give the child a chance of a better future, without ADHD. There is no reason to expect, provided that the child sticks to the diet, the dietary effects to disappear or diminish.

Two RED studies and the INCA follow-up have shown that the effects of an RED may continue unabated for a one-year period. Consequently, although more long-term research needs to be done especially to verify whether children may outgrow their specific vulnerability, it is timely to implement RED research in ADHD.

The concurrent economical effects of every child completing the RED research will be gigantic. According to a Dutch report, making a rough inventory of some of the costs of ADHD while comparing the costs including RED research with the current costs of ADHD, implementation of RED research may yield savings of 7.000 euros per year per child starting the RED research.[74] This sum is applicable to each child starting the RED research, independent of the fact whether the child proofs to be a responder or a nonresponder. The height of the sum may be explained by the fact that children diagnosed C-ADHD need expert supervision and medication for a great many years, while children diagnosed FI-ADHD need expert supervision for 1 year only. Consequently, if 100 children would start the RED research right now, the financial proceeds would, in a 10-year period, amount to 7 million euros (100 children x 7.000 euros x 10 years). Imagine the savings if all children with ADHD would start RED research!

9.7.5. An overview of the RED research according to the algorithm

1) RED research may be very effective, but certainly is not a quick fix method,
2) parents need to be motivated and need to have sufficient parenting capacities,
3) in the course of RED research a 5-week RED is necessary to establish whether the child is suffering from FI-ADHD (the RED diagnostic phase),
4) the diagnostic phase ends with making either the diagnosis FI-ADHD or the diagnosis classic ADHD (C-ADHD),
5) children diagnosed C-ADHD start assessment and treatment as usual,
6) children diagnosed with FI-ADHD will proceed with a challenge period to establish which foods are causal of the behavioural problems (the RED therapeutic phase),
7) the challenge period will take an average of 15 months,
8) following the challenge period the child's diet will be almost back to normal, the child only having to avoid a small number of foods,
9) the therapeutic phase ends with an individually dietary advice about which foods are incriminated and about the frequency in which the child is allowed to eat the incriminated foods,

10) it is not clear whether the child has to stick to the individual dietary restrictions perpetually, or whether children may overgrow the hypersensitivity,
11) occasional non-compliance with the therapeutic dietary advice will not be a problem, because in most children the behavioural problems occur only if the incriminated food is eaten for several days in succession and if the amount of the food exceeds an individually established threshold.

9.8. Suggestions for DSM-V

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) will be published in May 2013. The DSM is a renowned and widely used standard handbook describing and classifying mental disorders. Most classifications are based on specific symptoms which have to occur for a determined period of time and which have to cause significant impairment, consequently, most DSM diagnoses are symptomatic, i.e. based on symptoms instead of on causes (causal diagnoses). Of course, in psychiatric disorders it is common practice and justifiable to make symptomatic diagnoses, considering that the aetiology of most disorders is complex and unclear. Nevertheless, in some psychiatric disorders the diagnoses do refer to the cause, e.g. in Substance-Induced Delirium, Alcohol-Related Disorders, Amphetamine-Related Disorders and Cocaine-Induced Disorders. In accordance with these cause-related diagnoses the impact of an RED on ADHD has clearly been established, as a consequence of which part of the causal puzzle of this disorder is solved. Naming and blaming food as a cause of ADHD and integrating this knowledge (which was already incorporated in an algorithm for treatment of ADHD in 2001) in the DSM-V would be a considerable step forward towards understanding and treating ADHD, with concurrent beneficial effects for the children suffering from this disorder.

In addition to the suggestion to include food-induced ADHD (FI-ADHD) in the DSM-V, it is worth considering to substitute the current dichotomic symptom inventory ("often" versus "not often") by an inventory that specifies the rather vague and ambiguous indication "often". It is important to define the exact meaning of "often" in order to make a correct inventory of the behaviour of the child. The absence of a specific definition of "often" may lead to misinterpretation of the child's behaviour in parents with a lack of resilience as well as in parents

who abound in resilience. Parents who lack resilience may answer too negatively and may interpret a frequency of twice a week as “often”. Conversely, parents who abound in resilience may answer too positively, interpreting twice a day as “not often”. To prevent these diagnostic problems, the ADHD Rating Scale (ARS) would be a convenient instrument to make an inventory of the behaviour, at home as well as at school. The ARS, based on the DSM-IV criteria for ADHD, consists of the well-known nine inattention and nine hyperactivity/impulsivity criteria, but uses a four-point scale in which the occurrence of the behaviour is specified: 0 = never (less than once a week); 1 = sometimes (several times a week); 2 = often (once a day); and 3 = very often (several times a day). Three measures may be taken from the ARS: total score (0–54), inattention score (0–27), and hyperactivity/impulsivity score (0–27). A score of 2 (often= at least once a day) or 3 (very often = several times each day) points indicates that the child meets that specific ADHD symptom, while a score of 0 or 1 is considered normal behaviour.

It must be noted that some questionnaires apply the following 5 point scale: 0 = never; 1 = sometimes (occasionally); 2 = regularly (once a month); 3 = often (once a week); and 4 = very often (once a day).[93] It is important to note that whenever this questionnaire is applied, children will meet the criteria for ADHD when the ADHD symptoms occur once a week only. According to the ARS the same child would exhibit normal behaviour, because any child is expected to fidget, to be inattentive, or to talk before its turn once a week. To prevent children from being diagnosed with ADHD too easily, the DSM-V might add guideline suggestions in order to realise consistency in questionnaires used in ADHD, and might replace “often” by “at least daily”.

Furthermore, the DSM-V Task Force might also reconsider the DSM-IV notion that ADHD is a discrete disorder. According to the current categorical approach of ADHD children who show evident clinical significant impairment but who do not meet the required number of symptoms (children with 5/9 inattention symptoms *and* 5/9 hyperactivity/impulsivity symptoms) will *not* be diagnosed with ADHD, while children with *only* 6/9 inattention symptoms and none of the hyperactivity/impulsivity symptoms *will* be (see figure in *Chapter 1*). Of course, children not meeting the symptom criteria may meet the criteria for ADHD-NOS, but somehow, unlike PDD-NOS, this diagnosis does not appeal to physicians and is scarcely used. The above described diagnostic problem, in which some children who show more problems do not meet the criteria of ADHD while children

showing less problems do, would be solved if the categorical DSM-IV notion of ADHD was replaced by a continuous notion in the DSM-V.

To date the view that ADHD is a continuous rather than an discrete disorder seems to prevail.[94-97] The notion of behaviour as a continuum with ADHD at the extreme end is commensurable to high blood pressure at the extreme end of blood pressure and obesity at the extreme end of weight. In all three conditions, behaviour as well as blood pressure and weight, it is important to establish the turning point: which weight, blood pressure, or number of ADHD symptoms are considered normal, and where does pathology start? One of the diagnostic DSM-IV criteria for ADHD might be considered the ADHD turning point, namely: "there must be clear evidence of clinically significant impairment in social, academic or occupational functioning". This may be a common-sense approach with a decisive role for the child's impairment reported by parents and teachers to make the diagnosis, indepently of the exact number of symptoms.

In conclusion, the DSM-V will mark one the most anticipated events in the mental health field. Based on convincing evidence and the advices made in *Chapter 6* concerning the effect of an RED on ADHD some changes are suggested to incorporate in the diagnostic category of Neurodevelopmental Disorders, specifically in ADHD. First of all it is timely to focus on food and to incorporate FI-ADHD in the DSM-V. Furthermore, the inventory of the behavioural problems might best be made using the ARS, in which "often" is defined as at least once a day. And finally, the DSM-V Task Force might take into consideration the replacement of the categorical ADHD notion by a continuous notion, in which the child's dysfunction or impairment may be considered as the pivotal and decisive important factor to define where normal behaviour ends en ADHD starts. These changes may contribute to the improvement of our child mental health care and the focus on food may offer opportunities for prevention of ADHD.

9.9. To conclude

Right now, the main therapy of children with ADHD is medication, eliminating symptoms during 3-12 hours depending on the drug, with an effect size of 0.6-0.9 and with disappointing long-term effects. This dissertation has shown that in the majority of young children ADHD may be caused by food and that an RED is an

effective treatment of ADHD in children diagnosed FI-ADHD, preventing symptoms 24/7 with an effect size of 1.2 and with promising long-term prospects. The pros of an RED are to such an extent that the current treatment might be expanded with RED research, especially in young children with ADHD. Although expert supervision is needed to diagnose a hypersensitivity to food in ADHD, a recent overview of 35 years of research into diet and ADHD resulted in an advice to encourage motivated parents, whether the child is on medication or not, to follow an RED.[98]

The RED research consists of a diagnostic part to segregate between FI-ADHD (children responding favourably to the RED) and C-ADHD (nonresponders). Children diagnosed with FI-ADHD start a challenge period to establish the incriminated foods, and at the end of the challenge period the therapy consists of dietary advice to avoid certain foods. Offering children with ADHD the opportunity to follow an RED may result in prevention of ADHD and consequently in improvement of the children's prospects. Children diagnosed with C-ADHD start psychological research and treatment as usual, as has been shown in an algorithm for multimodal diagnosis and treatment of ADHD (see figure 4, chapter 9). Children of parents not motivated to start or to comply with an RED should start treatment as usual.

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Appendix

Research Protocol

A Study into the Impact of Nutrition on Children with ADHD

-INCA Study-

A Dutch randomised controlled trial into the effects of food on the behaviour of a random group of school-going children meeting the DSM-IV criteria for ADHD, including immunological testing

Reviewed and accepted by *The Lancet*; summary published on *The Lancet*'s website (www.thelancet.com/protocol-reviews/06PRT-7719)

Pelsser LM, Frankena K, Savelkoul HF, Buitelaar JK. Research Protocol for a Study into the Impact of Nutrition on Children with ADHD (INCA Study). A Dutch randomised controlled trial into the effects of food on the behaviour of a random group of school-going children meeting the DSM-IV criteria for ADHD, including immunological testing

Contents

1. In general

The study on the Impact of Nutrition on Children with ADHD (INCA) is a randomised controlled trial into the effects of a food elimination diet on the behaviour of a random group of school-going children who meet the DSM-IV criteria for ADHD. The study also includes immunological research on the effects of food.

2. Introduction

2.1. ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder which affects 3 to 5% of all school-going children. The disorder generally manifests itself before the age of 7 and is characterised by symptoms of inattention, impulsive behaviour and hyperactivity.(1) ADHD is generally diagnosed in combination with other psychiatric disorders such as Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD).(2) The demand for social and healthcare services is considerable among children with ADHD. Research has shown that in particular the attention deficit disorders are responsible for an early onset of criminal behaviour.(3)

2.2. Causes

Genetic factors play a dominant role in ADHD, but there are also a number of yet-to-be-identified environmental factors that may contribute to the disorder's development.(4) Our knowledge of the mechanisms that trigger ADHD is still based largely on speculation, so that opportunities for prevention cannot as yet be fully explored.(5)

One of the research areas meriting greater attention is the impact that food may have on behaviour and behavioural disorders. There is a growing awareness among healthcare providers that the composition and quality of our food may play a role in determining not only our physical well-being, but also our behaviour. In children who are (genetically) vulnerable to ADHD, for instance, external factors may well trigger symptoms of the disorder. A comparable triggering function has been observed in the development of asthma, which is also basically a genetic disease. Various external factors, including dust mites, pet animals, pollen or

foods, have been shown to contribute to the development of asthma, and avoiding these triggers may reduce the intake of drugs to a minimum. Similarly, therefore, as knowledge of the mechanisms triggering symptoms of ADHD increases, the need to prescribe drugs (see under 2.3.) may well decrease simply by avoiding certain triggers, such as specific foods.(6)

2.3. Medication and behavioural therapy as methods of intervention

At this point in time, medication and behaviour therapy are the main forms of treatment for children with ADHD.(7) There is no conclusive evidence, however, that any of these treatments improve the long-term prognosis.(7) Although methylphenidate, the drug most commonly used in the treatment of ADHD, has a statistically significant short-term clinical effect, there is a lack of long-term randomized trial evidence.(8)

Most current scientific research projects centre on medication. In an effort to shift the focus from fighting symptoms into averting risk factors, this Study into the Impact of Nutrition on Children with ADHD (INCA Study) focuses on the question of whether nutrition can be regarded as a potential ADHD risk factor in some children. If so, a diet eliminating the foods involved could be considered as a treatment of ADHD, thus eliminating the incriminated risk factors and preventing the ADHD-symptoms.

2.4. Diet as an intervention

The occurrence of adverse physical reactions to foods (e.g. eczema, asthma, allergic rhinitis, gastrointestinal disturbances)(9), stimulated speculation that such foods could also have an impact on the brain and produce adverse behavioural effects.(10) Studies looking only at food dyes in the 1970s (the additive studies), showed no cause-and-effect relationship between these additives and behaviour.(11-14) Since 1985 dietary studies, excluding not only additives but many different foods, have been conducted (the diet studies). (10,15-19) The main difference to the additive studies, in which the children adhered to their normal diet, was that the dietary trials involved a total change of diet: the children were put on a ‘few foods diet’ for a number of weeks, a diet in which only a few different foods were allowed. The rationale for using a highly restrictive diet during a few weeks was the assumption that a child might show adverse behavioural reactions to any foods. That might explain why excluding just

one or two different foods, as the additive studies (11-14) and sugar studies (20-22) have shown, is not an effective method to investigate the existence of a diet-behaviour connection in a child.(10)

Although different diet studies used different diets, the general idea of these randomised controlled trials was that only few different foods were allowed, including rice, turkey, lettuce, pears, and water.(10,15-19) These trials, exclusively involving children who met the criteria for ADHD, showed that 24% (in the most extensive diet and an unselected population (19)) to 82% (in the most restricted diet and a highly selected population (15)) of the subjects showed significant behavioural improvements. Unlike the additive studies, all trials based on the few foods diet showed improvements in behaviour, resulting in the conclusion that there is convincing double-blind controlled evidence for the efficacy of an elimination diet in a subgroup of children with ADHD.(22,23) Subsequently the National Institutes of Health recommends further research into the relationship between food and behaviour.(5) Hill and Taylor have meanwhile developed a protocol for treating ADHD patients based on both medication and dietary intervention (see Appendix 3).(24)

2.4.1. Dutch elimination diet

Following a few foods diet is difficult and puts a considerable strain on the whole family. Carter indicates that it may be possible to devise a less restricted diet, with similar levels of succes.(10) We have developed an elimination diet which is based on the few foods diet but is more extensive, allowing the children, on a limited scale, to use more foods than are permitted in the few foods diet. As a consequence, this elimination diet is easier to keep up and is much less burdensome for both parents and the children, which is an important issue for (grand)parents, children, and the Medical Ethical Board. The Dutch elimination diet consists of rice, turkey, lamb, a range of vegetables, pear, rice milk with added calcium and water. This basis is complemented with specific foods like potatoes, fruits, corn, some sweets and wheat, allowed in limited doses twice a week. Vegetables, fruits, rice and meat are allowed every day, in normal doses. Occasionally the diet will be varied to avoid foods for which the child has a particular craving or dislike.(10,15)

We have already tested this diet, which will be used in the INCA Study, in the context of two earlier studies in which 100 children participated: more than 60%

responded significantly to the dietary intervention, improving their behaviour by 50% or more.(25,26) The results of these Dutch studies are comparable to those shown in other diet studies.(10,15-19) Moreover, one of the Dutch studies showed that the dietary intervention had a positive effect not only on the ADHD symptoms but also on the comorbid ODD symptoms.(26) This is an issue because the prognosis of children also having comorbid problems like ODD, is relatively unfavourable.(2)

In some studies it was noticed that a substantial number of subjects also had physical complaints, such as abdominal pain, diarrhoea, headaches, eczema, or asthma.(10,15,25,26) Of the participants in one of the Dutch dietary trials, 20 in 31 participants even had three or more physical complaints. The diet caused a significant reduction in these complaints.(26) An elimination diet may not only have an beneficial effect on the behaviour of children with ADHD, but also on the comorbid physical complaints. Since children showing extensive physical symptoms tend to respond less favourably to drugs,(27) a dietary intervention may be optional for these children.

2.4.2. Practical aspects of dietary research

Dietary trials with ADHD children generally consist of two phases: an elimination phase and a reintroduction phase.(10,15,17) A phased approach is necessary because there is evidence that children who respond to food by showing ADHD-typical behaviour are generally sensitive to more than one food,(10) each child responding to different foods and in random combinations. This multiple sensitivity may explain the overall negative conclusions of the additive studies, eliminating or provoking just one element of the child's diet.

The elimination phase, can be considered as a investigation phase, after which the diagnosis "ADHD being triggered by foods", can be accepted or rejected. During this phase will be investigated whether the child's behavioural problems decrease when following a restricted diet during some weeks. All children who show a significant response to the elimination diet will proceed to the second phase, the reintroduction phase. During this phase will be determined which foods are provoking the child's behaviour, by reintroducing one by one the foods which were eliminated during the first phase of the trial. This phase will last until the child has returned as much as possible to his or her normal eating pattern. The second phase is a diagnostic phase, establishing which specific

foods are incriminated. Eventually this phase will lead to a therapy, which consists of an advice about which foods should be avoided.

Despite what parents expect, children seldom show ADHD behaviour after eating colorants or sugar alone,(11-14, 20-22) although a recent trial has shown that there is a general adverse effect of artificial food colouring and benzoate preservatives on the behaviour of all 3 year old children, not only in hyperactive or atopic subgroups.(28)

Parents generally experience the reintroduction phase as extremely heavy, especially because their children revert to their former ADHD-typical behaviour when eating certain foods and there is no way to anticipate when this will happen, because each child responds differently to different foods.(10) This is one of the conclusions to be drawn from the follow up of a recent Dutch trial, "A Randomised, Controlled Study into the Effects of Food on Young Children with ADHD".(29) This study has been registered in the trial register, International Standard Randomized Controlled Trial Number ISRCTN47247160, and is the forerunner to this INCA Study. Based on parents' ratings as well as teacher's ratings, the preliminary results of this study are that more than 70% of the children (N=27) show significant improvements in behaviour in response to the elimination diet, according to both the Abbreviated Conners Scale(17) and the ADHD Rating Scale.(30) The study also shows that the reintroduction phase is very strenuous, particularly when the behaviour of a child is triggered by several foods. This burden on child and family was confirmed by Carter.(10) Added to this is the fact that the reintroduction phase is long, because the foods are reintroduced one at a time.(10) It is very important, therefore, to find a method to lighten the reintroduction phase and thus alleviate the burden of the second phase of dietary research.

2.5. Immunological research

As yet many research has been done on the relation between ADHD and allergy. Initially, a relation was assumed between ADHD and food allergies.(31) Another study found a surprisingly high proportion of children with ADHD having associated symptoms such as allergic disorders.(15) But randomised intervention studies showed no conclusive evidence for this association,(32,33) finding no discrepancy in the number of children showing ADHD-typical behaviour with and without an allergic disorder.(32) Recent research on ADHD and allergy is also not leading to any definitive answers.(34-36)

Despite the range of diverse studies that attempt to understand the comorbidity of allergies and psychiatric diagnoses, the controversy whether or not ADHD and allergies are causally linked still exists in the literature. According to Bellanti, in light of the increasing evidence that food may play a role in some children with ADHD,(10,15-19) more research is necessary into the immunological background and the impact of hypersensitivity reactions to foods.(37) To gain an insight in this matter, we will investigate in the INCA study whether in some children with ADHD an immunological mechanism might be involved. Hypersensitivity is the coordinating term for all allergic and non-allergic reactions triggered by environmental factors (stimuli), according to the revised nomenclature for allergy. The definition in this nomenclature is as follows: "Hypersensitivity describes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects."(38) The manifestation of asthmatic symptoms following exposure to dust mites by a child who has shown to be sensitive to dust mites, will meet the definition of hypersensitivity, the dust mite being the defined stimulus. If a child shows symptoms of ADHD after eating normal amounts of specific foods, the foods may, like the dustmite, be regarded as clearly identified stimuli tolerated by normal subjects. This means that in some children ADHD may be the result of a hypersensitive reaction as described in the definition above. Preliminary studies on the effects of pollen and food exposure on ADHD symptoms (10,15-19,39) support the existence of a hypersensitive mechanism. When in a specific case ADHD symptoms originate in response to food components, and when an immunological mechanism can be defined which underlies this process, then in this specific case ADHD may be considered as a consequence of an allergic response. This is in accordance with the revised allergy nomenclature.(38)

Allergic hypersensitivity may be IgE- or non IgE- mediated. Immunoglobulin (Ig) molecules are the products of B-cells (unlike T-lymphocytes independent of the thymus) and are divided in several immunological classes (e.g. IgE and IgG), associated with a range of important biological properties.(40) Radioallergosorbent test (RAST) tests are commonly used to demonstrate food-specific serum IgE antibodies. Although the clinical relevance of the detection of IgG-antibodies is not quite clear, Strobel indicates that in non-IgE-mediated immunological adverse reactions to food, determination of IgG, detected by an enzyme-linked immunosorbent assay (ELISA) test,(41) may be an helpful adjunct.(40) According

to Gaitens, a behavioural response to food is probably not IgE-mediated, but there might well be a connection between ADHD and allergies based on a non-IgE-mediated mechanism.(42) Research by Atkinson on the Irritable Bowel Syndrome has shown that a diet, based on IgG antibodies in the blood, may have a positive effect on the complaints.(43) According to Bellanti, the results from Atkinson's research might also be useful in research on the potential hypersensitivities in other disorders.(37) Maybe in children showing an ADHD-response to foods, a delayed type of allergy (mediated by a chronic immune stimulus to T cells) is involved,which is generally coupled with the presence of specific IgG antibodies.(44)

Immunological tests on IgE and IgG-antibodies before and after a dietary intervention may provide additional information about the mechanisms of foods in children with ADHD, may enable us to segregate between non-allergic or allergic mechanisms in food-induced ADHD and may simplify the reintroduction phase. There have been no previous studies with a focus on the question into what extent the presence of IgG antibodies to specific foods in the blood might indicate a connection between those foods and behavioural disorders. As the connection between ADHD-like behaviour and allergy is still unclear and as it is important not only to know into what extent foods are playing a role in ADHD but also to unravel the possible mechanisms of action of foods, the INCA study not only investigates the influence of foods on ADHD, but also the possible mechanisms in which these foods exert their effects.

2.6. What is already known about this topic

2.6.1 A diet excluding just one food, like sugar or chocolate,(20-22) or an additive free diet is of little benefit to ADHD.(10) A recent trial has shown that some degree of hyperactivity, when exposed to artificial food colours and benzoate preservatives, may be applied to all 3 year old children, not exclusively to hyperactive or atopic subgroups.(28) These findings suggest that benefit would accrue for all preschool children, if these additives were removed from their diet.

2.6.2. All diet studies, unlike the additive studies using a restrictive elimination diet, show convincing controlled evidence of efficacy for a selected subgroup. (10,15-19,22,23,29)

2.6.3. In 2001 a basic algorithm for treatment of ADHD has been published, a protocol derived from standard recommendations and evidence, intended for outpatient medical clinic practice in secondary care. In this protocol the use of a few foods diet is being advised in predetermined cases of children with ADHD.(24)

2.6.4. To date hardly any research is done on ADHD in relation to foods. In general the existence and the results of the diet studies are ignored, only seldom an elimination diet as a possible treatment for ADHD is mentioned.(45) Mostly only additive studies or sugar studies are quoted to underline that the idea of foods causing ADHD is wrong.(46) In a recent "balanced review of the literature, both in support and against the possibility of foods or additives causing behavior disorders" not any of the diet studies is mentioned.(47)

2. 7. What this study adds

2.7.1. Most previously performed diet studies have focussed on selected subgroups, e.g. the participants were recruited via diet clinics. The INCA study will investigate the effects of a few foods diet in an unselected group of children with ADHD, in order to determine how generally applicable this treatment might be within a general group of children with ADHD.

2.7.2. The INCA study will investigate the effects of an elimination diet on ADHD as well as on comorbid disorders. In at least 50% of the cases, children with ADHD also suffer from ODD.(2) As children with ADHD and comorbid ODD are more at risk for long-term maladjustment(48), we hope that the results of this study eventually may improve the prospects of these children.

2.7.3. If the results of the INCA study will be in accordance with the results of all previous diet studies, then these findings are sufficiently strong to warrant attempts at replication in larger studies. We then also would advise to implement the basic algorithm for treatment of ADHD, as proposed by Hill and Taylor (appendix 3).

2.7.4. The INCA study will be the first study investigating the influence of foods on ADHD, as well as the possibility of underlying immunological mechanisms by

which these foods may exert their effects. Immunological tests before and after a dietary intervention may provide additional information about the mechanisms of foods in children with ADHD, may enable us to segregate between non-allergic or allergic mechanisms and may simplify eventually the dietary treatment of children with food-induced ADHD.

3. Trial objectives

The trial is two-phased, an elimination phase, phase 1, and a reintroduction phase, phase 2.

3.1 Objective of the elimination phase, phase 1

The **objective** of phase 1 is to determine the impact of food on the behaviour of a heterogeneous, random group of children with ADHD in a randomised, controlled trial. The null hypothesis is that there is no effect of treatment (i.e. food elimination) on the behavioural scores of the subjects.

3.2. Objective of the reintroduction phase, phase 2

The **objective** of phase 2 is to examine whether the determination of IgE and IgG antibodies to specific foods in the blood can contribute to the application of dietary intervention in children with ADHD. All foods without elevated IgE or IgG antibodies are reintroduced concurrently to the diet of the responders. The effects of this provocation on the behaviour of the responders will be tested in a randomised, controlled trial.
The null hypothesis is that there is no effect of treatment, i.e. there is no relationship between the level of IgE or IgG antibodies in the blood and the behavioural scores of the subjects.

3.3. Justification of phase 1 trial objective

Contrary to most diet studies, this trial will investigate the effects of a few foods diet in a heterogeneous group of children who will not be selected based on background or affinity with diet interventions. In view of the highly positive outcomes of earlier diet studies in and outside the Netherlands, it is important to find out to what extent the outcomes of those trials are applicable to a random

group of children with ADHD. We may even gain insight into common characteristics in responders or nonresponders. The significance of this INCA Study also lies, therefore, in the predictive value of the research: the question of predicting in which children, showing ADHD behaviour, this behaviour may be triggered by foods. The outcomes could be used to draw up guidelines with recommendations as to which children with ADHD might benefit from diagnostic dietary research. In these children a diet may contribute significantly to the provision of care, by professionals as well as at home, and may well reduce the intake of medication.

3.4. Justification of phase 2 trial objective

Once phase 1 ends, only the responders will be subjected to phase 2. This phase is used to identify the foods to which the child responds. In previous diet studies foods were reintroduced one by one and only one a week. In the unfortunate case of relapse in behaviour the reintroduced foods were eliminated again. This method takes long and demands much energy from the child, the parents and the child's social environment. But not knowing anything about the mechanisms in which foods exert its effects, no other method is available.

Phase 2 of the INCA study, therefore, is based on blood tests, which will provide us with information about the possible existence of immunological mechanisms of foods and may simplify phase 2 by tracing the foods that trigger ADHD-typical behaviour. The reliability of the IgE- and IgG-values found will be tested by concurrently reintroducing to the elimination diet all foods for which no increased IgE and IgG levels were found in the first blood sample. If the behaviour of the responders has a relapse, we may conclude that blood tests on IgE and IgG do not play any significant role in the diagnostic process concerning ADHD and foods. But if the behaviour does not change, we may conlude that these blood tests can inform us about foods which do not trigger ADHD symptoms, which will make the appliance of dietary interventions in practice much easier.

Immunological testing may simplify the reintroduction phase and yield a number of positive effects: (1) the reintroduction phase can be shortened considerably; (2) the reintroduction phase will become less strenuous, since foods identified as not producing a hypersensitive response can be reintroduced without further investigation after the elimination phase has been completed; (3) compliance will improve as a result of the shorter reintroduction phase and the quicker return to normal eating patterns.

Therefore, immunological research may form the basis for a more effective application of dietary research and may hence contribute to the prevention of ADHD symptoms in children who have been shown to respond to food by exhibiting ADHD-typical behaviour.
If the response is IgG- rather than IgE-mediated, a determination of total IgG might help identify potential responders to the therapy and determination of food-specific IgG will be a useful tool in identifying the specific foods that trigger ADHD in a child. No research in this field has been published to date!

4. Target group and selection

4.1. Target group

4.1.1. Inclusion criteria:

(a) ADHD diagnosed according to DSM-IV(1); diagnoses based on structured psychiatric interviews and standard questionnaires (Abbreviated Conners Scale, ADHD Rating Scale, Strengths and Difficulties Questionnaire) to be completed by parents and teachers;
(b) Children aged between 4 and 8;
(c) Children not taking medication such as methylphenidate;
(d) Parental permission for three blood tests;
(e) Sufficient command of the Dutch language.

4.1.2. Exclusion criteria:

(a) Family circumstances hampering completion of the elimination diet;
(b) Children already on a diet or having been on a diet in the past two months;
(c) Children receiving behavioural therapy or medication at the time of registration.

4.1.3. Justification of inclusion and exclusion criteria

All children have to meet the DSM-IV criteria for ADHD, the presence of comorbid disorders is no reason for exclusion. As the questionnaires will not only be completed by parents but also by teachers, we exclude children younger than 4 years, being the age for Dutch children to go to primary school. We have choosen a maximum age of eight years old in order to increase the compliance with the diet. The older a child becomes, the more freedom of movement it has, which inevitably

comprises more possibilities to eat foods that are not allowed during the elimination diet and more problems in monitoring the behaviour and the intake of foods.

Children receiving medication or behavioural therapy at the time of registration are excluded, because we like to investigate the influence of foods on ADHD without the behaviour also being affected by other therapies. Children already on a diet are being excluded for the same reason. If the medication or the behavioural therapy was ended two months before entering the trial, than the child may be included, provided that it meets the other criteria. But we will not encourage parents to interrupt or stop these therapies, as we obviously do not want to undermine other medical advices.

4.2. Registration and randomisation

4.2.1. Registration

Hundred participants will be recruited at medical and psychiatric centres, and through media announcements. Parents who are interested must contact the researcher for the study. If they wish to register their child, an intake interview will be conducted by telephone. This intake will include a structured psychiatric interview based on DSM-IV criteria (see under 5.4.4.) During the intake interview will be checked whether the child meets all inclusion and exclusion criteria listed above. Also the study will be thorougly described and the parents will be comprehensively and clearly informed about the possibility of their child being allocated to the control group. If it appears that the child meets all criteria, the parents who are still interested will receive a comprehensive Information Sheet, providing them with more detailed information on the study, including again the issue of the allocation to one of two groups. Before the randomisation process, the parents must consent in writing to an anonymous processing of all research data. The child will then be registered for participation.

4.2.2. Randomisation

Immediately after the first measurement (see under 5.2.1.) the children will be randomly allocated to (A) an intervention group and (B) a control group. This moment of randomisation, i.e. after the first measurement, has been choosen to prevent any feelings of disappointment of the parents, which might arise when the child will be allocated to the control group, to impede the first measurement. Randomization will be performed using randomised blocks, by means of ten

boxes each containing 10 sealed envelopes (5A+5B). The sealed envelopes will contain computer-generated cards with concealed assignment codes. This procedure will be organised and administered by an independent research associate. The parents will pick and open one of these envelopes in the presence of the researcher. Assignment will be dispensed in accordance with the allocation in the envelope. Whenever the first box will become empty, it will be replaced by the next box. Blocks are deemed necessary to prevent an unequal distribution of treatments over time and to adjust for possible trends in scoring over time due to a learning effect of the observers or seasonal trends in efficacy of the treatment.

4.3. Paediatric examination and single blinded measurements

All children will be examined by an independent and blinded paediatrician at Catharina Hospital in Eindhoven. This paediatrician is experienced in assessing ADHD in children and is member of the Dutch ADHD Paediatric Network. The blinded measurements will be conducted indepentently of the measurements of the researchers. The paediatrician will use the same questionnaires as the researchers, the ADHD Rating Scale (5.4.2.) and the structured psychiatric interview (5.4.4). The first examination consists of a general physical examination and a diagnostic assessment for ADHD and co-morbid disorders, to verify the diagnosis. This will be combined with the first taking of blood. The second and third examination consist of a diagnostic assessment for ADHD and co-morbid disorders, and will be combined with the second and third taking of blood, also at Catharina Hospital (see appendix 1).

5. Study design

5.1. General

The diet used in this trial is very restrictive, it would be impossible to compose a reliable placebo diet without parents or teachers noticing this, thus impeding a placebo controlled trial. Therefore the INCA study is a a randomised controlled trial (RCT), as is also used by other studies where no placebo is available, such as studies into the effects of cognitive behaviour therapy,(49,50) eczema,(51), or other medical intervention trials.(52-54)

It is not possible for the researchers to be blinded,(51) as they have to advise

the parents about the diet. Data entry will be done by administrative assistents, blinded to the assigned treatment.(54) In addition, an independent and experienced paediatrician who will be blind to treatment conditions, will execute three assessments to investigate whether the children meet the DSM-IV criteria for ADHD and co-morbid disorders.(55) The paediatrician will not be informed about the group the children have been assigned to. Children and parents will be instructed not to reveal this information to the paediatrician.(55) The paediatrician has to open a new file every time a child visits him, independently of the fact whether it is the first, second or third time the child is visiting the paediatrician.

The dietary trial consists of two phases (see **table I**): the elimination phase (see under 5.2.) and the reintroduction phase (see under 5.3.). Three blood samples will be taken during the trial (see Chapter 6): in week 0 (start of the trial), week 9 (after the elimination phase) and week 13 (after the reintroduction phase). The trial will be conducted randomised and controlled (for an overview see Appendix 1). At week 13 the trial stops, not only out of ethical consideration (13 weeks in a waiting list group is extremely long for families with an ADHD child) but also for practical reasons (parents who must wait too long will be sooner inclined to withdraw from the trial). All in all, 100 children will participate (see Chapter 7).

Table I Overview of elimination and reintroduction phases

Elimination phase: weeks 1-9	Reintroduction phase: weeks 9-13
Baseline diet (see 5.2.2.) weeks 1-3	IgG-0 provocation (see 5.3.) weeks 9-13
Elimination diet (see 5.2.4.) weeks 3-9	

5.2. Phase 1, elimination phase, weeks 0-9

The elimination phase lasts 9 weeks and comprises a baseline diet, an elimination diet, and three measurement points. Following the first measurement in week 0 (see under 5.2.1.), the children will follow a 2-week baseline diet (see under 5.2.2.). After the second measurement in week 3 (see under 5.2.3.), the children will start with the elimination diet (see under 5.2.4.). At the end of this elimination diet, the third measurement will be conducted in week 9 (see under 5.2.5.).

The interviews in which the measurements are recorded will be held with the parents in the absence of the child. The child's behaviour is registered with the aid of questionnaires to be completed by the parents and the child's teacher, but not by the child itself. The interviews and questionnaires highlight the less agreeable aspects of the child's behaviour and could, therefore, be experienced as very negative by the child and, for that matter, by the parents as well. This is why we have chosen not to conduct the interviews in the child's presence. The child will be examined by a paediatrician (see 4.3.).

5.2.1. Week 0, entrance measurements: first interview, first measurement (M1), first measurement by blinded paediatrician (MBP1)

All 100 participants will start the trial with an interview, comprising a detailed anamnesis in which we discuss the child's medical and social history, the family situation, the mother's pregnancy and delivery of the baby, and the child's school career, personal development and behaviour. In addition, four questionnaires are to be completed (see under 5.4.). After the first measurement M1, the participants are assigned at random to the intervention or waiting list group, as discussed under 4.2.2. The first measurement time is also the time that the first blood sample is taken (see Chapter 6) and that the first assessment by the blinded paediatrician (MBP1) will take place, both at Catharina Hospital in Eindhoven (appendix 1).

5.2.2. Weeks 1-3, baseline period: between first and second measurements

After the first measurement, all 100 children start with the baseline period, which is a 2-week period in which each child follows his or her own specific diet. No changes are made to the diet and no foods should be avoided. The parents will use this time to keep a detailed diary from which the child's normal eating habits may be inferred. In addition, the child's behaviour and any physical complaints and potential risks to compliance, such as before- and after-school care, staying at a friend's, or sports activities, are closely monitored and recorded. At the end of the baseline period the effects of this extra attention for the child are measured (M2). It is not entirely inconceivable that the child's behaviour already improves because of the special attention which parents give their child in order to fill in the diary correctly.

Both the intervention group and the control group will keep a diary, which means that the two groups still run parallel to each other during the baseline diet.

5.2.3. Week 3: second interview, second measurement (M2)

The second measurement point for all 100 children, that is, both the intervention group and the control group, takes place after the baseline period. This measurement is particularly important to identify possible changes that may have occurred during the baseline period as a result, for instance, of the special attention given to the child. Parents and teacher fill in the questionnaires referred to under 5.4. This measurement point is also the time when the children from the control group are placed on a waiting list; their eating pattern will not change. The children from the intervention group proceed to the elimination phase (see 5.2.4.)

5.2.4. Weeks 4-9: between second and third measurements: elimination period for intervention group, waiting period for control group

Children assigned to the control group are placed on a waiting list whilst the intervention group follows the elimination diet. The waiting list group continues their normal eating pattern. No alternative form of treatment is offered to them, and parents are at liberty in this period to explore other research or treatment options. Like the intervention group procedure, the procedure for the control group also involves completion of all questionnaires, and the measurement points for this group coincide with those established for the intervention group, that is in weeks 0, 3, 9, 11, and 13 (see **table II**). To motivate families who have been placed on the waiting list to complete the trial, all families in the control group are offered an opportunity to start the elimination diet after the final measurement in week 13 and to follow the same procedure as that followed by the intervention group.

Children assigned to the intervention group will start a 5-week elimination diet. The diet will be preceded by a 'gradual transition week' in which the child's eating pattern will slowly be adjusted to the new diet and the parents are able to do the shopping and get accustomed to new foods. The elimination diet is based on the few foods diet, but it is more extensive, allowing the children, on a limited scale, to use more foods than are permitted in the few foods diet. We have tested the usability of the diet in three earlier studies, in which more than 60% of the subjects showed significant improvements in behaviour (>50%) in response to the diet.(25,26,29) (see 2.4.1.) All major allergen foods, ingredients and/or additives associated with behavioural disorders are eliminated from the diet. (15,16,19) The diet basically consists of bread, rice, corn, turkey, lamb, various vegetables and fruits, rice milk with extra calcium, margarine, and pear juice from

concentrate. This basis is complemented with specific foods like potatoes, fruits, corn, some sweets and wheat, allowed in limited doses twice a week. Vegetables, fruits, rice and meat are allowed every day, in normal doses. Occasionally the diet will be varied to avoid foods for which the child has a particular craving or dislike. (10,11) The diet clearly prescribes for each day which products and snacks the child may eat and drink. All ingredients are listed, and parents receive a grocery list, so that the risk of errors in the diet is reduced to a minimum. The diet is adjusted to the individual child in order to take into account the child's specific food preferences and to leave out all foods which the child does not like.

Parents are given a diet programme which must be strictly observed at all times. They must also continue to keep a diary during this phase, registering not only the behaviour of the child but also any dietary infractions. If recurrent infractions are noticed, the child will be excluded from the trial. The intention to treat analysis of these children and of children who leave the trial prematurely, will be performed using two methods: last-observation-carried-forward (LOCF) and group mean imputation (GMI).(56) If the parents have any questions about the diet, they should contact the researcher for consultation. If the diet does not result in any behavioural changes after the first 2 weeks, the diet will be further restricted in consultation with the parents.(10) In the end, therefore, the diet may vary for each individual child, depending on the need to make interim adjustments.

5.2.5. Week 9: third interview, third measurement (M3) ,second measurement by blinded paediatrician (MBP2)

The third measurement (M3) for both the intervention group and the control group is conducted at the end of the elimination diet (intervention group) or halfway through the waitinglist period (control group) at week 9. All questionnaires must be filled in once again and a second structured psychiatric interview is held. This third measurement point coincides with the second taking of blood samples from participants in the intervention group (see Chapter 6) and with the second measurement by the blinded paediatrician (MBP2). This MBP2 in week 9 is reserved for the children in the intervention group. The children from the control group will return to the hospital in week 13 (second blood test control group). We considered we would be demanding too much of the parents and children in the control group if they should have to travel four times instead of three times to Eindhoven, considering the fact that children are recruited from all the Netherlands.

So the MBP2 for the children in the control group will take place in week 13, combined with MBP3 and the third blood test for the children of the intervention group.

After M3 the children in the intervention group are split up in responders and nonresponders. Responders are children who show significant improvements in behaviour in response to the elimination diet. Improvements are significant if the scores on the Abbreviated Conners Scale and/or the ADHD Rating Scale (see under 5.4.) show a minimum difference of 40% before and after the dietary intervention. Children with improvements of 40% or more on one or more questionnaires, i.e. the responders, proceed to the reintroduction phase. The nonresponders, who show no or insufficient behavioural improvements after the elimination phase, are referred back to their treating physician for further research and/or medication. They may return to their normal eating pattern; for these children, the trial has come to an end. The responders proceed to the reintroduction phase (see under 5.3). Children from the control group will remain on the waiting list for another 4 weeks after the third measurement.

5.3. Phase 2, reintroduction phase, weeks 9-13

The reintroduction phase is based on the IgE and IgG-levels, determined in the first blood test. The focus is on whether or not foods having yielded an IgG-0 value during he first blood test and without increased IgE level, can be reintroduced to the child's diet without triggering any behavioural problems and, hence, whether IgG and IgE testing is useful in children with ADHD. This will be tested during weeks 9-13, all foods with IgG-0 value and without increased IgE-level, will be reintroduced concurrently to the diet of the responders.

After these 4 weeks, the controlled trial will be terminated in order to avoid families in the control group having to wait too long before they can start with the elimination diet. Too long a waiting list period poses the risk that parents may decide to withdraw during the course of the trial or not even start. Furthermore, the 4 week reintroduction of hypo-allergenic foods, i.e. according to the first blood test, will provide sufficient information to accept or reject the hypothesis that there is no relationship between low IgE / IgG levels and sensitivity to foods in children with ADHD.

5.3.1. Participants and reintroduction

5.3.1.a. Selection

After the elimination phase, the responders, i.e. those children who have shown significant improvements in behaviour in response to the elimination diet, will proceed to the reintroduction phase.

5.3.1.b. Number of participants

Earlier Dutch trial has shown that approximately 10% of the parents are unable to comply with the diet consistently during the elimination phase.(25,29) We expect that, out of the 50 families starting the elimination diet, 45 families will successfully complete the first phase. We assume that 60% of the 45 children concerned will respond to the diet,(see chapter 7) and we expect that nearly all families with a child that has responded to the diet will be motivated to proceed to the reintroduction phase. So approximately 27 children will presumably start with the reintroduction phase.

5.3.1.c. Reintroduction and measurements

All foods without increased IgG value during the first blood test, i.e. foods with an IgG-0 value, and without increased IgE-value, will be reintroduced concurrently. To start the reintroduction phase, the results of the IgG and IgE analysis of the first blood samples will have to be known to the researcher before the end of the elimination diet. All other laboratory results will be made known at the end of the trial. To prevent bias in interpreting the child's behaviour, all parents, of responders and nonresponders alike, will receive the results of the blood tests at the end of the trial. Measurements M4 and M5 will take place during the reintroduction phase, at week 11 and week 13. The questionnaires will be completed as described in chapter 5.4.

5.3.2. Control group

The children from the control group are still on the waiting list during this phase. The measurement points are equal to the measurement points of the intervention group and will take place in week 11 (M4) and week 13 (M5). (**table II**) The 5th measurement, in week 13, will be combined with the measurements by the blinded paediatrician (MBP2) and the second blood test. After M5 the INCA study ends. All children from the control group will be offered an opportunity to start the elimination diet.

5.3.3. Responders of elimination group

Immediately following the elimination phase, the responders will proceed to the reintroduction phase, during which all foods that did not yield any increased IgG value during the blood test, i.e. IgG-0 value, are added concurrently to the elimination diet, provided that there are no increased IgE-levels for these foods. The number and combination of foods reintroduced may differ for each individual child, depending on the results of the IgG and IgE analyses of the first blood samples. All the foods that will be reintroduced may be eaten in normal quantities during the reintroduction phase (weeks 9-13). At the end of weeks 11 and 13, the 4th and 5th measurements (M4, M5) will be conducted. M5 in week 13 will coincide with the 3rd blood sample (see chapter 6, **table III**) and with the 3rd measurement by the blinded paediatrician (MBP3). Using the questionnaires described under 5.4. we will examine whether the child's behaviour in response to the IgG-0 provocation (M5) is comparable to its behaviour at the end of the elimination phase (M3). In addition, the behaviour of these children is compared to that exhibited by children in the control group. Based on these comparisons, conclusions may be drawn as to the usefulness of IgG and IgE blood tests in children with ADHD who are sensitive to foods.

If the child's behaviour does not change, the conclusion seems warranted that none of the foods with an IgG-0 value an no increased IgE-value are affecting the child's behaviour.

If the child's behaviour changes during the reintroduction phase, which can be assessed during the 4th or 5th measurement or earlier (i.e. when the parents report such a change in behaviour that they wish to terminate the IgG-0 provocation immediately), the conclusion must be that foods with an IG-0 value may cause behavioural change and that there is probably no connection between IgG antibodies to specific foods and the impact of those foods on the child's behaviour. When parents want to stop prematurely with the reintroduction phase, the next measurement moment will not be awaited. Instead, the parents and the teacher will immediately complete the questionnaires and the provocation will be stopped. The third blood sample, scheduled for week 13, will be taken earlier, depending on when the decision is made to stop the provocation.

Table II Measurement points (M1-M5), blinded measurements (MBP1-MBP3) and blood tests (B1-B3) in intervention group and control group

Measurement Points Weeks 0-9: Elimination Phase Weeks 9-13: Reintroduction Phase	**Intervention group**	**Control group**
Week 0 1st Measurement (M1) 1th Blind Measurement (MBP1) Blood test (B1)	Start Trial M1, MBP1, B1 Start baseline period	Start trial M1, MBP1, B1 Start baseline period
Week 3 2nd Measurement (M2)	End baseline period M2 Start elimination diet	End baseline period M2 Start waiting period
Week 9 3rd Measurement (M3) 2nd Blind Measurement (MBP2) Blood test interv. group (B2)	End elimination diet M3, MBP2, B2 Nonresponders: end Trial Responders: Start Reintroduction Phase	Waiting period M3
Week 11 4th Measurement (M4)	Halfway IgG-0 provocation M4	Waiting period M4
Week 13 5th Measurement (M5) 2nd and 3rd Blind Measurements (MBP2, MBP3) Blood test control group (B2) Blood test interv. group (B3)	End IgG-0 provocation M5, MBP3, B3 End RCT	End of waiting period M5, MBP2, B2 End RCT Optional: start elimination diet

5.4. Dependent variables and measurement points

In the INCA study five questionnaires will be used to assess any behavioural or physical changes during the trial. The four questionnaires assessing behavioural changes are the Abbreviated Conners Scale (5.4.1.), the ADHD Rating Scale (5.4.2.), the Strengths and Difficulties Questionnaire (5.4.3.) and a Structured Psychiatric Interview based on DSM-IV criteria (5.4.4.). The Other Complaints Questionnaire will be used to assess any physical complaints (5.4.5.).

The Abbreviated Conners Scale (ACS) and the ADHD Rating Scale (ARS) are the two major rating scales for the outcomes of this study. They will be used during all measurement points, i.e. M1 (week 0), M2 (week 3), M3 (week 9), M4 (week 11) and M5 (week 13). The other questionnaires will be used three times, in order not to overburden the parents:

- The Strengths and Difficulties Questionnaire (SDQ) at M2, M3 and M5.
- The Physical Complaints Questionnaire (PCQ) at M2, M3, M5.
- The Structured Psychiatric Interview (SPI) at M1, M3, M5.

The measurement points of the researcher are in accordance with the measurement points of the blinded paediatrician. The measurement points by the blinded paediatrician are at M1, M3 and M5, using the ARS and the SPI.

5.4.1. Abbreviated Conners Scale

The ACS, also called the hyperkinesis index, is a commonly used questionnaire in studies into the relationship between nutrition and behaviour.(19) The ACS was also used in the three Dutch studies conducted prior to this INCA Study,(25,26,29) and consists of 10 questions using a 4-point scale. A score of 15 represents two standard deviations (SDs) above the mean cut-off.(17) Scores can range from 0 to 30. Three measurement points have been integrated into the elimination phase: M1 at the start of the trial (week 0), M2 after the baseline diet (week 3), and M3 in week 9, at the end of the elimination diet (intervention group) or halfway through the waiting period (control group).

The responders to the elimination diet will proceed to the reintroduction phase after the 3rd measurement. The 4th and 5th measurements are conducted during the reintroduction phase: M4 halfway through the IgG-0 provocation, i.e. the reintroduction of foods who did not produce any increased IgG and IgE-values in the first blood test (see under 5.3.); M5 at the end of the IgG-0 provocation, that is, in week 13 (see under 5.4.2.). M4 (week 11) and M 5 (week 13) will also be

conducted in the children of the control group. The ACS is completed by the parents and the child's teacher at M1, M2, M3, M4 and M5.

5.4.2. ADHD Rating Scale

The second questionnaire is the ADHD Rating Scale (ARS).(57) This questionnaire, based on the DSM-IV, is often used in ADHD diagnostics.(45) The questionnaire consists of 9 inattention items and 9 hyperactivity/impulsivity items, and uses a 4-point scale. The answers to each question vary from Never or Rarely (0 points), Sometimes (1 point), Often (2 points) to Very Often (3 points). For inattention, the mean cut-off score plus 1.5 SDs, based upon normative data, is 13.6 for boys younger than 7 (girls, 11.2); for hyperactivity / impulsivity, that score is 14.9 (girls, 11.8); the total score for boys is 27.5 (girls, 21.8).(57) This questionnaire has also been used in two of the earlier Dutch studies.(26,29) The measurement points coincide with those of the ACS.

The ARS is completed by both the parents and the teacher at M1, M2, M3, M4 and M5. This questionnaire will also be used at all measurement points by the blinded paediatrician: MBP1 in week 0, MBP2 in week 9 (intervention group) and week 13 (control group) and MBP3 in week 13 (intervention group).

5.4.3. Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) is a standardised questionnaire on behaviour that is easy to complete by parents and teachers and is suitable to use for children aged 4 to 16.(58) The questionnaire is often used in research on behavioural problems in children.(45) Dutch research supports the use of the SDQ as an index for psycho-pathological problems among children.(59) Parents and the child's teacher must fill in the SDQ at M2, M3 and M5.

5.4.4. Structured Psychiatric Interview

Professor Jan Buitelaar, professor of child psychiatry at Radboud University in Nijmegen has prepared a Structured Psychiatric Interview (SPI) based on DSM-IV criteria. The SPI will be used to assess comorbid disorders like ODD and CD. This interview is taken on three occasions, at M1, M3 and M5 and will be completed by both the parents and the teacher.

This questionnaire will also be used at all measurement points by the blinded paediatrician: MBP1 in week 0, MBP2 in week 9 (intervention group) and week 13 (control group) and MBP3 in week 13 (intervention group).

5.4.5. Other Complaints Questionnaire

The purpose of the fourth questionnaire, the Physical Complaints Questionnaire (PCQ), is to identify other complaints the child may have. Questions concern the presence or absence of physical complaints such as gastrointestinal problems, headaches, eczema, unusual perspiration, sleep disturbances and asthma. Making a list of the child's physical complaints serves a purpose: Many of the subjects included in earlier studies appeared to have additional, physical complaints.(10,15) According to Barkley, medication may be less effective in children with ADHD who also suffer from physical ailments.(27) The PCQ was also used in the earlier Dutch studies.(25,26,29) The questionnaire is filled in as often and at the same time as the SDQ. Only the parents are required to fill in the PCQ.(60)

5.5. Follow-up after the end of the trial

After the end of the trial all children assigned to the control group will be offered an opportunity to start the elimination diet. The responders, like the responders of the intervention group, will also start with the reintroduction phase. All responders, from control group and diet group, will be offered after the end of the trial a monitoring period of 8 months, during which the food provocations will be continued, without any costs.

5.6. Involvement of dietician

The elimination diet contains all necessary nutrients, according to the Dutch Guidelines for Healthy Foods.(61) As no milk products are allowed, rice milk with extra calcium is added to the diet. If it occurs that a child does not want to eat some of the foods that are allowed, the diet will be adjusted. If the child refuses to eat any fruit or vegetables, a dietician will be called in to monitor the child's diet and check for any deficits and, where applicable, to provide the necessary supplements.

5.7. Reporting

All parties concerned will be informed about the results of the study. Parents will receive separate reports on the elimination phase and the reintroduction phase, in which they will also be advised about the relevance of a diet for their child. Parents will also receive a report on the group results. The results of the laboratory

tests will be made known to the parents after the trial has ended. Interim progress reports to the sponsors and the Medical Ethical Review Board will be issued every six months and at the end of the study.

6. Laboratory tests

From each child there will be taken at least two blood samples during the trial (see **table III**). Only responders to the elimination diet will be asked to provide blood samples thrice: in week 0 (start of the trial), week 9 (after the elimination phase) and week 13 (after the reintroduction phase). In week 0, blood samples will be taken from all 100 children, that is, from both the intervention group and the control group. In week 9, blood will be taken only from the children in the intervention group, that is, from 50 children. In week 13, finally, blood samples will be taken from the children in the control group (50 children) and from the responders to the elimination diet (x children).

Table III Blood sampling in intervention and control groups

	1st blood test, B1	2nd blood test, B2	3rd blood test, B3
week 0	All children, of Intervention Group and Control Group		
week 9		All children of Intervention Group	
week 13		All children of Control Group	Responders of Intervention Group

The first analysis is a baseline analysis of the IgE and IgG values in the children's blood whilst they follow their normal eating pattern. The second analysis will be made at the end of the elimination phase (intervention group, week 9) or, as the case may be, the end of the waiting period (control group, week 13). The purpose of this analysis is to determine possible fluctuations in the IgE and IgG values. The results of the intervention group are compared to those of the control group.

A comparison of measurements is also made for each individual child and, after the elimination diet in week 9, between the blood values of nonresponders and responders.

After week 9, the responders proceed to the reintroduction phase and undergo 4 weeks of IgG-0 provocation. A third blood test is then conducted in order to determine possible changes in the IgE and/or the IgG levels to specific foods caused by the change in diet. Since the mean half-life of IgG is 3 weeks, the third blood analysis in week 13 (after 9 weeks of diet, i.e. 5-week elimination phase plus 4-week reintroduction phase) should be sufficient to measure changes. The results of the blood tests in week 13 are compared to the results of the first measurements, and the blood values of the responders are compared to the participants in the control group.

The amount of blood required to conduct the blood analysis is 12 ml per test (less than 1 % of the total blood volume). The blood tests are carried out by the Cell Biology and Immunology Group of Wageningen University and Research Centre (IgE and other measurements) and by the Pro Health laboratory in Weert (IgG). The results of each blood test, properly coded, are sent to the researcher.

6.1. IgE blood tests

Immunoglobulin E (IgE) is an antibody that can be found in case of an allergic reaction. Preliminary studies have suggested the possibility of an allergic mechanism concerning ADHD, finding a surprisingly high proportion of children with ADHD having associated symptoms such as allergic disorders.(15) When the serum IgE level is elevated, indicating that there might be IgE-mediated hypersensitivity reactions, the specific IgE antibody levels to food products and other allergens, such as mites, pets, and pollen will be measured in the blood of the child concerned.

6.2. IgG blood tests

The presence of IgG antibodies to 266 different foods will be tested using a traditional Enzyme-Linked ImmunoSorbent Assay (ELISA, see Appendix 2). (43,62) For each individual product, the level of IgG antibodies will be determined in the blood, following which a value of IgG-0, 1, 2, 3, or 4 will be assigned to the product based on the quantities of μg IgG / ml serum measured. All foods with IgG-0-value will be reintroced during the reintroduction phase, provided that there are no elevated IgE levels measeured for these foods.

6.3. Other blood tests

As there are associations reported between minerals, trace elements, carnitine, fatty acids and other dietary components and behavioural changes, these constituents are also included in the blood tests.(63-77) The children's blood will be kept during the trial period in order to be able to trace inflammatory mediators (cytokines) and/or other antibodies, such as anti-tissue transglutaminase IgA (anti-tTG IgA). In the Netherlands, physicians increasingly diagnose a genetic predisposition to hypersensitivity to gluten (a protein found in wheat, barley, and rye).(78) Zelnik has indicated that patients suffering from coeliac disease tend to develop neurological disorders, such as ADHD, more often (51.4%) than the subjects placed in a control group (19.9%) and recommends that further research be done into the impact of gluten-free diets on these neurological disorders.(79) Since wheat can be a trigger of ADHD,(10) it is important in the context of this study to find out whether the subjects show a response to gluten. A serological test on transglutaminase IgA would be a usable tool to screen children for gluten hypersensitivity.(80)

6.4. Coding and storage of bodily materials during the trial

Each time a blood test has to be done, the child will be assigned a code number by the researcher, in sequential order, which means that the codes will range from INCA-01 to INCA-227, i.e. 100 children having their first blood test plus 100 children having their second blood test plus approximately 27 children having their third blood test. These codes are forwarded to the blinded paediatrician who will examine the children and who will state the code on the blood analysis request form. The only persons with access to the code key are the project leader, the researcher, and the independent supervisor (see under 8.7.).

The Wageningen University will store the blood at minus 80 °C. After the trial is completed, all bodily materials will be collected in special hospital containers and destroyed according to standard medical waste removal procedures.

7. Statistical considerations and data analysis

Dr. K. Frankena, senior researcher at the Wageningen University, will participate in the trial as epidemiologist/statistician.

7.1. Statistical considerations

The samples size for this study is estimated to be 100 children (50 children in each group) calculated using the package Stata version 9,(81) and based on the following assumptions:

1. In a recent small-scaled Dutch randomised controlled study (29) 73% of the children in the diet group (n=15) showed behavioural improvements of 40% or more. The control group showed an overall behavioural improvement of 8%, none of the children of the control group (n=12) showed an improvement of 40% or more. As we do not want to be overly optimistic about these figures, we assume that improvement (of at least 40%) in behaviour occurs in 60% of the children that follow the diet and in at maximally 20% of the children in the control group
2. Power of 80%,
3. Two-sided α of 5 %.

The needed sample size is then 28 children per group. Due to a potential block effect (loss of 7 degrees of freedom) and potential drop outs (10%) the sample size needs to be increased further and we need approximately 40 children per group. To prevent loss of power due to a potential higher percentage of drop-outs, 10 children per group are included above the originally calculated sample size of 40 (+25%).

The parents of the participating children fill in an informed consent. This consent is compulsory for participation. We assume that each participant is thus motivated and therefore a drop-out level of 10% is assumed, comparable to the drop-out level of 10% in the previous Dutch controlled study (29). Children will be randomly assigned to one of both groups, 50 to the intervention group and 50 to the control group (see 4.2.2.).

7.2. Data analysis

All statistical analyses will be carried out with SPSS Windows-version 9.0 and are based on 'intention to treat', using two methods: last-observation-carried-forward (LOCF) and group mean imputation (GMI).(56). The statistical unit of analysis is

the individual child. A p-value less than 0.05 will be deemed significant. All analyses concern the ratings of the parents as well as the ratings of the teachers. Ratings of the blinded paediatrician will be compared to those of the researchers using the kappa statistic which indicates an agreement beyond chance of 2 raters.(81) Because a gold standard is not available it is only possible to assess the agreement between raters without assuming beforehand that one is the best. The logic of using kappa is that agreement beyond chance between raters is evidence of validity, whereas disagreement suggests that the ratings are untrustworthy. In general, if *kappa* = 0 (or smaller), then there is no agreement at all beyond chance. *Kappa* values greater than 0.75 may be taken to represent excellent agreement beyond chance. Values of *kappa* below 0.40 may be taken to represent poor agreement beyond chance and values between 0.40 and 0.75 may be taken to represent a fair to good level of agreement.(81) The kappa for interrater agreement between the researchers and the paediatrician will be computed in every analysis. In cases where the ratings of the blinded paediatrician disagree with the ratings of the researchers (kappa $<$ 0.40), the ratings of the blinded paediatrician will be used for further analyses.

Prior to the start of this study the researchers and the paediatrician will independently assess 3 to 5 cases, to reduce the chance of serious rater disagreement. After the assessments of each case, the results will be discussed together.

7.2.1. Analysis of ACS, ARS, SDQ and SPI scores (behaviour measurements)

Scores indicating behaviour will be analysed using linear regression, a Normal distribution of scores will be initially assumed; fit of the models will be evaluated using normal plots and the Wilk-Shapiro statistic.(see 82 and 83 as standard works)

7.2.1.A. The first analysis of these scores will be restricted to the data collected during the elimination phase and will cover the first 8 months of the trial. Differences in behaviour measurements at M3 between intervention and control group will be analysed according to the regression model:

$M3_{ijk} = \mu + C_i + B_j + M2_{ijk} + e_{ijk}$ (1)

Where:

$M3_{ijk}$ = ACS, ARS, SDQ or SPI score of individual k (k = 1 to 50) of group i (i = 1, 2) and block j (j = 1 tot 10) at week 9

μ = intercept

C_i = effect of treatment i (1=intervention, 2=control)

B_j = effect of block j (j = 1 to 10)

$M2_{ijk}$ = ACS, ARS or SDQ score of child k of group i and block j at week 3 (M2) or SPI score at week 0 (M1)

e_{ijk} = residual

The null hypothesis is that there is no effect of treatment on the respective scores. Interaction between block and treatment will be evaluated as well.

7.2.1.B. The second analysis of the behavioural scores is restricted to the responders of the intervention group only and includes data that cover the IgG-0-provocation period. The total number of children included in this analysis is unknown as the number of responders is unknown but it is estimated to be 60%. With a potential drop-out percentage of 10, it is expected that this group consists of at least 27 individuals.

Differences in behaviour measures between M5 and M2 (ACS scores, ARS scores and SDQ scores), between M5 and M1 (SPI scores), and between M5 and M3 (ACS scores, ARS scores, SDQ scores and SPI scores) of the responders of the intervention group will be analysed using the model:

$M5_{ij} = \mu + B_i + Mx_{ij} + e_{ij}$ (2a)

Where:

$M5_{ij}$ = ACS, ARS, SDQ or SPI-score of individual j (j = 1 to n) of block i at week 13 (M5)

μ = intercept

B_i = effect of block i (i = 1 to 10)

Mx_{ij} = ACS, ARS, SDQ or SPI-score of child j of block i at M1, M2 or M3

e_{ij} = residual

The null hypothesis is that there is no effect of treatment on the behaviour scores. Ideally, a group of responders of the intervention group that were not supplemented with IgG neutral food elements should be included in the analysis as reference group. However, we deemed this unethical as these children should take the strict diet for another 4 weeks. Instead, an additional analysis (model 2b, analogous to model (1)), including data of the control group will be carried out.

7.2.2. Analysis of IgG scores

Initially logistic regression for polytomous outcomes (IgG score has 4 classes) will be used; fit of the model will be evaluated using Hosmer-Lemeshow statistic. (84)

7.2.2.A. Model (3) will be used to analyse the effect of treatment on the IgG scores.

$IG2_{ijk} = \mu + C_i + B_j + IG1_{ijk} + e_{ijk}$ (3)

Where:

$IG2_{ijk}$ = IgG-score of individual k (k = 1 to 50) of group i (i = 1, 2) and block j (j = 1 to 10) at week 9 (intervention group) or week 13 (control group)

μ = intercept

C_i = effect of treatment i (1=intervention, 2=control)

B_j = effect of block j (j = 1 to 10)

$IG1_{ijk}$ = IgG-score of individual k of group i and block j at week 0

e_{ijk} = residual

The null hypothesis is that there is no effect of treatment on the IgG score.

Interaction between block and treatment will be evaluated as well.

7.2.2.B. IgG-measurements of responders and nonresponders within the intervention group will be evaluated according to model (4):

$IG2_{ijk} = \mu + R_i + B_j + IG1_{ijk} + e_{ijk}$ (4)

Where:

$IG2_{ijk}$ = IgG score of individual k (k = 1 to 50) of responder class i (i = 1,2) and block j (j = 1 to 10) at week 9

μ = intercept

R_i = effect of responder class i (1 = responder, 2 = nonresponder)

B_j = effect of block j (j = 1 to 10)

$IG1_{ijk}$ = IgG score of child k of responder class i and block j at week 0

e_{ijk} = residual

The null hypothesis is that there is no effect of responder (yes/no) on the IgG score.

Interaction between block and responder group will be evaluated as well.

7.2.2.C. Model (5) will be used to analyse the difference in IgG-scores between samples taken at week 13 and week 9 within the intervention group.

$IG3_{ij} = \mu + B_i + IG2i_j + e_{ij}$ (5)

Where:

$IG3_j$ = IgG-score of individual k (k = 1 to 50) from block j (j=1 to 10) at week 13

μ = intercept

B_i = effect of block i (i = 1 to 10)

$IG2_j$ = IgG-score of individual j at week at week 9

e_{ij} = residual

The null hypothesis is that μ equals zero, i.e there is no difference in IgG scores of samples taken at week 13 and 9.

7.2.3. Additional analyses

The association between responder (yes/no) and atopic background (yes/no) will be evaluated using Fisher's exact test. The null hypothesis is that there is no association between both characteristics. The association between responder (yes/no) and reduction of physical complaints (PCQ) (yes/no) will be evaluated using logistic regression and/or Fisher's exact test. The null hypothesis is that there is no association between both characteristics.

Similar to IgG-scores, IgE-scores of responders and nonresponders, and other blood values will be analysed.

8. Ethical considerations

8.1. General

The INCA Study will be conducted in full compliance with the ethical principles laid down by the WMA in the Declaration of Helsinki (as amended in October 2000) as well as the rules of Dutch legislation.

8.2. Ethical review

The INCA Study will not be conducted until the Dutch Medical Ethical Review Board [(Medisch Ethische Toetsing Commissie (METC)] of Wageningen University has fully approved this protocol, which has already been submitted to the METC for review.

8.3. Informed consent

It is the responsibility of the clinical researcher to obtain signed, legally valid consent forms from all participants. The information to be provided to obtain these consent forms must clearly specify the purpose and nature of the research and must also describe how the parents and the children are supposed to cooperate and what the pros and cons are of participating. The researcher will have to point out in very clear terms that the participants may withdraw from the study at any time without this having any consequences for them. If and when possible, the consent forms should be signed by both parents. The forms will be kept with the children's files.

8.4. Participation fee

Parents are not required to make any financial contribution in exchange for participating. We will not pay a financial fee for participation either, but the children will be given a little present every time their blood is taken. Parents and children will be motivated to complete the trial by offering them the following tokens of attention:

- All children receive birthday cards;
- All families receive season's greetings cards;
- All children will be sent a certificate during the course of the trial.

8.5. Involvement of family doctors and treating physicians

If parents consent to their child participating in the trial, the family doctor and treating physician (if any) will be informed of the child's participation. They will also be sent an information sheet on the INCA Study. If the doctor involved with the child's medical care has concerns about the impact of participation on the child and his or her family, this will be discussed with both the parents and the doctor. If the parents still want to enter the study, they may feel free to do so.

8.6. Burden on the child

The main burden on the child is that it will have to follow a different eating pattern for a period of 5 weeks. The children who participated in the earlier studies had no real problems in practice with their diet. The social environment, grandparents, for instance, had more problems in dealing with the new situation than the children themselves. After the first 5 weeks, the nonresponders to the elimination diet may

resume their former eating habits, whilst the diet for the responders is extended significantly, which even further reduces the burden for the participants. Blood will be taken two or three times. This may be stressful for a number of children. However, all children will be allowed to pick a present after their blood has been taken. There are no additional risks involved in the trial.

8.7. Independent medical supervisor

Dr. Rodrigues Pereira, a paediatrician at the Rijnmond-Zuid Medical Centre in Rotterdam and chairman of the ADHD Paediatric Network, will act as independent medical supervisor for this study. He will monitor compliance with all regulations. Parents may contact him at any time if they have any questions. See also the information sheet that has been prepared for the parents.

9. Administrative affairs

9.1. Contacts

- The contact person for all questions regarding this Research Protocol is the researcher, Lidy Pelsser of the ADHD Research Centre (telephone number +31 (0) 40 2488393).
- The contact person for all questions regarding the IgG-laboratory test is Theodoor Scheepers of the Pro Health Laboratory in Weert (telephone number +31 (0) 495545000).
- Prof. Dr. Huub Savelkoul, professor of Immunology at Wageningen University (telephone number +31 (0) 317 483925), is the project leader and can be contacted for all other matters.

9.2. Insurance

The Wageningen University and Research Centre has a valid insurance contract providing cover against all loss and damage, injury or death caused by participation in the INCA Study. This insurance is in full compliance with the Dutch Act regarding Medical and Scientific Research on Human Beings.

9.3. Use of information, publication

All new data acquired and all outcomes of the study will be published in scientific

journals. The INCA Study also forms part of PhD research into the impact of nutrition on behaviour.

9.4 Documentation

Before starting the trial, the researcher will have obtained the following documents:

- Letter of approval from the METC
- Sufficient sponsoring commitments to finance the trial
- ISRCTN Registration

9.5. Reporting

During the course of the trial, the (anonymised) data collected will be analysed at the end of each phase, and analysis reports will be sent to the supervisory committee, the sponsors, and the METC. No personal data of the participants will be used, neither in the scientific publications nor in the reports or the thesis. All personal data is treated as strictly confidential.

9.6. Duration of the trial

9.6.1. Period of recruitment and selection

Participants will be recruited through doctors, hospitals, child psychiatrists and the media. It will take approximately 3 months for the first children to start with the trial. In the mean time the recruitment efforts will be continued until there are 100 eligible participants.

9.6.2. The first phase, the elimination phase

It is logistically not feasible to have all children start at the same time. Approximately ten children will start with the trial each month. Children will not be able to enter the trial during the summer holiday, as this would impede the teachers' measurements. All in all this phase will take about 14 months.

9.6.3. The second phase, the reintroduction phase

All responders to the elimination diet will proceed to the reintroduction phase after having completed the first phase of the trial. Expectations are that at least 27 children from the intervention group will proceed to this phase. The reintroduction phase will take 4 weeks and will be executed directly following the first phase of the trial.

9.6.4. Data processing

The processing of data, preparation of reports, and writing of publications for journals will take approximately 3 months.

9.6.5. Total duration

The anticipated overall duration of the study is approximately 1¾ years.

10. Supervision

The supervisory committee is made up of the following persons, all from the Netherlands:

Prof. Dr. Jan Buitelaar, professor of child psychiatry
Radboud University, Nijmegen
Reinier Postlaan 10, P.O. Box 9101
6500 HB Nijmegen
Telephone: +31 (0) 24 3613490
E-mail: j.buitelaar@psy.umcn.nl

Prof. Dr. Huub Savelkoul, professor of cell biology and immunology
Wageningen University & Research Centre, Wageningen

Marjan de Boer, representing Dutch Food Allergy Foundation

Ton Haagen, paediatrician, neurologist
Medical Centre VieCuri, Venlo

Prof Dr Ewoud Dubois
University Medical Centre Groningen,
Beatrix Child Clinic, Child Allergology, Groningen,

Rob Rodrigues Pereira, paediatrician
Maasstad Hospital, Rotterdam

Jan Toorman, paediatrician
Catharina Hospital, Eindhoven

11. Current Controlled Trial register

This INCA Study, which is conducted independently, will be registered and recorded in the International Standard Randomized Controlled Trial register.

12. Field contacts, implementation

The outcomes of this study may lead to new insights into the use of dietary intervention and of blood tests in children with ADHD. Moreover, the study can verify results from earlier Dutch studies which showed that food could be a cause of ADHD in 60% of the participating children.(25,26,29) If behavioural disorders are triggered by food, they can be prevented or be countered with an adequate diet, so that the children concerned need not be subjected to medical and social care procedures, and further costs can be saved. Given the fact that blood tests, whether or not combined with an elimination diet, can be conducted quickly and efficiently, a blood analysis might become a standard differential diagnostic tool in any examination of children with behavioural problems if the results of the immunological research as part of this study are promising. The results of the INCA study may provide additional leads for the diagnostic and therapeutic procedures concerning ADHD.

Post-study action (4 steps):

1. Protocol: Based on the results and the methodology of this study, a protocol will be developed enabling blood tests and dietary interventions to be applied in general practice, subject, of course, depending on the outcomes of the study, to specific conditions and only where specific patients are concerned.
2. Guidelines: Based on the results, guidelines will be formulated, describing which children with ADHD may benefit in particular from dietary intervention and blood tests, e.g. children who may suffer from a combination of physical complaints and behavioural responses to food.
3. Education: Universities and institutions for higher education will be contacted in order to have new insights integrated into the teaching materials of doctors, psychologists, educators, teachers, and dieticians.
4. Publications: an article describing the outcomes of the study will be submitted for publication.

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Appendix 1

Time Schedule: Weeks 0 to 13

	Week 0 Elimination phase starts	Week 1 Elimination phase	Week 2 Elimination phase	Week 3 Elimination phase	Week 4 Elimination phase
Intervention group	M1 B1 MBP1	baseline diet	baseline diet	M2	transitional week
Control group	M1 B1 MBP1	baseline diet	baseline diet	M2	waiting list

	Week 5 Elimination phase	Week 6 Elimination phase	Week 7 Elimination phase	Week 8 Elimination phase	Week 9 Elimination phase ends, Reintroduction phase for responders starts
Intervention group	elimination diet	elimination diet	elimination diet	elimination diet	elimination diet, M3 B2 MBP2
Control group	waiting list	waiting list	waiting list	waiting list	waiting list, M3

	Week 10 Reintroduction phase starts	Week 11 Reintroduction phase	Week 12 Reintroduction phase	Week 13 Reintroduction phase
Responders of intervention group	IgG-0 provocation	IgG-0 provocation M4	IgG-0 provocation	IgG-0 provocation M5 B3 MBP3
Control group	waiting list	waiting list M4	waiting list	waiting list M5 B2 MBP2 start of elimination diet (optional)

M1 = first measurement
B1 =first blood test
MBP1=first measurement by a blinded paediatrician

Appendix 2

Details of IgG Measurements

The presence of IgG antibodies to 266 different foods will be tested using ELISA, a traditional Enzyme-Linked ImmunoSorbent Assay (ImuPro test). This testing system was CE certified in 2004._

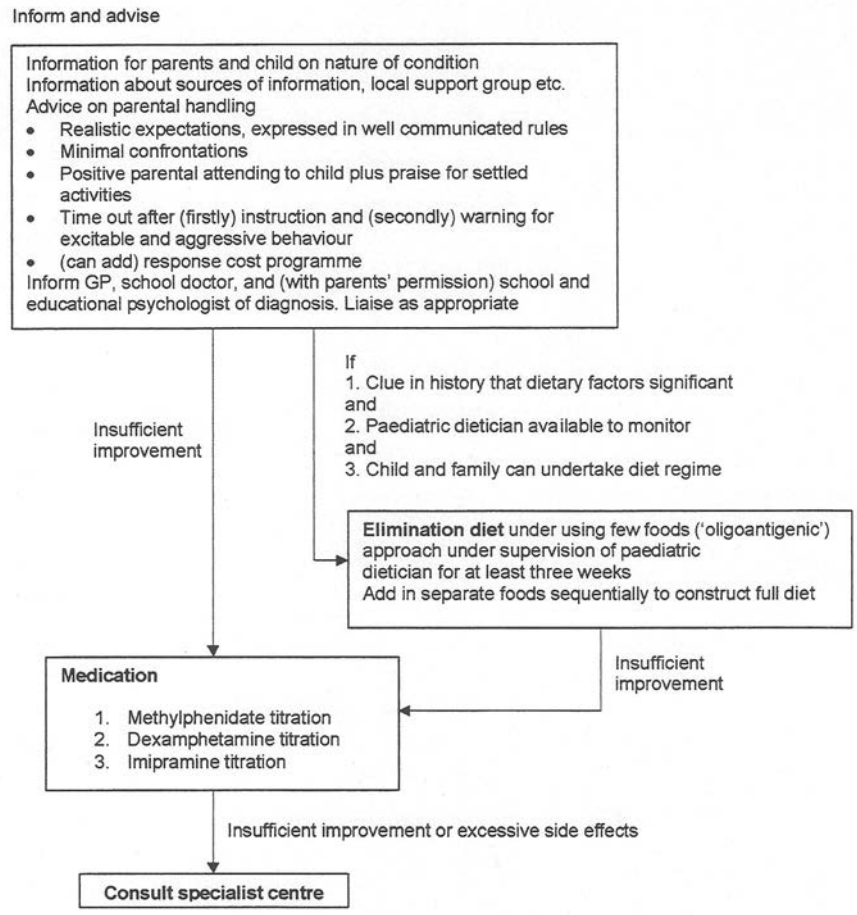
ELISA operates as follows: Extracts from foods are fixed to a microtiter plate. Antibodies in the serum bind to available antigens. This binding is made visible in colour by adding an antibody-enzyme complex and a suitable reagent. The intensity of the colouring is straight-line proportionate to the concentration of antibodies and can be read using an ELISA reader. The exact concentrations of IgG antibodies can be determined with the aid of a standard curve, that is a curve of standards calibrated against a WHO standard.

Standard 1 contains 2.5 μg IgG / ml of standard fluid.
Standard 2 contains 10.0 μg IgG / ml of standard fluid.
Standard 3 contains 40.0 μg IgG / ml of standard fluid.
Standard 4 contains 200.0 μg IgG / ml of standard fluid.

To eliminate irregular antibodies, each microtiter plate is fitted with an internal control system. In addition, internal positive and negative checks are performed on each microtiter plate.
Based on the measured quantities of μg IgG / ml serum, each analysed food can be assigned an IgG value ranging from 0 to 4. The hypothesis is that IgG-0 represents no response to the food, IgG-1 corresponds to a minor response, etc. The higher the value the greater the response to the food in question. Level 4 should, therefore, correspond to a significant response to the product.

Appendix 3

Basic algorithm for treatment of ADHD



Source: **P Hill[a], E Taylor[b]** (2001). An auditable protocol for treating attention deficit/hyperactivity disorder. In *Archives of Disease in Childhood*, **84,** 404-409 (May).

[a] Great Ormond Street Hospital for Children, London WC1N 3JH, UK
[b] Institute of Psychiatry, London SE5 8AF, UK

Amendments Protocol INCA study, 10 July 2008

Reference: THELANCET 06PRT7719

1. In the protocol the children assigned to the control group are placed on a waiting list during week 4-13 (see INCA protocol page 15), whilst the intervention group will follow the elimination diet. The intervention group has to keep an extended diary during this period, and has to follow an elimination diet, i.e. they will be focussed on food. The waiting list group will just be waiting.

The first change in the protocol is that we would like to increase the resemblance between the control group and the intervention group. Therefore we suggest that the control group, like the intervention group, has to keep an extended diary as well. We also suggest to provide the control group with broad recommendations for a healthy diet, conform the guidelines of the Netherlands Nutrition Centre, so that the control group will be occupied by their food as well.

2. During weeks 9-13 the responders of the intervention group will start with the reintroduction phase (see INCA protocol page 17). All foods with IgG-0 value and without increased IgE will be reintroduced concurrently to their diet. This is an open introduction, of only IgG-0-foods.

We would like to change this open introduction phase in a double-blind cross-over design of not only IgG-0- foods, but of IgG-4-foods as well. Children will be independently and randomly allocated to the IgG-0-group or the IgG-4-group. Raters and parents will be blinded to this design. For the record, both reintroductions will only concern foods without increased IgE.

Parents' and children's accounts: RED research in real life

How a boisterous, bothersome boy calmed down and got friends

Teun had always been a lively boy. He couldn't sit still for a moment, was constantly chattering and seemed to be unlucky all the time: he often had bruises and scrapes. His teacher at nursery school once sighed: "I would not mind if Teun became a little less enthusiastic." When he grew older he became increasingly boisterous and impulsive, he talked a lot and very loudly, and he constantly touched and bothered other people. In the end children didn't want to play with him anymore and Teun was no longer invited to birthday parties. It was very sad. On top of that, his school results suffered from his behaviour. When Teun was six years old, his teacher suggested to have him tested for ADHD. Considering the nine month waiting list for an ADHD examination we decided to apply for the INCA study.

During the first weeks of the RED we already noticed a change at home. Teun behaved more calmly, was less impulsive, talked less and stopped touching or bothering others all the time. Results at school were positive as well: Teun managed to finish his work, wasn't constantly talking out of turn and was able to sit next to other children without bothering them. Given the positive results, Teun was eligible to enter the RED challenge period, during which foods were added to the diet. This period, lasting at least one year, was very tough but we couldn't have made a better decision for Teun. Halfway, my husband and I almost wanted to give up, exhausted from Teun's mood swings during the challenge period. But our son insisted on continuing the research, he did not want to loose his friends again. The RED research ended some time ago. We now know which foods are causal of ADHD, and we make sure he doesn't eat them. Right now he is almost nine years old and he is a great child – he still is a lively boy, but without ADHD.

Peace and quiet through medication: a blessing for school

In primary school we were already told that Monica showed worrisome behaviour. She constantly claimed the teacher's attention, couldn't sit still during group discussions and exhibited bossy behaviour towards other children; she even hit or threatened them sometimes. Those were the moments she had 'tickles in her body', as Monica explained her behaviour. She also complained about headaches

several times a week. In second grade rewards for good behaviour were introduced, and we all wondered whether Monica might need more challenging school tasks. In third grade at first her behaviour improved, but than got worse again by autumn holiday. A psychologist diagnosed Monica with ADHD, combined with an above average intelligence. Medication was advised and after consulting a paediatrician Monica started to take ritalin. Results were good, she was able to focus on her school tasks, and she behaved more calmly towards other children. It was a blessing for school!

We also had an appointment at ADHD Research Centre as well, as we weren't too eager to have Monica taking medication. We started the RED and took her off medication. Five weeks later, at the end of the RED, the headaches had diminished but her behaviour had not improved: she was not able to focus on her schoolwork, she had a lot of angry moods and she behaved badly towards other children.

Considering that Monica's behaviour did not react to food, we were advised to start medication again. Fortunately, she reacts well to that. We would like to have her participate in a special training course to improve her social skills and to support the effect of medication. Although the diet did not change her behaviour, we're happy she participated in RED research, as we wanted to know whether our child might be able to do without medication. We also know now that Monica has great perseverance; she stuck to the diet even on her own birthday and on two other children's parties! And she likes to eat mango now (but no rice crackers anymore…).

How a troublesome toddler turned into a cooperative adolescent

Bram's start of life wasn't easy. He was a whiny baby and seemed to have bellyaches all the time. His defecation was always too thin and definitely too often, the diapers could not be bought fast enough. Doctors called it toddler diarrhoea and tried to treat it, but whatever they did, the problems did not disappear. When he grew older he often complained of stomach-aches, he also drank a lot – he was always thirsty – and every night he was dripping with sweat. Apart from these physical complaints he couldn't sit still, not even a minute, and not only was he very active, he also developed tics, like squeezing his eyes, coughing, and pulling strange faces. He just couldn't stop doing it. He was compulsive as well: if it happened that he was not the first to go downstairs, he started screaming and shouting until everyone was upstairs again, letting him go first. At school he could

be aggressive, beating other kids for no reason, pinching them or pushing them off their chairs. In fact, he had been a 'troublesome child' ever since playgroup. Several examinations of intestines and blood did not reveal a cause of the physical problems, although he had been suffering from diarrhoea for more than four years. And his defiant behaviour, well, that might be resolved by parent training and maybe some medication, according to the physician.

I did not intend to settle for the doctors answer. Our other children were doing just fine, so I considered it unlikely that our parenting capacities were causal of Bram's behaviour. But something had to be done, because not only our son, but also the siblings and everyone around suffered from his behaviour. Considering that he never had had normal defecation, I thought that food might be the cause of that problem. I contacted the food allergy foundation and happened to find information about the RED research on their site. We decided to give it a try. We started the RED when Bram was four years old and within three weeks we knew he strongly responded to food. His unmanageable, oppositional and aggressive behaviour disappeared, at home as well as at school. The teacher thought it was a miracle. Moreover, for the first time in his life he had normal defecation and his tics diminished, incredibly! His compulsory behaviour disappeared as well, he didn't feel the need to go downstairs first anymore. After four years of struggling and all kinds of examinations this *fantastic* result was achieved in no more than three weeks!

The following months were difficult. It's not easy for a child to continue a diet but with help of teachers, other parents and friends, Bram completed the RED challenge period with positive results. We found the foods he reacted to; products we were used to eat daily before we started the RED. Of course we stopped to eat these foods. Bram is 15 years old now, a son I'm proud of. He's a very social, cooperative and humorous adolescent with a lot of friends. He is doing quiet well at school and he wants to go to college. He is allowed to eat almost anything, but he still had better not eat some foods. Sometimes he eats them anyway, for example when he's with friends and can't resist the temptation. Than we all notice the effects. He becomes restless, the tics and compulsive behaviour return, he starts wiggling and coughing, and the intestinal problems return as well. Fortunately, we now know the cause of these problems, and they will disappear again, at least, if he sticks to his diet.

Friends and fun

Jeroen, a 7 year old boy suffering from ADHD started RED-research in 2007. He sent this letter at the end of the challenge period, resulting in the diet prescription to better not eat strawberries, liquorice or tomatoes.

"Hi Mrs Pelsser!
I am glad that you help us with my diet, and that you advise my mother about what I may and may not eat, and that you are working so hard for all this. I am very happy that I feel better now, and that I am calm. I really have much more fun at school, because now I have more friends. I found it hard if someone was eating treacle waffles at a party, but other than that the diet was not so bad. And I really think I am nicer now.
Thank you that you invented this diet for me.
With many regards Jeroen"

In 2011 Jeroen is 11 years old and he wrote another letter.
"I am still very happy and I am very calm now. I don't mind to stick to the diet. I have got many friends, at school and in the neighbourhood. I also do ice hockey and I have to listen very carefully to the instructions of the coach. I am very good at it, and it is no problem to listen and to keep quiet.
I am very happy that we did the RED. Everything is much more fun. I never want to have ADHD again.
Jeroen"

Rebellious behaviour disappeared like snow in summer

Sigrid was a cheerful although very lively toddler, but she got more rebellious as she aged; she became angry a lot, opposed rules, wouldn't listen and had a hard time dealing with changes or disappointments. She also had sleep problems and did not fall asleep until late in the evening, lying awake for hours. At home we were able to deal with her behaviour, although it was very demanding and aggravating. But at school Sigrid did not come up to the mark, she could not concentrate at all. Finally, a child psychiatrist diagnosed her with ADHD and medication was prescribed.

As Sigrid started to take medication, she changed. She looked washed-out and displayed robotic behaviour, unnatural to her real character. She seemed depressed and even said she wanted to die, even though she was only seven years old. In a newspaper we read about the RED research. It seemed like a good

idea to participate. Wouldn't it be great to prevent all the trouble by just not eating some foods? Maybe our daughter would no longer need medication.

After the first four weeks of diet we didn't know what was happening to us. Sigrid became balanced and was able to deal with everyday events, without getting upset or defiant. All the above-mentioned complaints disappeared like snow in summer, she wasn't angry and rebellious anymore but became reasonable instead. She listened when she was told to do something without protesting right away. The sleep problems disappeared simultaneously with the behavioural problems. The teacher at school noticed a big difference: Sigrid's concentration was fine, she was able to do her work independently and she got better grades. Sigrid has followed her diet for three years now. She will start secondary school and tests have revealed that she will be able to go to a higher level than expected. We are convinced that this wouldn't have happened without the RED.

Constantly vigilant to prevent trouble

The most striking memories I have from Joris as a toddler are the everyday struggles. If he got his coat put on, he immediately would take it off again. The very same happened when he had to put on his shoes, or his socks, or when he had to get in the car; he made an issue of anything and life turned into a constant struggle. He easily got angry if something didn't work out the way he wanted, for example when a tower he had built would collapse. Joris often lost his temper, he was uncontrollable and he never listened. When we warned him *not* to do something, he interpreted it as an encouragement to do it right away. I was prepared for anything, since everything seemed to challenge him. He misbehaved in shops, running away, climbing on things and throwing with everything, so I had to keep him in the pram.

When Joris was two years old, we started homeopathy. We found that his concentration improved, but the therapy did not result in structural improvements. He grew older and his behaviour got worse. He never played with toys for a good while, but he constantly turned from one toy to another, in the mean time calling for a lot of attention. He also was selfish, the last piece of apple-pie was always supposed to be his, he didn't show any consideration for his brothers. It really isn't easy to be constantly vigilant, anticipating what might happen in order to prevent troubles and quarrels. Somehow things seemed to occur in his head and he was not able to suppress them.

When Joris was six years old, we learned about the INCA study. Joris was diagnosed with ADHD and ODD, and we decided to participate. After a 3-months waiting-period we could start the RED. It made a world of difference: our son, who never took 'no' for an answer, now accepted it and he listened to us, without arguing all the time. He calmed down and he became less angry and less rebellious. He could play with his brothers without fighting and we could drink our coffee without having to be alert and to intervene all the time. We really had to get used to this new situation, it was both bizarre and wonderful. Right now we're still sorting out to what products Joris reacts. He is doing very well, unless he eats something he should not eat. Then the 'old behaviour' returns. Those moments, when he behaves as he used to behave, we really wonder how we ever managed to cope with that behaviour.

Good marks at school

Simon followed the RED in 2008, when he was 10 years old. He suffered from ADHD and ODD. Right now he is aged 13 and he still adheres to his diet prescription, consisting of the advice to avoid potatoes, vanilla, peanut and cocoa. He wrote a letter.

"Hallo, I am Simon and I have been on a diet for several years now. Right now I feel fine, and I am doing well at school, but before I followed the diet I often felt terrible, especially when my medication had worn off, in the evening. Then I became restless, and I felt terrible and stupid, because I could not do my homework properly. Everything went wrong and I was full of grumbles. Then we started the diet, and at first I did not like it at all, and I did not want to stick to it, but then I felt better, and now I am used to it. Many different foods were tested, like sugar, and nuts and peanut and cheese and colourings and everything. Sometimes I felt worse, but most of the time I really was happy and I got good marks at school. Now I am allowed to eat almost anything because we now know which foods are causing my ADHD, and I am doing fine at school."

Medication definitely needed

Our son Michael is diagnosed with ADHD and he followed the RED. Unfortunately, it did not affect his behaviour, he remained hyperactive, unfocused and impulsive.

During the RED we took him off medication, but his teacher immediately raised the alarm: Michael did not finish his schoolwork anymore. We quickly started medication again, the diet was adjusted and once more we took him off medication, but again the problems returned. The diet just did not change our son's behaviour. We would have been happy if Michael were not to take his medication anymore, but now we know for sure that he really needs it, and the effects are quite well.

Although Michael's behaviour was not affected by the diet, we do not regret that we participated in this RED research. Michael stuck well to the diet, so he has shown that he really is able to go for something. We have supported him all the time, and that felt good; this experience has positively influenced our sense of family. We have also learned a lot about healthy food. Most of all, it is a good thing to know that for Michael there is nothing for it but to take medication.

From psychiatric day-care to public primary school

Our daughter Femke had serious behavioural problems, she suffered from extreme mood swings, compulsive behaviour and severe temper tantrums. She also often complained about headaches and bellyaches, but her behaviour was our most important concern. When she was six years old, our daughter was referred to psychiatric day-care. After an extensive period of examination, in the course of which, among others, MCDD was suggested, she finally was diagnosed with ADHD. We were told that she most likely would not be able to focus at school or even to learn at all without medication. Femke was advised to start medication and she was referred to a special education primary school.

We did not mind to send her to a special education school, but we did not like to start medication, so we asked for other options that might be helpful. The psychiatric institute's doctor told us about a diet that seemed to achieve spectacular results. We read all about it on the website, and we learned that RED research was a method to investigate the cause of ADHD and that this diet had high success rates. We considered this diet to be a more healthy approach than fighting symptoms through medication, therefore we decided to participate in the INCA study before starting medication.

When we started the RED we knew it wasn't going to be easy, so we decided that the whole family would follow the diet, not Femke only. First we were shocked when we received the RED instruction, however, within 2 weeks we were used to

it, we baked cookies ourselves and – to our surprise – the children did not protest. We didn't notice much of a result in the first weeks, whereupon my husband concluded that "we could not expect miracles from a diet, could we". But the INCA-team was of a different opinion and they prescribed a more stringent diet. 2 Weeks later a miracle did happen: the temper tantrums, compulsive behaviour and mood swings disappeared, she became calm, happy and flexible and she could handle setbacks easily. For the first time in years we enjoyed ourselves during dinner, even though our dinner options were limited! Headaches and bellyaches disappeared as well, and her teacher was lyrical: Femke now finished schoolwork that used to take her one week in one day! She obviously felt good. She changed so drastically that even people who didn't know that we had started a therapy noticed the change.

One year later Femke had improved to such an extent that she switched to a public primary school, and she is doing really fine. Although she has some difficult moments, such as parties and birthdays, she is pleased with the diet that now is close to normal. During holidays, when it is difficult to stick to the diet, she may fall back in her old behaviour and she may become sad, angry and easily upset, fighting a lot. Fortunately that behaviour disappears quickly when we exclude the triggering foods, and Femke will be the first to stop eating them, stating: "I don't want to be angry and fighting anymore". We're all really happy that the RED has solved a really difficult problem and has given us a happy child. We hope this method will become widely accessible.

How a diet made a beehive in an adolescent's head disappear

We already noticed that Dennis was hyperactive and unable to focus when he was attending nursery school, and this behaviour continued when Dennis started primary school in 1998. Although he found himself lying under his chair more often than sitting in it, and although he could hardly be described as an attentive pupil, he kept up remarkably well. Through the years his behavioural problems increased, his social behaviour did not develop as it should, and he even tended to walk away from school if he did not like the way things went. Other children did not really like him, because they constantly needed to say things like: "Dennis, stop it; Dennis, don't do that; no Dennis, we're not changing the rules; Dennis, don't touch that; Dennis, be quiet," etcetera. Especially during school trips and other activities he did not know how to behave and seemed completely on the wrong track.

When he was nine years old it was not quit clear whether he should be diagnosed with ADHD or PDD-NOS. Eventually, PDD-NOS was chosen and it was advised to put Dennis on medication. In secondary school, a special education school for children with serious behavioural problems, we actually decided to start medication, risperdal. We definitely noticed distinct beneficial effects, but Dennis still needed a lot of structure and we always had to keep an eye on him, one never knew what would happen or what he would do when he was in company. His fantasy was boundless (what if…, imagine…, suppose we…), and he still talked all the time, mostly very quickly and unintelligibly. We were worried about his future, whether his maladjusted behaviour might lead him astray. Nevertheless, we also enjoyed Dennis and although there were some problems and conflicts in school (Dennis had been suspended for a couple of days), he graduated for his lower secondary education and started higher education.

Dennis remained an extremely restless adolescent, and our paediatrician advised to switch medication to Concerta. This change turned out well, Dennis indicated that his concentration improved substantially and he was able to play the piano for a longer period of time. Unfortunately, he still felt “a pressure in his head like a beehive hidden behind a wall”, being his very words. When he happened to see a television program about the RED he knew for sure that he wanted to try that diet. He wanted the beehive to disappear. Although he was aged fifteen already, he was so highly motivated that he was allowed to participate and one and a half years ago we started the RED.

Now, in 2011, Dennis is still on the diet and he is off Concerta. He talks more calmly and clearly and most of all he does not sail close to the wind anymore. He is happy with the diet and indicates that the beehive has disappeared, except for the moments he eats foods he should not eat. We really had to unlearn to vigilantly watch him every moment in order to correct him if things went wrong, as we were used to. When he is among others we don’t need to interfere anymore to keep things pleasant. There has been taken a weight off our shoulders. Meanwhile we have finished the RED challenge period and we know to what foods he reacts. Dennis is very aware of the effects of food and he is determined to stick to his diet. We’re really proud of our son! He does not feel sorry for himself about not being able to eat certain things, on the contrary, he would rather feel sorry if he didn’t stick to his diet, because then all his behavioural problems would return. We completely agree with him: the diet isn’t a restriction, but an enrichment of his life.

Homework

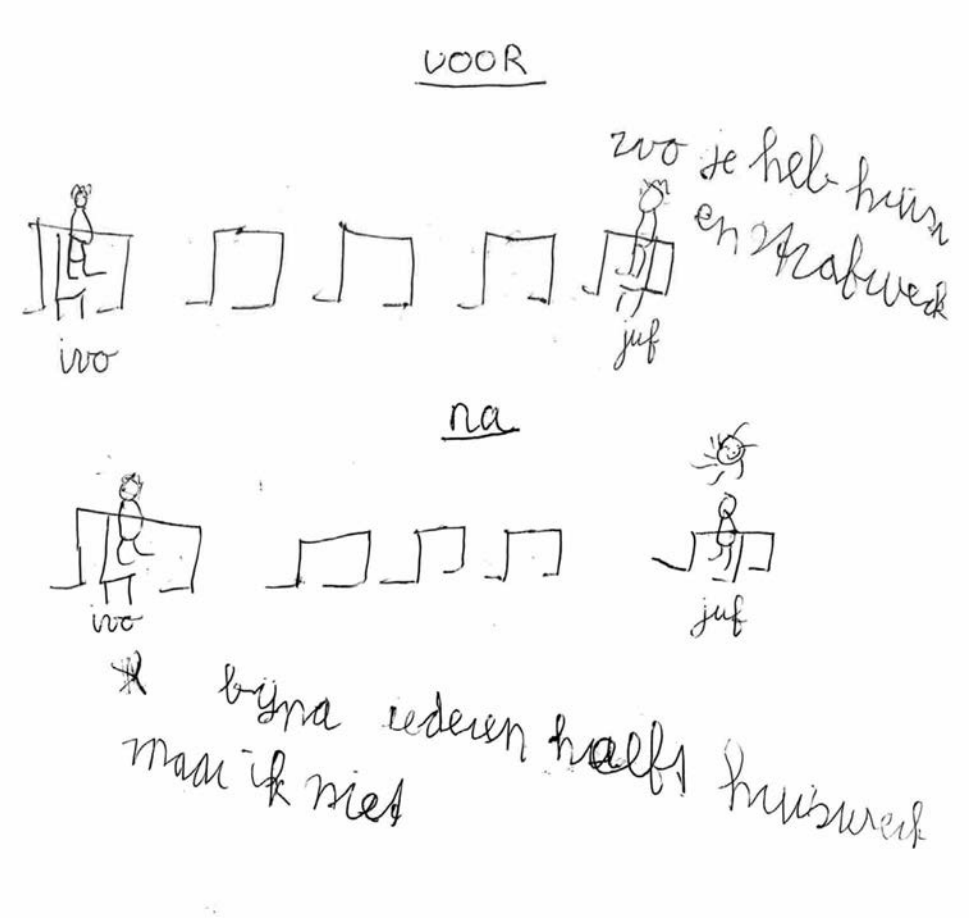
Ivo, an 8 year old boy diagnosed ADHD started RED-research in 2011. He made these drawings at the end of the 5-week RED. During the challenge period, which has only just started off, he reacted adversely to cheese.

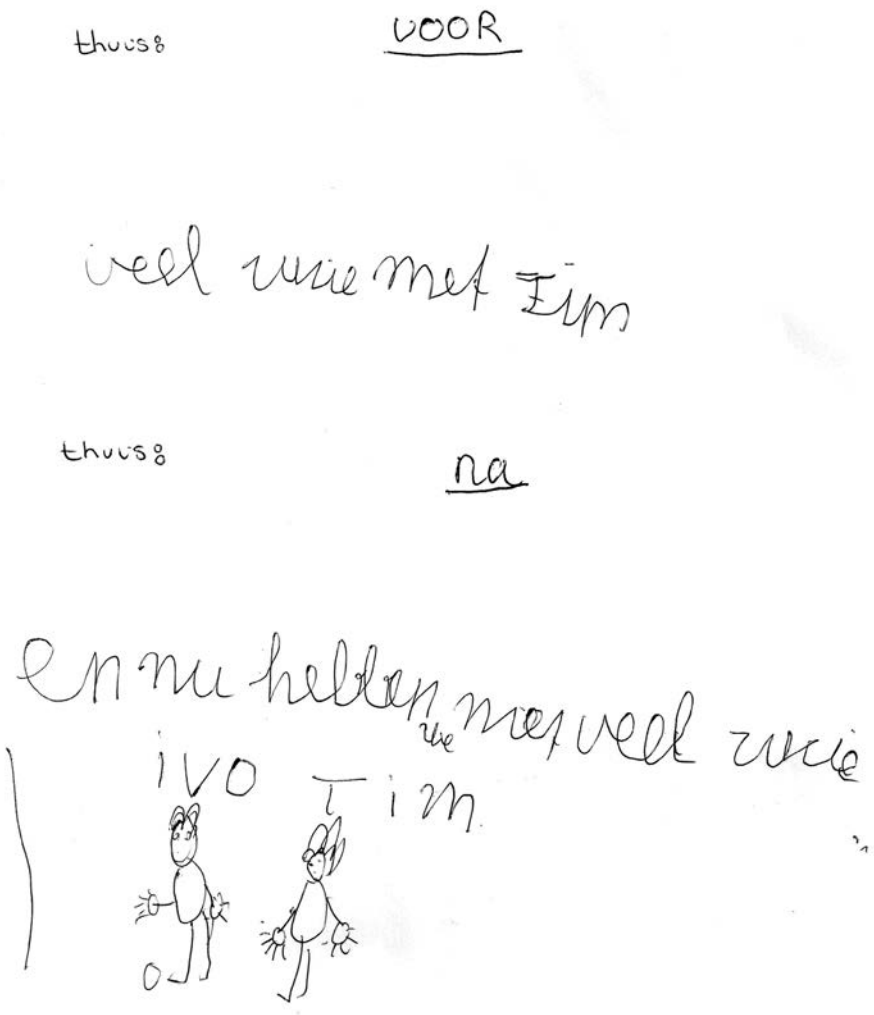
Before the RED

At school: the teacher says: "Ivo, you've got homework and you'll have to write lines."

After the RED:

At school: Almost every child has got homework, but I haven't.





Before the RED

At home: I am always fighting with my brother

After the RED:

At home: my brother and I hardly ever fight

More support needed during RED challenge period

Thom especially had behavioural problems at school and at football. He just couldn't focus, whether it was on his schoolwork or on the ball. Eventually, he even was forbidden to participate in football matches, because he was rather a nuisance in the field than anything else. Of course, that is a woeful experience for a boy who loves to play football. We had him tested and he was diagnosed ADHD. We also were informed about the RED research, so we put forward our son for this investigation. To put it briefly, the improvements in Thom's behaviour were gigantic, at school and at football. He was allowed to play games again, which really was wonderful. He even scored a goal! We were very happy, and so was his teacher, he did well at school.

We started the RED challenge period, but this really was a disappointment. Every time we introduced a new food I spent the next ten days anguishing about how it would turn out, because I desperately wished him, and us, a less strict diet. I also found it aggravating that we always had to take his diet into account, we just couldn't have a day out or go out for dinner, because we always had to bring something along for him to eat and drink. Furthermore, the longer we participated, the more difficulties I experienced in judging his behaviour. I knew this challenge period would take about 15 months and would eventually come to an end, but I did not know *when* it would end or to what foods Thom would react, and this uncertainty unbalanced and unsettled me. In truth, more guidance, a coach, someone to lean on, someone who might visit us and might offer practical assistance would have been very welcome. The monthly consultations at ADHD Research Centre unquestionably were encouraging, but it was not enough to help us see this period through. One month ago we have stopped, and we're not sure how we will proceed. It really is great not to have to think about his food anymore and to be able to eat whatever and wherever we want, but Thom's behaviour definitely has worsened. Right now it is our summer holiday, so we will manage. In September, when he has to go to school again, we must decide whether we will start medication or give the RED challenge period another try. If we opt for the RED, then I honestly wish we would get some more help.

Medication if a diet doesn't work

Jeffrey, our 10 years old son, started the RED four months ago, with remarkable effects. We're definitely not opposed to medication: after he was diagnosed with ADHD in 2007 Jeffrey got medication, for three years, with varying success. He first was on Concerta, which worked quite well in the beginning, but eventually the effects diminished. We switched to Strattera but Jeffrey did not react favourably to this medication, so we continued with Medikinet. This worked out fine, although in the evening when the effect of medication had worn off, the restlessness in his head returned. That's why we started the RED research. During the RED we took him off medication and we honestly couldn't believe what happened: our son became calm and concentrated, sat still at dinner table but most of all, he was cheerful, laughing and enjoying life. This was our Jeffrey.

In the RED challenge period we figured out what products were causing Jeffrey's behaviour. We started with beef, slowly increasing the amount. Within a few days he started bouncing through the room and the ADHD behaviour completely returned. We couldn't really believe this, we were doubting ourselves. We stopped the beef challenge and one week later his peaceful behaviour returned. It was unbelievable, but true!

We think it is remarkable how well Jeffrey continues the diet. It's not easy, so he says, but it's worth it. He pointed out that the motor in his body has been switched off now and he is feeling much better. The every evening's restlessness in his head has disappeared, and he is keen on keeping it that way. Not only Jeffrey, but also his environment (his family, his teacher and the children at school) profits from the behavioural changes, it seems a win-win situation. We would like to advise other parents to try this diet first. In case it does not help, medication will always be an option.

Temper tantrums

Floor, 8 years old, was diagnosed ADHD and ODD. She entered the INCA study in 2009. She responded favourably to the RED, and the ADHD and ODD behaviour returned when eating too much wheat, corn or fish. She sent a postcard and a drawing at the end of the challenge period. Now she is 10 years old, she still adheres to the diet prescription based on the results of the challenge period and she is doing fine.

Text postcard:

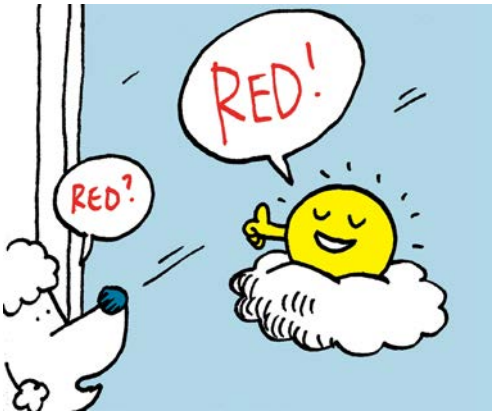
Dear Mrs Pelsser, I made a drawing for you. Thanks to your diet I hardly ever have a temper anymore. That makes me very happy.

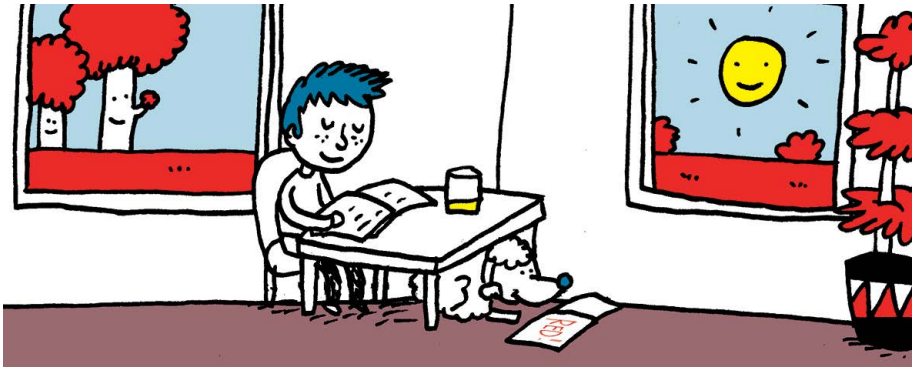
Text drawing:

Before the RED: grrrr, I am angry and I've got a headache

After the RED: I am not angry anymore, I don't have a headache anymore

Samenvatting





ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD), een aandachtstekort-hyperactiviteits-stoornis, is een psychiatrische stoornis die wereldwijd bij ongeveer 5% van alle kinderen voorkomt en die een sterke erfelijke lading heeft. Hoewel de naam ADHD nog maar enkele decennia bestaat, is de stoornis zelf al bijna honderd jaar bekend in de geneeskunde. In de eerste helft van de twintigste eeuw sprak men nog niet van ADHD, maar van Minimal Brain Damage (MBD). Toen men ontdekte dat er eigenlijk geen sprake was van beschadiging van de hersenen, werd de naam gewijzigd in Minimal Brain Dysfunction. Rond 1980 werd de stoornis onder de naam ADHD opgenomen in de derde versie van de "Diagnostic and Statistical Manual of Mental Disorders" (DSM-III). Dit classificatiesysteem, waarin de symptomen en kenmerken van psychiatrische stoornissen worden omschreven, wordt ook in Nederland gehanteerd.

De diagnose ADHD wordt gesteld aan de hand van de huidige versie van de DSM, de DSM-IV, en is niet alleen gebaseerd op het aantal en de ernst van de symptomen, maar ook op de impact van de symptomen op het leven van het kind. Het gebruik van de term "diagnose" is verwarrend, omdat een diagnose idealiter zou moeten verwijzen naar een oorzaak. Dit is echter bij ADHD, evenals bij bijna alle andere psychiatrische stoornissen, niet het geval, vandaar dat de benaming "symptomencomplex" of "syndroom" een betere omschrijving zou zijn.

Aan de hand van de klachten wordt ADHD in 3 subtypes onderverdeeld: 1) ADHD met voornamelijk concentratieproblemen (voorheen ADD genoemd); 2) ADHD met vooral hyperactiviteitproblemen; en 3) ADHD met zowel hyperactiviteitproblemen als concentratieproblemen. Deze laatste subgroep komt het meeste voor. Kinderen met ADHD kunnen dus zeer uiteenlopende problemen hebben. ADHD komt in de meeste gevallen samen met andere stoornissen voor, zoals bijvoorbeeld Oppositional Defiant Disorder (ODD), een oppositioneel opstandige gedragsstoornis. Kinderen met ODD zijn snel driftig, opstandig en houden zich vaak niet aan de regels. Kinderen met ADHD en ODD lopen een groter risico om ook Conduct Disorder (CD), een antisociale gedragsstoornis, te ontwikkelen en om te ontsporen. Ze behoren vaker tot de vroegtijdige schoolverlaters en zijn oververtegenwoordigd in het jeugdcriminele circuit. Driekwart van de kinderen met ADHD heeft nog steeds problemen als ze volwassen zijn, ADHD verdwijnt dus bij de meeste kinderen niet als ze ouder worden.

Oorzaak van ADHD

Erfelijke en omgevingsfactoren spelen beide een rol bij het ontstaan van ADHD, echter de precieze oorzaak van ADHD is niet duidelijk. Het is heel goed mogelijk dat er meerdere factoren zijn die ADHD kunnen veroorzaken, en dat per kind met ADHD de precieze samenstelling van deze factoren anders is. De behandeling van ADHD bestaat op dit moment vooral uit medicatie, gericht op het verminderen van de symptomen, en gedragstherapie, eveneens gericht op het verminderen van symptomen en het leren omgaan met ADHD. De lange-termijn effecten van de huidige therapie zijn helaas teleurstellend te noemen, daarom is verder onderzoek naar de oorzaak van ADHD en naar nieuwe therapieën belangrijk. Vooral de interactie tussen genetische en omgevingsfactoren verdient meer onderzoek.

Een belangrijke omgevingsfactor die een rol zou kunnen spelen bij ADHD is de voeding, net zoals voeding van invloed kan zijn op andere erfelijke ziektes, zoals astma en eczeem. De relatie tussen voeding en ADHD is sinds de jaren zeventig van de vorige eeuw uitgebreid onderzocht, waarbij de onderzoeken in te delen zijn in twee categorieën: de kleurstofonderzoeken en de dieetonderzoeken.

Onderzoeken naar de invloed van kleurstof, conserveermiddelen en suiker op ADHD hebben overtuigend aangetoond dat ADHD niet veroorzaakt wordt door kleurstoffen of door suiker. Wel is gebleken dat *alle* kinderen, met of zonder ADHD, van additieven iets drukker kunnen worden. Maar of dit effect nu veroorzaakt wordt door kleurstoffen, door conserveermiddelen of door beide is nog niet onderzocht. Ook blijkt uit onderzoek dat er weinig bewijs bestaat voor de effectiviteit van supplementen zoals visolie.

Onderzoeken naar de invloed van voeding op ADHD hebben overtuigend aangetoond dat er een sterk verband is tussen voeding en ADHD. Tijdens deze onderzoeken volgden de kinderen een restricted elimination diet (RED), een streng eliminatiedieet. Tijdens het RED wordt gedurende 5 weken het volledige dieet van het kind aangepast. Het kind mag dan uitsluitend voedingsmiddelen eten waarvan bekend is dat ze geen allergieën of ADHD veroorzaken. Op basis van de resultaten van eerdere RED-onderzoeken werd in 1999 geconcludeerd dat er voldoende en overtuigend wetenschappelijk bewijs is voor de effectiviteit van een RED bij kinderen met ADHD. In 2001 werd door Engelse wetenschappers de toepassing van een RED bij kinderen met ADHD aanbevolen. Al deze gegevens leidden er echter niet toe dat RED-onderzoek standaard werd toegepast. Daarom

werd in Nederland nieuw onderzoek opgestart om meer duidelijkheid te krijgen over de invloed van een RED op ADHD.

Resultaten van het onderzoek in dit proefschrift

In dit proefschrift worden meerdere onderzoeken naar de effecten van een RED (in Nederland het Pelsser Voeding en Gedrag (PVG)-dieet geheten) op ADHD beschreven. Deze Nederlandse onderzoeken bevestigen de resultaten van eerder buitenlands onderzoek: bij 60% van de jonge kinderen met ADHD kan een RED grote gedragsverbeteringen tot gevolg hebben, zowel volgens oudermetingen als leerkrachtmetingen. Het effect van het RED op ADHD (gemiddelde effect size 1.2) is groter dan het effect van medicatie (gemiddelde effect size 0.8). Bovendien werkt het RED de hele dag, terwijl medicatie 's ochtends nog niet is ingewerkt en 's avonds weer is uitgewerkt, waardoor het kind en zijn/haar omgeving op die momenten nog steeds geconfronteerd worden met de gedragsproblemen. Een RED kan dus belangrijke voordelen hebben.

Het RED heeft niet alleen een gunstig effect op ADHD, maar ook op ODD. Dit is een belangrijke bevinding, want niet alleen komt ODD bij driekwart van alle kinderen met ADHD voor, ook lopen deze kinderen een groter risico om later te ontsporen. Uit de RED-onderzoeken blijkt dat het RED eveneens een gunstige invloed heeft op lichamelijke klachten, die net als ODD vaak voorkomen bij kinderen met ADHD. Vooral hoofdpijn, buikpijn, slaapproblemen en overmatige dorst en overmatig zweten zijn klachten die nagenoeg verdwijnen bij kinderen die het RED volgen. Tenslotte is onderzocht of het RED mogelijk kan zorgen voor structuurverbetering in een gezin: wellicht zou deze structuurverbetering de veranderingen in het gedrag van het kind tijdens het RED kunnen verklaren. Dit bleek echter niet het geval te zijn: de gezinnen die deelnamen aan het onderzoek vertoonden voorafgaand aan het onderzoek een goede gezinsstructuur, en het RED had vervolgens geen positieve of negatieve invloed hierop.

Concluderend kan gesteld worden dat uit de dieetonderzoeken blijkt dat bij 60% van de kinderen met ADHD een overgevoeligheid voor voeding een belangrijke oorzaak is van ADHD. De term 'overgevoeligheid', in dit geval dus het krijgen van ADHD na het eten van normale hoeveelheden van een voedingsmiddel dat normaliter prima verdragen wordt, wordt gehanteerd voor allergische en voor niet-allergische reacties die veroorzaakt worden door bepaalde omgevingsfactoren. Bij een allergische overgevoeligheid is er sprake van een immunologisch

mechanisme (hetgeen vastgesteld kan worden door middel van bloedonderzoek); bij een niet-allergische overgevoeligheid wordt geen immunologisch mechanisme gevonden. Tijdens een van de onderzoeken, de INCA-studie (zie hoofdstuk 6), is onderzocht of er een immunologisch mechanisme aanwezig is bij kinderen die na een RED geen ADHD meer hebben. Dit bleek niet het geval te zijn: bloedonderzoek naar immunoglobulines (IgE en IgG) is bij kinderen met ADHD dus niet zinvol.

Bij kinderen met ADHD die na het volgen van een maximaal 5 weken durend RED geen gedragsproblemen meer hebben, kan gesproken worden van food-induced ADHD (FI-ADHD), om duidelijk te maken dat bij deze kinderen voeding een belangrijke oorzaak is van ADHD. Deze kinderen gaan na het RED verder met een provocatieperiode, waarin uitgezocht wordt op welke voedingsmiddelen elk kind reageert; in deze periode wordt het RED dus steeds verder uitgebreid. Uiteindelijk hoeft het kind slechts enkele voedingsmiddelen te vermijden en heeft het weer een zo normaal mogelijk voedingspatroon.

Bij kinderen die geen gedragsverbeteringen vertonen na het volgen van een RED, kan gesproken worden van Classic-ADHD (C-ADHD). Deze kinderen mogen weer alles eten en starten met de gangbare therapie.

Toepassing in de praktijk en aanbevelingen voor verder onderzoek

Gezien de resultaten van RED-onderzoek bij kinderen met ADHD verdient het aanbeveling om dit onderzoek in de praktijk standaard toe te passen bij jonge kinderen met ADHD. Hoewel uit onderzoek is gebleken dat het RED ook effectief is bij oudere kinderen, wordt algemene toepassing vooral aanbevolen bij jonge kinderen, omdat deze kinderen minder buitenschoolse activiteiten hebben en zich meer “onder moeders vleugels” bevinden. Hierdoor is het gemakkelijker om het RED toe te passen en vol te houden.

Een voorstel voor een diagnostisch protocol, uit te voeren door artsen die hiervoor een speciale training hebben gevolgd, wordt weergeven in hoofdstuk 9.7, figuur 4. Toepassing van het RED-onderzoek bij kinderen met ADHD kan:

1) er voor zorgen dat de gedragsproblemen voorkómen worden waardoor de kwaliteit van zorg sterk kan verbeteren,
2) het aantal kinderen dat medicatie nodigt heeft verminderen,
3) de prognose van veel kinderen verbeteren, en
4) veel kosten besparen, zoals is berekend door de Stichting Kind en Gedrag.

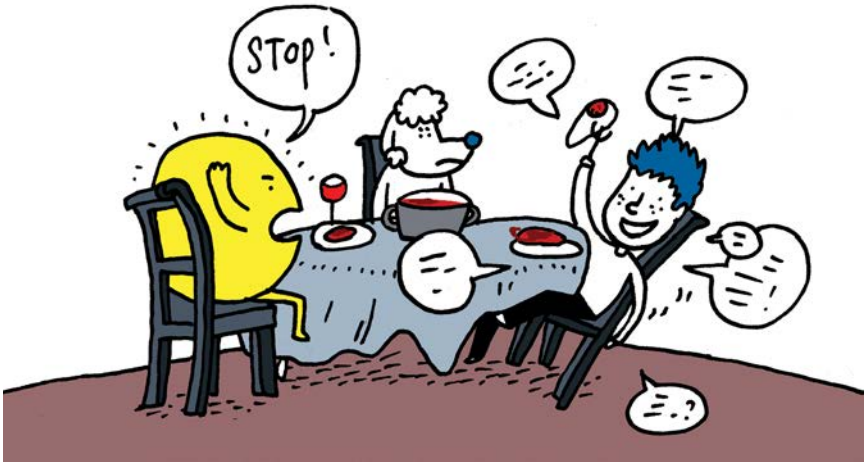
Naast implementatie is verder onderzoek van belang. Dit onderzoek zou zich allereerst moeten richten op de provocatieperiode waarin onderzocht wordt op welke voedingsmiddelen een kind reageert. Dit is een zware periode die veel vraagt van ouders en kind. Het inzetten van gezinscoaches zou dit traject wellicht sterk kunnen vergemakkelijken, waardoor hopelijk meer gezinnen de provocatieperiode tot een goed einde brengen. Ouders die het RED-onderzoek niet vol kunnen houden, zouden daarnaast ook extra opvoedondersteuning kunnen krijgen. De provocatieperiode zou wellicht eenvoudiger kunnen worden wanneer door verder onderzoek meer inzicht verkregen wordt in het werkingsmechanisme van voeding. Tenslotte is ook meer onderzoek nodig naar de effecten van een RED op andere psychiatrische stoornissen, naar de effecten op lichamelijke klachten (ook bij kinderen zonder ADHD), naar de lange-termijn werking (kunnen kinderen eroverheen groeien) en naar de effecten van voeding op hersenen en genen.

Samenvattend kan gesteld worden dat de RED-onderzoeken hebben aangetoond dat ADHD bij veel kinderen veroorzaakt wordt door een overgevoeligheid voor voeding. Het gaat hierbij niet om kleurstoffen of suiker, maar om gewone voedingsmiddelen zoals bijvoorbeeld vis, soja, aardappel, sinaasappel of broccoli. Elk kind met ADHD dat gunstig op het RED reageert, blijkt uiteindelijk overgevoelig te zijn voor meerdere voedingsmiddelen en bij elk kind kunnen dat andere voedingsmiddelen zijn. Verder is gebleken dat niet alleen ADHD, maar ook ODD en lichamelijke klachten veroorzaakt kunnen worden door voeding. Gezien de grote effecten van het RED op kinderpsychiatrische stoornissen en de daarbijbehorende gunstige gevolgen voor het kind en de samenleving is, naast verder onderzoek naar het werkingsmechanisme van voeding, vooral implementatie van groot belang, zodat kinderen met ADHD de kans krijgen op een betere toekomst.

The story of Perky Peter

(restrict your diet and be quiet)

A poem by Lidy Pelsser, a Dutch researcher, published in 2011

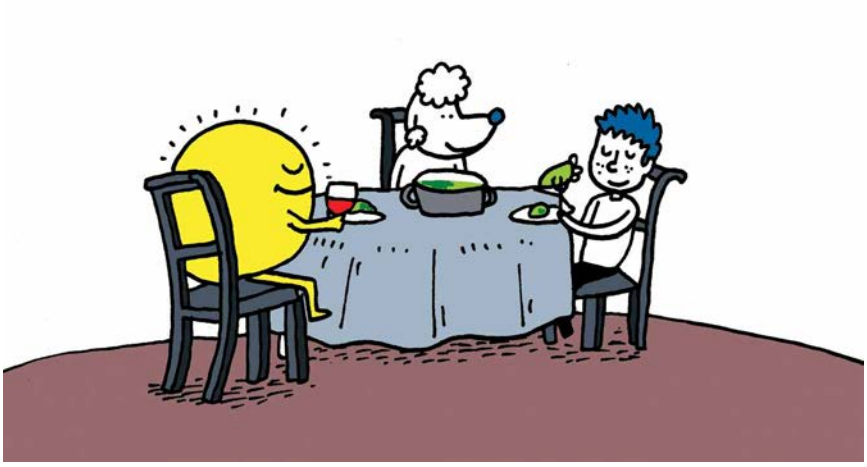


This story is a tale of woe,
Of Peter, always on the go,
His feet, they run, he never walks,
He doesn't listen, but he talks,
And the meals, we don't know how,
They always end up in a row,
A game with Pete turns into fight,
We just can't leave him out of sight!

How we love our perky Peter,
And how we wish he would be sweeter,
We know he tries with all his might,
Still, it never turns out right.
What to do with his behaviour,
Could a diet be his saviour?
His life right now it is a curse,
A 5-week diet cannot be worse!

That very evening mum and dad
Talked about their little lad,
Gravely they deliberated,
Pros and cons considerated,
Might they prevent their Pete run riot,
By following this 5-week diet?

"All right, let's try, let's start and see,
What happens with an RED!"



Within 5 weeks of stringent food,
A change was seen in Peter's mood,
The stormy boy became so quiet,
A miracle cure for Pete, this diet,
Our thoughtless, hasty, turmoil boy
Changed into our greatest joy,
This RED sure did delete
The bad behaviour of our Pete!

This tale's end is full of joy,
And if you had a similar boy
Then let this story be a plea
For diagnostic RED,
To apply in every child
Impulsive, turbulent and wild!
If RED does not succeed,
Then medication is a need.

Postface: how it all turned out

I wrote my first research protocol on ADHD and food, the "Validation of early Intervention and Prevention (VIP)" study, fifteen years ago. The VIP study was meant to be the continuation of the Restricted Elimination Diet (RED) studies conducted between 1985 and 1994, all showing convincing evidence for the effects of an RED on ADHD. The study consisted of a 5-year research including 2 groups of young children with behavioural problems, a VIP group and a control group. The VIP group was not only to follow the RED but also to receive Very Important Person (VIP) treatment (i.e. psychological research, improvement of parenting capacities, and coaching of parents, siblings and teachers), whilst the control group would neither follow the RED nor the VIP treatment, but would receive treatment as usual only.

Unfortunately, in spite of all efforts to find a university to support and a sponsor to fund this study, I did not succeed. Daring to think outside the box makes one vulnerable and my research proposal was ridiculed and dismissed, many times. There was nothing else for it but to try a different approach. I decided to start all over again and write a new proposal as though no RED research ever had been conducted. Now I found a professor (thank you, Jan), we found a sponsor (thank you, Stichting Kinderpostzegels Nederland) and the results of this study are described in chapter 2.

The reader may have noticed the time span between the first (2002) and the second study (2009), which is attributable to several factors: 1) fund raising of the second study took some time; 2) recruitment of subjects proved difficult: parents willing to participate were often discouraged to do so by GP, psychologist or psychiatrist; and 3) editors' and reviewers' unfamiliarity with the subject. Most editors dismissed the manuscript by return of post, and even when it survived the editor's scrutiny, the reviewers dealt summarily with it. One reviewer motivated his rejection as follows: "…, this means that 83.3% of the children responded to dietary intervention!" Apparently this reviewer was shocked by the results, which may be understandable considering the subject, but rejecting a paper based on the surprising results is not quite a scientific attitude.

While the above mentioned manuscript was sent from one journal to the other, I wrote a hypothesis paper (see chapter 5), I wrote the protocol for the INCA study, I tried to raise the funds necessary to start the INCA study, and I stubbornly went

on studying. I was especially interested in fish oil. Could it be true that a simple capsule a day would keep ADHD away? I was very keen to find out, because if it were true it would be a much more convenient and easier therapy than an RED. I contacted companies manufacturing fish oil and presented a research proposal to compare the effects of an RED with the effects of fish oil. Surprisingly, none of them were interested, and one of the companies politely explained the rejection as follows: "We will not cooperate in this study because the risks for negative results with respect to the effectiveness of the supplements are substantial". My further study into this subject showed that the anxiety reflected by the polite company was appropriate, indeed. In chapter 1.7 and chapter 9.6 the negative results of recent studies investigating the effect of fish oil on ADHD are discussed.

Studying fish oil (omega-3 fatty acid) also means studying sunflower oil (omega-6 fatty acid), and I read a lot about the differences between omega-3 and omega-6 fatty acids. Not only do they differ in biochemical structure, they also differ in function (omega-3 inhibiting inflammation, omega-6 promoting inflammation). The most striking distinction, though, is the at least tenfold increased omega-6/omega-3 ratio in our food during the last 50 years. Given that omega-6 and omega-3 compete for the same enzymes it seems rather useless to supply omega-3 without a concurrent drastic decrease of omega-6. There is evidence that the huge increase of omega-6 fats in our food may be causal of the Western world's lifestyle diseases characterised by an increase of inflammation, like type 2 diabetes and obesity (see chapter 9.6). I am convinced that it would be worthwhile to investigate whether a major decrease of omega-6 in our food might result in an equally major decrease of our chronic Western diseases, and I earnestly stand wondering why scientists continue to focus on less saturated fats and more unsaturated fats (omega-6 and omega-3), while simultaneously lifestyle diseases unabatedly increase.

I would have loved to study this subject more comprehensively, but my fatty acid adventures were interrupted by a sudden rapid development of the ADHD research. The protocol of the INCA study was accepted by *The Lancet* (see appendix), the manuscript that had travelled from one editor to another for more than 3 years was finally accepted for publication (see chapter 3), and the long-lasting fund-raising campaign to raise money for the INCA study ended with a passionate plea broadcasted by EenVandaag, a Dutch television station, after which a maecenas generously donated the money needed to start.

And here we are now. The INCA study has been published in *The Lancet* (see chapter 6), which of course may be considered the crowning glory of this thesis. Still, there it is, in my drawer, the protocol of the VIP study. Unabated a highly topical subject, and I would love to conduct this implementation study as well as the other RED–ADHD studies I have in mind (see chapter 9.6). It is evident that many children may benefit from our findings, as you may read in chapter 9.7, describing the pros and cons of both treatment-as-usual and RED treatment. It would be truly sad if it took another fifteen years before follow-up research like the VIP study might be realised. I sincerely hope that this thesis may lead to an RED–ADHD Research Centre and may instigate a paradigm shift necessary to improve child psychiatric health care (whether that be an RED or, if necessary, medication and psychological interventions or any combination of these), thus offering our children suffering from ADHD the ultimate chance of a more favourable future.

Dankwoord

Net zoals een topscorende spits zijn doelpunten niet kan maken zonder de andere spelers van zijn team, zo kan een wetenschapper geen onderzoek doen en zeker geen proefschrift schrijven zonder de hulp van haar omgeving. Daarbij zijn niet alleen de medespelers belangrijk, maar ook de coaches, scheidsrechters, sponsoren, verzorgers en supporters. Elk zijn zij op hun eigen wijze onmisbaar om uiteindelijk te komen tot die ene goal, in dit geval tot dit ene proefschrift.

Belangrijke spelers waren allereerst de ouders en kinderen die deelnamen aan de onderzoeken. Aan een half woord hadden zij genoeg om hun onbaatzuchtige medewerking te verlenen aan vele activiteiten, zoals rondetafelgesprekken in de tweede kamer, interviews in kranten en tijdschriften, of optredens voor radio en tv. Zonder hen was er hoogst waarschijnlijk geen subsidie geweest voor de INCA-studie en was ook dit proefschrift er niet geweest. Daarom wil ik al deze ouders, hun kinderen en ook de leerkrachten heel hartelijk bedanken.

Twee andere spelers die een zeer grote rol hebben gespeeld, vanaf de eerste kiem van dit proefschrift in 1993 tot nu toe, wil ik in het bijzonder noemen: Jan C. Karman en Marjan de Boer. Jan, ik weet niet of ik zonder jouw niet aflatende steun dit onderzoek ooit van de grond had gekregen, en zonder de altijd weer bemoedigende woorden van Marjan had ik het denk ik niet volgehouden. De tegenslagen waren talrijk en meerdere malen hebben jullie mij ervan moeten overtuigen dat ik toch echt door moest zetten en dat ik al die kinderen niet in de steek kon laten. Dank jullie wel!

Geen proefschrift zonder coaches: mijn promotoren prof.dr. J.K. Buitelaar en prof.dr. H.F. Savelkoul, mijn copromotor dr. N.N. Lambregts-Rommelse, en mijn statisticus dr. K. Frankena. Beste Jan, als je destijds niet akkoord was gegaan met mijn voorstel om samen subsidie aan te vragen voor onderzoek naar ADHD en voeding, dan had ik nu nog in je kamer in Utrecht gezeten, vrees ik, zo vastbesloten was ik om me niet weer te laten afschepen. Ik ben je heel dankbaar dat je het hebt aangedurfd om je nek uit te steken voor dit onderwerp, dat destijds zeer controversieel was. Zonder jouw steun en medewerking had het onderzoek naar de invloed van voeding op ADHD niet zo'n vlucht kunnen nemen. Dank je wel voor je vertrouwen! Huub, je speelde een belangrijke rol bij het tot stand komen van de INCA-studie en ik heb veel geleerd van al je kennis op het gebied van de allergologie. Er is op dit gebied nog een wereld te ontdekken. Nanda, ik

had me geen betere copromotor kunnen wensen. Ik ben zeer onder de indruk van al je kennis en inzicht en ik heb zeer veel van je geleerd, niet alleen qua tact, hetgeen niet mijn sterkste punt is, maar ook wat betreft het schrijven van artikelen. Het was een voorrecht om met jou te mogen samenwerken. Ik hoop dan ook dat we hierna, op wat voor manier dan ook, ons samen verder kunnen verdiepen in dit uitdagende en boeiende onderwerp. Klaas, je nuchtere kijk op het leven en de wetenschap, je statistische kennis, je humor, het was werkelijk geweldig om met jou te mogen samenwerken. Al mijn vragen werden per kerende mail beantwoord, en grafieken en tabellen werden met eindeloos geduld steeds opnieuw ontworpen als ik het weer eens anders wilde hebben. Dank je wel!

Zonder scheidsrechters geen voetbalwedstrijd, maar ook geen promotie: ik wil dan ook de leden van de promotiecommissie, prof.dr. R. de Groot, prof.dr. E. Taylor, prof.dr. J.J. van Binsbergen, prof.dr. R.J. van der Gaag, prof.dr. M. Danckaerts, dr. H de Groot, prof. dr. G.J. van der Wilt en dr. A.P.J. Scheres heel hartelijk bedanken voor hun bereidwilligheid om het proefschrift kritisch te lezen en om te opponeren. Dear professor Taylor: thank you so much for participating in this PhD committee, I feel truly honoured that you came to the Netherlands for this occasion.

Zoals voetbalclubs niet alleen sponsoren maar vaak ook een maecenas hebben, zo prijst dit onderzoek zich eveneens gelukkig met een maecenas zonder wie de INCA-studie niet gerealiseerd had kunnen worden, simpelweg omdat na jaren van lobbyen de benodigde gelden nog steeds niet bijeen waren. Na een tv-uitzending van EenVandaag op 1 april 2008, waarin ik een wanhopige en laatste poging deed om de INCA-studie gefinancierd te krijgen, kreeg ik een telefoontje waar ik nu nog stil van ben. Ik wil vanuit de grond van mijn hart, mede namens alle gezinnen die hierdoor de kans kregen om deel te nemen aan dit onderzoek, de maecenas die zo genereus de ontbrekende gelden doneerde heel hartelijk danken. De Stichting Kind en Gedrag, met Camilla Waelen als drijvende kracht en enthousiast voorzitter, verdient eveneens een apart woord van dank. De betrokkenheid van de Stichting, die zich niet alleen zorgen maakte over financieringsproblemen maar ook over mijn gezondheid, was van onschatbare waarde. Ook alle andere subsidiegevers ben ik heel dankbaar voor hun belangeloze betrokkenheid en inzet.

De verzorgers, dat zijn natuurlijk de paranimfen dr. N. de Jonge en drs. C.J. Brink. Nicolaas en Carla, ik ben er trots op dat jullie mijn paranimfen zijn. Nicolaas,

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Abbreviations

ACS	Abbreviated Conners scale
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-NOS	ADHD not otherwise specified
ARS	ADHD rating scale
C-ADHD	Classic ADHD
CD	Conduct Disorder
DBPC	Double-blind placebo controlled
DBPCFC	Double-blind placebo controlled food challenge
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ES	Effect size
FC	Food challenge
FES	Family environment scale
FI-ADHD	Food-induced ADHD
FRI	Family relationships index
FSI	Family structure index
IgE	Immunoglobulin type E
IgG	Immunoglobulin type G
INCA	Impact of Nutrition on Children with ADHD
ISRCTN	International standard randomised controlled trial number
MCDD	Multiple Complex Developmental Disorder
NICE	National Institute for Health and Clinical Excellence
ODD	Oppositional Defiant Disorder
OR	Odds ratio
PCQ	Physical complaints questionnaire
PDD	Pervasive Developmental Disorder
PDD-NOS	PDD not otherwise specified
RCT	Randomised controlled trial
RED	Restricted elimination diet
SD	Standard deviation
SDQ	Strengths and difficulties questionnaire
SPI	Structured child psychiatric interview