

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

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

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

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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 children⁶ 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

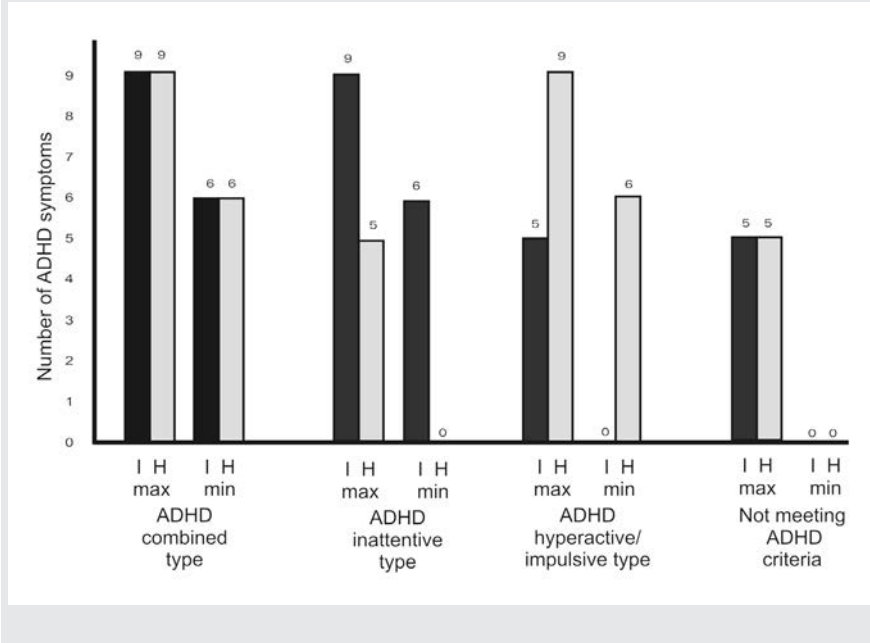
dysfunction of the brain, the aetiological formulation of the problem, i.e. MBD, evolved into a more descriptive formulation, making an inventory of symptoms without referring to a cause.

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 scrutiny¹⁰ 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 category¹⁶ 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 et 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 categorical 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 reported⁴⁶ and the comorbidity 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 disorders⁵¹ 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 behaviour⁶² 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 crime⁶⁸ 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 ADHD⁶⁹ 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 research 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 ADHD⁸⁵ 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 provoking 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 panacea, 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 statistical 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 unsuccessful 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 related¹¹⁵ 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 microbionics 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 neuropsychological 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 algorithm¹⁰⁰ 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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