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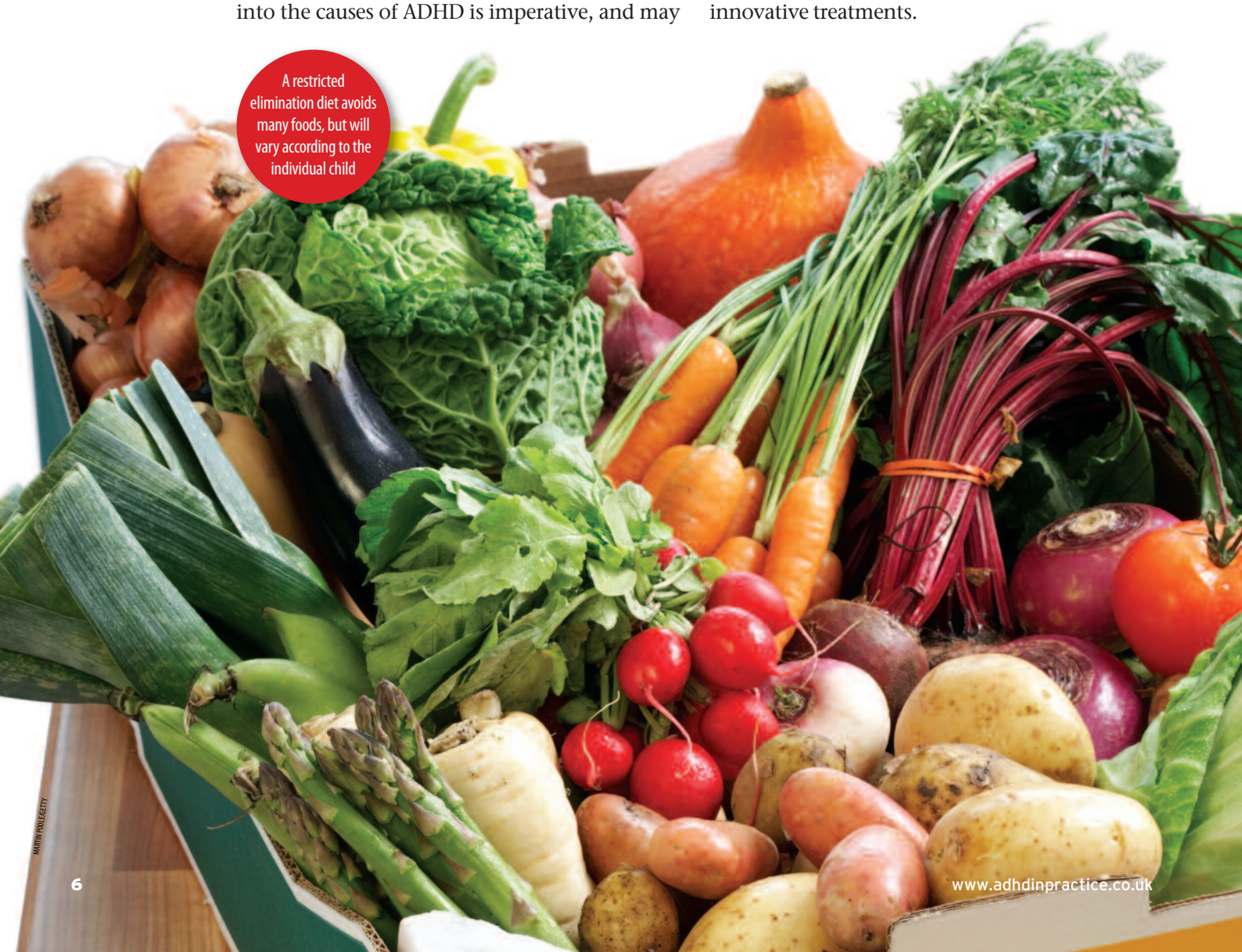
Food as a trigger for ADHD symptoms: time for a paradigm shift?

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder in children that often leads to significant impairment of the child's social and family life. A large number of children with ADHD suffer from comorbid oppositional defiant disorder (ODD): these children are even more difficult for parents and teachers to handle, and show increased risks of academic failure.[1] The exact causes of ADHD are unclear; ADHD treatment, perforce, is bound to focus on addressing symptoms – mostly by means of medication like methylphenidate and behavioural therapy.

The short- to medium-term therapeutic effects of methylphenidate are beneficial, but the long-term effects are disappointing.[2] Further research into the causes of ADHD is imperative, and may eventually lead to new diagnostic procedures and innovative treatments.

Editor's note

Some readers may be taken by surprise that we are including an article that emphasises the role that certain foodstuffs may play in the genesis and/or exacerbation of symptoms associated with ADHD. This is a long-neglected area that has received little attention in the past due to the relatively small effect size that elimination diets confer to the treatment of ADHD symptoms. There is already good evidence for the effectiveness of a few-foods diet, and diligent, committed and well-organised parents will have already tried it. Others may have found it impossible to implement. With many of these studies it is difficult to know whether children adhere to the prescribed diet or whether the improvement in behaviour was down to parental expectations. Be that as it may, we will continue keeping an open mind ■



A restricted elimination diet avoids many foods, but will vary according to the individual child

MARTIN POOLE/GETTY

Table 1. All eight randomised controlled RED trials, including effect sizes[14]

Article	RCT type	Age (years)	Diagnosis at start	Methods	Selection Weight	RED period	ES	ACS	Contribution to weighted ES
Egger *et al*[6] (1985)	DBPCFC	2–15	Hyperkinetic syndrome	Open RED n=76, open challenge n=56, DBPCFC* **n=25**	Selected group†	4 weeks	1.03	0.11	0.12
Kaplan *et al*[7] (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
Carter *et al*[8] (1993)	DBPCFC	3–12	DSM-III	Open RED n=78, open challenge n=59, DBPCFC* **n=19**	Selected group†	3–4 weeks	0.61	0.09	0.05
Boris and Mandel[9] (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
Schulte-Körne *et al*[11] (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
Schmidt *et al*[10] (1997)	DBPC diet	6–12	DSM-III	RED vs placebo diet, DBPC* **n=49**	Aselected group	8 days	0.59	0.22	0.13
Pelsser *et al*[12] (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
Pelsser *et al*[13] (2011)	Open RCT, blinded measurements	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 Conners' scale; DBPCFC = double-blind, placebo controlled food challenge; DSM-III/-III-R/-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn/3rd edn, text revision/4th edn; ES = effect size; ICD-9 = WHO *International Statistical Classification of Diseases and Related Health Problems*, 9th rev; RCT = randomised controlled trial; RED = restricted elimination diet
* crossover; † subjects selected via diet clinics; ‡ subject selected via allergy clinic; § exclusion of children with risk factors for ADHD (for example, premature, dysmature, foster child, IQ<70)

Nutrition and its effects on the brain

A research area showing promising results is that which examines the relationship between everyday foods and child psychiatric disorders. There are two different types of research study that have been conducted to investigate the effects of food on children with ADHD: additive research studies and restricted elimination diet (RED) research studies.

Additive research, which involves eliminating or supplementing only a few food components, like colourings or preservatives, has shown that additives are not causal of ADHD – although they may have a small effect on the behaviour of all children, independent of any psychiatric morbidity.[3,4] Consequently, avoiding additives is not part of ADHD treatment.[5]

RED research – which involves changing the patient's diet completely and eliminating a wide range of foods – has shown that a five-week RED may have an impressive beneficial effect on the behaviour of children with ADHD and ODD.[6–13]

Double-blind RED trials

The effects of an RED on ADHD have been investigated in five independently conducted randomised controlled trials, using a double-blind, placebo controlled design (see Table 1)[6–10] – a meta-analysis of which resulted in an overall effect size of 0.9 (range 0.6–1.1).[14,15] (For comparison, the average effect size of methylphenidate is 0.6–0.9.)[16,17] All five studies have shown that an RED may result in statistically significant and clinically relevant beneficial effects on ADHD, which are – taking the double-blind, placebo controlled design into account – not attributable to parental expectations or improvement of parenting abilities.

A restricted diet, like behavioural therapy, is very difficult to blind

It may be obvious that a restricted diet, like behavioural therapy, is very difficult to blind. Consequently, to conceal the treatment conditions and secure the blinding, some dietary sacrifices had to be made. For instance, to prevent jeopardising the double-blind conditions in two of five studies using a placebo versus verum design, the placebo diet had to be restricted as well, while the verum diet could not be restricted as much as optimally desired.[7,10] Despite the unfavourable conditions, these studies resulted in an effect size of 0.6 (see Table 2). Three of five studies used a double-blind, placebo controlled challenge design: following an open RED (to identify the diet responders) and an open challenge period (to identify the incriminated foods), a double-blind, placebo controlled challenge was

performed using foods suitable for blinding.[6,8,9] Considering that only small amounts of foods can be blinded, the dose of challenged foods had to be limited. Nevertheless, these studies demonstrated an effect size of 1.1 (see Table 2), resulting in inclusion of RED research in an algorithm for treatment of ADHD.[18]

Randomised controlled RED trials

To date, additional randomised controlled trials investigating the effect of an RED in randomly assigned, heterogeneous groups of children with ADHD have been conducted, with the aim of defining the effect size of an optimal RED on ADHD[11–13] and ODD[12,13] in an open design. Considering the limitations of the double-blind, placebo controlled design – as described above – and the evidence already available (where double-blind, placebo controlled randomised controlled trials[6–10] resulted in effect sizes comparable with, or exceeding the effect size of, methylphenidate, and the open findings of parents were convincingly corroborated in a double-blind, placebo controlled design[6,8,9]), the choice for an open design is legitimate. The open randomised controlled trials resulted in an effect size of 1.8 (see Table 2), and the parent measurements were confirmed by those of teachers[11–13] and blinded paediatricians[13] – thus strengthening the previous study results in heterogeneous groups of children with ADHD.

Additionally, in two out of three studies, the effect of an RED on ODD was investigated,[12,13] demonstrating impressive effects on ODD as well. Following the RED, 60% of children with ADHD and ODD did not meet the criteria for those conditions anymore; according to parents', teachers' and the blinded paediatrician's measurements, they displayed 'normal' behaviour instead.

Disregarding of RED research

Unfortunately, although RED research 1) goes back to 1985,[6] 2) has from the first study been shown to be a very promising ADHD intervention approach, 3) has been published in well-known journals[6–13] and 4) has shown an average effect size exceeding that of medication,[14] many scientists and physicians are taken by surprise when confronted with the evidence. This may be due to the predominant disregarding of RED trials in review articles analysing the current literature concerning the treatment of children with ADHD;[16,19,20] quite a few authors discussing the connection between food and ADHD seem to have missed the RED studies, mentioning the most recent Dutch open randomised controlled trial only,[21] or erroneously referring to additive studies to underline that there is no connection between food and ADHD.[16,19,20,22]

It is unfortunate that the RED studies have not received wider recognition.

Table 2. Effect size per randomised controlled RED study design[14]

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

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 – that is, the weighted average ES of the open design studies (see Table 1[11–13]), including 86 children (21+15+50) = 1.26*21/86+2.35*15/86+1.82*50/86 = 1.78. The average ES of all studies (n=8) is 1.2; DB = double-blind; DBPCFC = double-blind, placebo controlled food challenge; ES = effect size

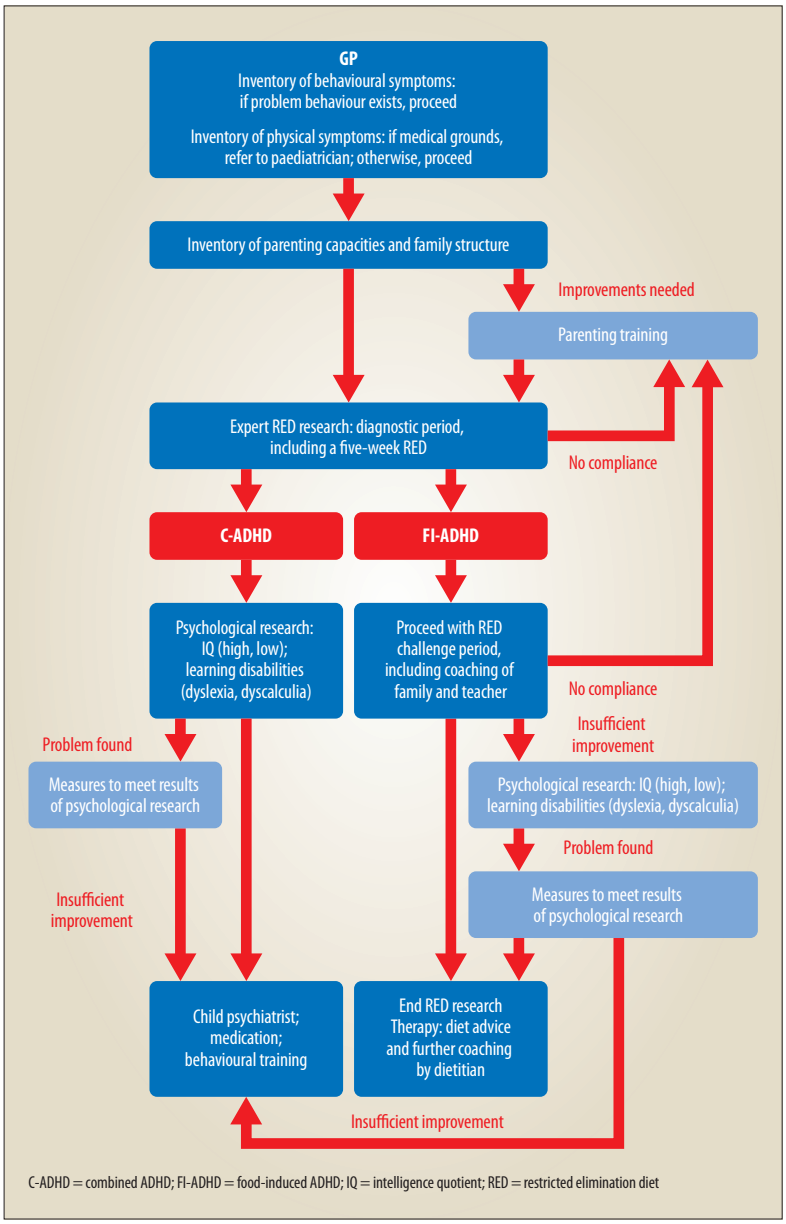


Figure 1. Algorithm for multimodal diagnosis and treatment of ADHD[14]

Conclusions

Research results provide convincing evidence for a statistically significant and clinically relevant effect of an RED on ADHD and comorbid ODD, with an

overall effect size on ADHD of 1.2 (see Table 1). Taking these results into account, and considering the limitations of the current approach to ADHD treatment (where the long-term effects of medication have been shown to be disappointing: 50% of children discontinue their medication within a two-year period, 75% still suffer from ADHD in adolescence and adulthood, and those with comorbid ODD have a worse prognosis),[1,2,23,24] a paradigm shift concerning the diagnosis and treatment of ADHD is timely, and implementation of RED research in children with parents motivated to follow a five-week RED is warranted. Interventions that may lessen ADHD symptoms and ODD have clinical potential, and RED research implementation may provide such an opportunity.

Furthermore, incorporation of RED research into the chapters on ADHD and ODD in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) is warranted, so that the definition includes a reference to a trigger in a manner that is commensurable with other DSM-5 diagnoses with similar motivations (for example, substance-induced delirium, alcohol-related disorders and cocaine-induced disorders).

Children with ADHD who respond favourably to a five-week RED may be diagnosed with food-induced ADHD (FI-ADHD) symptoms; in these cases, ADHD may be considered both a psychiatric disorder and a hypersensitivity disorder triggered by certain foods. These children are advised to enter an RED challenge period to identify the incriminated foods, eventually resulting in as wide-ranging a diet as possible.

Children with ADHD who do not respond favourably to an RED may be diagnosed with classic ADHD symptoms, and may start treatment as usual, including medication.

New algorithm and further research

In 2001, RED research was included in a basic algorithm for treatment of ADHD,[18] based on the favourable results of the randomised controlled trials into REDs that were available at that time. This algorithm has never been put into effect. Now, ten years later, additional randomised controlled trials investigating REDs have been performed, confirming and strengthening the previous study results in randomised groups of children with ADHD and ODD, thus warranting a revised algorithm for multimodal diagnosis and treatment of ADHD (see Figure 1).[14] Further research in the area is imperative, to define the mechanism of food in children with FI-ADHD symptoms and the long-term effects of an RED ■

Declaration of interest
The author is franchiser of the ADHD Research Centre.

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Key points

- In children with attention deficit hyperactivity disorder (ADHD), a five-week restricted elimination diet (RED) may result in significant improvement of the child's behaviour, both at home and school. In RED responders, ADHD may be considered both a psychiatric and hypersensitivity disorder, with symptoms triggered by everyday foods.
- RED research results are applicable to the general paediatric ADHD population, as long as parents are motivated to follow an RED and expert supervision is available.
- Children diagnosed with food-induced ADHD symptoms following an RED should engage in follow-up to establish the incriminated foods; those with classic ADHD symptoms should start treatment as usual.
- Findings from RED research need to be implemented and incorporated into the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* and further research into the mechanisms of food in ADHD is warranted.