

# Iron supplementation for breath-holding attacks in children (Review)

Zehetner AA, Orr N, Buckmaster A, Williams K, Wheeler DM



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[Intervention Review]

# Iron supplementation for breath-holding attacks in children

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**Editorial group:** Cochrane Developmental, Psychosocial and Learning Problems Group.

**Publication status and date:** Edited (no change to conclusions), comment added to review, published in Issue 7, 2010.

**Review content assessed as up-to-date:** 14 October 2009.

**Citation:** Zehetner AA, Orr N, Buckmaster A, Williams K, Wheeler DM. Iron supplementation for breath-holding attacks in children. *Cochrane Database of Systematic Reviews* 2010, Issue 5. Art. No.: CD008132. DOI: 10.1002/14651858.CD008132.pub2.

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## ABSTRACT

### Background

Breath-holding attacks are common during childhood. Iron supplementation has been claimed to reduce the frequency or severity, or both, of breath-holding attacks in children.

### Objectives

To assess the effect of iron supplementation on the frequency and severity of breath-holding attacks in children.

### Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE, PsycINFO, CINAHL and the metaRegister of Controlled Trials (up to April 2009). We scanned references of included trials. Pharmaceutical companies manufacturing oral iron supplements and some trial authors were contacted for any unpublished data or trials.

### Selection criteria

Randomised and quasi-randomised controlled trials comparing iron supplementation with placebo or no therapy in children < 18 years with recurrent (more than three) breath-holding episodes. These were reported by an observer.

### Data collection and analysis

The primary outcome was reduction in the frequency (number over time) or severity (leading to cessation of loss of consciousness or convulsive movements), or both, of breath-holding attacks. Two authors (AZ and NO) independently selected studies and extracted data. Study authors were contacted for missing data, where necessary. Risk of bias was assessed using domain-based evaluation. In the presence of low heterogeneity, a fixed-effect meta-analysis was performed with pooled results presented as odds ratios (OR) and 95% confidence intervals (CIs).

### Main results

Two trials (87 children) fulfilled the inclusion criteria. In these trials, iron supplementation significantly reduced the frequency of breath-holding attacks in children (OR 76.48; 95% CI 15.65 to 373.72;  $P < 0.00001$ ). A meta-analysis that solely examined iron supplementation causing complete resolution of breath-holding attacks maintained this significance (OR 53.43; 95% CI 6.57 to 434.57;  $P = 0.0002$ ).

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Iron supplementation for breath-holding attacks in children (Review)

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## Authors' conclusions

Iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks. Supplementation is of particular benefit in children with iron deficiency anaemia, responses correlating with the improvements in haemoglobin values. Iron may still be of assistance in children who are not anaemic or who have low, normal haemoglobin levels. Further high-quality randomised control trials of iron supplementation to treat breath-holding attacks in children are required.

## PLAIN LANGUAGE SUMMARY

### Iron supplementation for the treatment of breath-holding attacks in children

Iron may reduce the frequency and severity of breath-holding attacks (or spells) in children but more research is needed to determine the extent of this effect. Breath-holding attacks are a common disabling phenomenon during early childhood. They are distinct from seizures and it is common for them to spontaneously resolve by the time the child reaches seven years of age. This review of controlled clinical trials found that iron supplementation, which is generally well tolerated orally, may reduce the frequency and severity of breath-holding attacks, particularly if the child is anaemic. It is not known if this benefit is sustained after three months or if iron therapy should be continued until the child grows out of the breath-holding episodes.

## BACKGROUND

### Description of the condition

*"There is a disease. . . in children from anger or grief, when the spirits are much stirred and run from the heart to the diaphragms forceably, and hinder or stop the breath. . . but when the passion ceaseth, this symptom ceaseth"* (Culpeper 1651).

Breath-holding attacks (BHA) are paroxysmal events affecting approximately 5% of healthy children. Breath-holding attacks are also called breath-holding spells by some. Two clinical forms of BHA have been delineated; these are cyanotic and pallid BHA. Diagnosis is based on a distinctive and stereotyped sequence of clinical events that begin with a provocation resulting in crying or emotional upset. This leads to a noiseless state of expiration accompanied by colour change and ultimately loss of consciousness and changes in postural tone (Lombroso 1967; DiMario 1992). Severe breath-holding attacks are defined as those attacks resulting in loss of consciousness or 'convulsions' (convulsive movements), or both (Linder 1968; DiMario 1992; DiMario 1999).

Breath-holding attacks occur in specific circumstances, thus they are reproducible, and rarely occur when seated or lying. Sympathetic nervous system activation (the 'fight-or-flight' response) may occur resulting in the child sweating and becoming pale, taking on an almost 'deathly' appearance (a pallid breath-holding attack) or becoming blue in the face and lips (a cyanotic breath-holding attack). Should the attack continue, loss of consciousness

may result from a fall in cerebral blood flow. This may be accompanied by sinus bradycardia (slow heart rate) and a period of asystole (a pause in heart beats) on the electrocardiograph (ECG). The child falls to the ground (and may later recall this). Tonic-clonic (jerking) movements secondary to hypoxia may occur for up to 30 seconds duration in up to 15% of children with breath-holding attacks (DiMario 2001). The brainstem is electrically silent during the episode (Aicardi 1998). The electroencephalogram (EEG) is usually normal between episodes and anticonvulsants are neither indicated (Mocan 1999) nor effective (Stephenson 1978). The period of confusion following the event is short, typically less than 30 seconds. Breath-holding attacks usually do not last more than one to three minutes in total and only occur when the child is awake.

The majority of children with breath-holding attacks have multiple episodes per week; as many as two thirds have two to five attacks per day (Lombroso 1967). Attacks often spontaneously cease without any medical treatment by seven to eight years of age (Tam 1997), with most remitting between three and four years of age.

Breath-holding episodes can be confused with apnoeas (cessation of breathing) or seizures. Apnoeas can occur anytime while awake or asleep and are associated with the premature neonate. Breath-holding attacks only occur during wakefulness, the infant is generally older (aged from six months) and the episodes occur as a predictable response to an unpleasant stimulus or situation. Epileptic seizures, like apnoeas, may occur spontaneously in any situation,

including during sleep. Generalised tonic-clonic seizures usually begin with a cry or moan followed by stiffening of all limbs with superimposed jerking, often lasting more than one minute. There may be cyanosis (rather than pallor), dribbling of saliva and tongue biting. The period of confusion following an epileptic seizure typically lasts more than two minutes. The EEG displays widespread cortical electrical activity (Somerville 2007).

Although a clinical distinction between pallid and cyanotic breath-holders has been made (Lombroso 1967), it has never been clear whether a different underlying mechanism exists to cause these two different appearances in colour of the child's face. Both types of attacks have been described as occurring in the same family and within the same individual. A long-held belief has been that the clinical appearance of the breath-holding attack reflected the underlying pathophysiological mechanism (Gastaut 1958; Lombroso 1967; Stephenson 1980). Pallid attacks reflected predominantly parasympathetic nervous system-mediated cardiac inhibition (bradycardia), whilst cyanotic attacks were thought to be predominantly due to intense sympathetic nervous system-mediated respiratory inhibition. Respiratory sinus arrhythmia, an indirect measure of parasympathetic (vagal) tone, and a prolonged asystole ( $\leq 1$  to 2 seconds) occur in both pallid and cyanotic breath-holding attacks. Although these have been reported to occur more often in pallid breath-holding attacks, the results have not been statistically significant (Kolkiran 2005). In a case report by Tam and Rash (Tam 1997), an infant was described as having cyanotic breath-holding attacks but was noted to have pallor with loss of consciousness. In breath-holders, various combinations of sudden apnoea, bradycardia, asystole and cerebral ischaemia may produce various clinical 'types' (pallid, cyanotic or mixed) of breath-holding attacks. No specific clinical sign has been found to be pathognomonic for the type of breath-holding attack. No significant differences in clinical follow-up data have been observed between breath-holders with predominantly cyanotic or pallid attacks. The approximate ratio of cyanotic to pallid and to both has emerged as a 5: 3: 2 ratio fairly consistently (DiMario 2001). More importantly, the presence of iron deficiency significantly prolongs the duration of asystole during breath-holding attacks regardless of type (Kolkiran 2005).

Some centres report a prevalence of simple or 'benign' breath-holding attacks (that is those attacks occurring without loss of consciousness or jerking movements) that is as high as 27% of well children (Bridge 1943; Colina 1995; Daoud 1997). This high value may be accounted for by the inclusion of other behavioural phenomenon, such as temper tantrums. Severe breath-holding attacks of either pallid or cyanotic type occur in approximately 0.1% to 4.6% of healthy children (DiMario 1992). There is no gender difference. The youngest case reported in the literature is a 3-day old infant with positive family history (Breukels 2002), whereas the oldest reported case involved a patient 11 years and 8 months old (Low 1955). Breath-holding attacks are most common in children aged 6 months to 6 years, with 76% of cases occurring be-

tween 6 and 18 months of age (Zubcevic 2000). Since breath-holding attacks rarely occur outside the range of six months to six years, an alternate diagnosis should be sought and considered for children outside this age group before an attack is labelled as such. A prospective cohort study (DiMario 2001) recorded a weekly median frequency of breath-holding attacks, with 30% of children experiencing one or more attacks per day.

Between 20% and 30% of children have an affected family member (Lombroso 1967; DiMario 1990), suggesting a genetic contribution, with equal frequency distributed between paternal and maternal sides. DiMario and Sarfarazi demonstrated a low-penetrance autosomal trait (DiMario 1997; DiMario 1997a) meaning that whilst breath-holding attacks tend to occur in children with a positive family history, more often than not, this is not always the case. Family structure and mother's attitude do not seem to have an effect on the development of breath-holding attacks (Hannon 1997).

If a treatment reduced the severity or frequency of breath-holding attacks and in turn improved the child's quality of life and reduced parental stress, this would be clinically beneficial. Issues of cost, administration and possible adverse effects of the treatment need to be considered.

Children who have had breath-holding attacks have a higher incidence of syncope as adolescents than the rest of the population (Zubcevic 2000).

## Description of the intervention

The pathophysiologic mechanism and the treatment of breath-holding attacks remain controversial and unclear (DiMario 1992; Colina 1995). Autonomic nervous system dysfunction appears to play a role in the development of breath-holding attacks (DiMario 1990). Autonomic dysregulation that results in vagally mediated cardiac arrest and subsequent cerebral anoxia has been proposed (Holowach 1963; Daoud 1997).

Anaemia has been suggested to exacerbate the likelihood of breath-holding episodes because the lower haemoglobin results in more rapid cerebral anoxia, secondary to decreased oxygen-carrying capacity (Holowach 1963; Colina 1995). Also, iron-deficient children are more irritable, which increases the likelihood of an attack (Colina 1995).

First reports of an association between breath-holding episodes and anaemia came from a retrospective study (Holowach 1963). In that population, the lower the haemoglobin at onset of breath-holding episodes the more likely the patient was to respond to iron supplementation, with several children free of attacks after the anaemia was treated (Holowach 1963). From this study it was unclear whether the iron therapy or simply the resolution of the anaemia resulted in the cessation of the breath-holding attacks. However, one case study (Tam 1997) showed that breath-holding attacks improved with iron supplementation before the resolution

of anaemia. This suggests that iron deficiency, with or without anaemia per se, is implicated in breath-holding attacks.

In 2003, the United Nations Children's Fund (UNICEF) estimated that 40% to 50% of children under five years of age in developing countries were iron deficient (United Nations Children's Fund 2003). Children aged less than two years in metropolitan areas of developed countries have a prevalence of iron deficiency of approximately 7% (Karr 1996), with higher rates in indigenous populations. The diagnosis of iron deficiency in children is problematic, with no single laboratory test having sufficient sensitivity and specificity to be used as the sole diagnostic criterion. Whilst the use of multiple tests of iron status (transferrin saturation, red cell protoporphyrin, serum ferritin) improved the ability to identify children with iron deficiency, some children were still missed (Cook 1976). Furthermore, reference ranges for red cell indices, serum ferritin and iron saturation vary with age. Intercurrent infection also affects the laboratory parameters used to diagnose iron deficiency, for example reduced serum haemoglobin or raised ferritin levels. The 'gold standard' for assessment of iron stores in adults, bone marrow examination, is less useful in children given that the majority of normal children have minimal iron stores until adolescence. Erythrocyte indices such as hypochromicity, microcytosis and reticulocyte count offer more practical investigations with treatment (Grant 2007). Soluble transferrin receptor levels may improve the diagnosis of anaemia in settings with high burdens of infectious diseases and iron deficiency (Richie 2004). Alternatively, an increase in haemoglobin of more than 10 g/L after one-month treatment with 3 mg/kg/day of elemental iron is indicative of iron deficiency (Osiki 1993).

Two prospective studies (Donma 1998; Azam 2008) of the drug piracetam, a cyclic derivative of gamma-aminobutyric acid (GABA) and pharmacologically unrelated to iron, suggest that this may be an effective prophylactic treatment for severe breath-holding attacks in children without anaemia (Garg 1998). However, in comparison to iron this drug is relatively new, more expensive, has little data for use in children and may cause side-effects such as agitation. It requires cautious use in the presence of renal impairment. For these reasons, and until more is known about the drug, it will not be considered in this review.

Implantable cardiac pacemakers have been used to treat some cases of severe, prolonged breath-holding attacks associated with life-threatening bradycardia or asystole (Kelly 2001). This small, select group of children who were aged one to five years have been trialled on anticonvulsant, anticholinergic and theophylline medications to try to prevent breath-holding attacks, all without success (iron was not used). The pacemakers reduced the severity of the attacks but the onset of breath-holding attacks was not completely prevented. If a simple, readily obtainable, inexpensive and non-invasive treatment option for breath-holding attacks was available to these children, clearly this would be preferable. Oral iron supplementation fulfils these criteria and has been suggested as a means of reducing the onset and frequency of breath-holding attacks (which

were not completely prevented by implantable cardiac pacemakers), making it an exciting treatment modality worthy of further study.

## How the intervention might work

It is not known whether, or if so how, iron deficiency leads to breath-holding attacks. Iron deficiency anaemia may lead to adverse effects on oxygen uptake in the lungs and so reduce available oxygen to the tissues, including central nervous system tissue (Samuels 1991; Poets 1992). Not all children with breath-holding attacks are iron deficient at baseline (Daoud 1997; Mocan 1999). The majority of studies classify children as being iron deficient on the basis of low haematological indices such as haemoglobin, serum transferrin, mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV) without any evidence of bone marrow failure. Values below the normal range signify iron deficiency anaemia. It is unclear why iron-replete children may respond to iron therapy for breath-holding attacks.

It is possible that iron supplementation maximises neurotransmitter synthesis and function. Iron has a role in catecholamine metabolism and the functioning of enzymes and neurotransmitters in the central nervous system (Osiki 1978). The resolution of attacks during treatment with iron may be related to the functional restoration of these neurotransmitters.

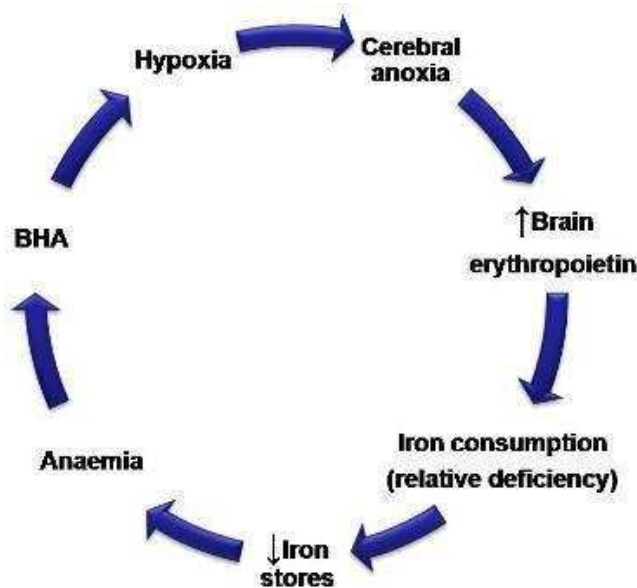
The role of iron in the maintenance of a functional nervous system has been studied by a variety of investigators. One study (Voorhess 1975) found increased urinary excretion of adrenaline as a result of reduced monoamine oxidase activity in patients with iron-deficiency anaemia. The activity of aldehyde oxidase, a key enzyme in serotonin degradation, was also noted to be reduced with iron deficiency (Mackler 1978). Iron plays an important role as a cofactor in neurotransmitter synthesis and nerve myelination (Connor 1994). Iron-deficiency anaemia therefore appears to affect neurologic function.

It has been hypothesised that the clinical and haematological picture of breath-holding attacks relates to the interactions of cerebral erythropoietin (EPO), nitric oxide and interleukin-1 (Masuda 1994; Mocan 1998). It has been suggested that "increased brain erythropoietin production has a protective effect during breath-holding attacks, but where this does not compensate for the severity of anoxic attacks, tonic-clonic movements may develop" (Mocan 1999). In addition, it has been postulated that the enhanced erythropoiesis resulting from increased EPO secretion during hypoxia can also induce at least a temporary state of iron-deficient erythropoiesis in iron-replete patients (Mocan 1998).

The inter-relatedness of breath-holding attacks and iron deficiency anaemia is proposed in the following cycle (Figure 1). Repeated breath-holding attacks cause episodes of hypoxia, including cerebral anoxia. Short-lived tonic-clonic movements of the limbs may occur as a result of the cerebral anoxia. A further and protective response to cerebral anoxia is for brain EPO production to increase.

As iron is consumed in erythropoiesis, a relative deficiency of iron stores occurs. Over time the child may become anaemic and exhibit behavioural 'irritability', leading to further breath-holding attacks. This theory may also explain why breath-holding attacks occur in non-anaemic children, as there is a relative deficiency of iron stores and distribution rather than a depletion of the total amount of body iron.

**Figure 1. Postulated cycle of iron-deficiency anaemia and breath-holding attacks.**



Iron deficiency has also been associated with a variety of neurologic and behavioural manifestations, including pseudotumor cerebri, papilloedema, syncope, cranial neuropathy and decreased intellectual function (Oski 1979; Bruggers 1990). Iron deficiency with or without anaemia per se may adversely affect autonomic nervous function.

### Why it is important to do this review

Breath-holding attacks are a common ailment of childhood. Although it is a self-resolving condition, the attacks are stressful for the parents and carers and provoke frequent presentation to primary healthcare facilities and emergency departments when associated with tonic-clonic movements. Iron therapy is a relatively low-cost and freely available treatment that is believed to assist in reducing this condition without causing unacceptable adverse drug effects. Although a few trials have shown promising results, results from individual trials have varied. A systematic review of

iron use for breath-holding attacks brings together existing evidence to assess whether there is sufficient information to recommend this therapy as an effective treatment (Zehetner 2010).

### OBJECTIVES

To assess the effect of iron supplementation on the frequency and severity of breath-holding attacks in children.

### METHODS

#### Criteria for considering studies for this review

## Types of studies

Randomised and quasi-randomised controlled trials.

## Types of participants

Children aged 0 to 18 years with recurrent (more than three) episodes of breath holding reported by an observer (usually a parent, care-giver or clinician).

## Types of interventions

Iron supplementation versus no therapy or placebo.

## Types of outcome measures

### Primary outcomes

Reduction in the frequency (number over time) or severity (leading to cessation of loss of consciousness or reduced convulsive movements), or both, of breath-holding attacks.

### Timing of outcome assessment

Outcomes were examined post-intervention (immediately and up to one month) and as short-term (one to three months), medium-term (three to six months) and long-term (six to 12 months or longer) outcomes, where data were available.

### Secondary outcomes

The following outcomes were considered and examined, if data were available.

- Adverse effects of intervention (eg gastrointestinal upset and dark stools with oral iron therapy).
- Number of admissions or presentations for medical care.
- Days of school missed.
- Days of work missed (parents).
- Quality of life measures (using a standardised, validated instrument).
- Parental stress and attitudes (reported on a standardised, validated measurement scale).
- Costs.

## Search methods for identification of studies

### Electronic searches

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2); MEDLINE (1950 to April 2009); EMBASE (1980 to 2009 week 14); PsycINFO (1806 to April 2009); CINAHL (1982 to April 2009) and the metaRegister of Controlled Trials (April 2009). The search strategies can be found in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5 and Appendix 6.

No language or date restrictions were applied to the searches. No randomised controlled trial (RCT) filter was used as it was felt that the inclusion of a filter may lead to relevant references being missed.

Reference lists of all reviews and summary articles identified by our search were examined to identify any additional trials.

Two of the authors (NO and AZ) wrote to known content experts and to pharmaceutical companies involved in producing iron supplementation products for use in children to ascertain if any unpublished studies relating to the use of iron supplementation for breath-holding attacks exist.

## Data collection and analysis

### Selection of studies

The titles and abstracts of all studies identified by the search strategy were reviewed independently by two authors (AZ and NO) to determine suitability for inclusion. Where there was insufficient information to make a decision, the full text of the articles was reviewed. Any disagreements were resolved by consensus and arbitration by a third author (AB or KW). Justification for exclusion of studies was documented (see [Characteristics of excluded studies](#) section).

### Data extraction and management

Data from included studies was extracted independently by two review authors (AZ and NO) using a pre-determined standardised form. The following data were extracted.

- Characteristics of trials - publication status, year, country of study, funding, setting, design, inclusion and exclusion criteria, recruitment, methods, analysis and results



(Continued)

• Study methods - method of allocation, blinding and losses after randomisation (follow-up losses and dropouts)
• Characteristics of participants - study population, number of participants in each treatment group, age, gender, nationality and diagnostic criteria
• Characteristics of interventions - preparation used, dose, length of treatment and follow up, compliance, co-interventions and intervention used in control group
• Outcomes - symptom score, change in clinical, laboratory or radiological findings, complications and adverse events, dropouts etc.
• Length of follow up

### Assessment of risk of bias in included studies

Two authors (AZ and NO) independently assessed, without blinding to authorship or source, each included study using the risk of bias criteria outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). The assessments were compared to identify inconsistencies. Any differences in interpretation were resolved by discussion with a third author (AB or KW) and consensus reached. Risk of bias was assessed according to the following five domains, with ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias).

#### 1. Sequence generation

Was the allocation sequence adequately generated?

'Yes' (computer-generated random numbers, table of random numbers, coin tossing or similar); 'No' (day of week, even and odd clinic record numbers, clinician judgment, participant preference, laboratory test result such as haemoglobin level or similar); or 'Unclear' (insufficient information about the sequence generation process to permit judgment).

#### 2. Allocation concealment

Was allocation adequately concealed?

'Yes' (central independent unit, sequentially numbered drug containers or sealed envelopes of identical appearance, or similar); 'No' (alternation or rotation, date of birth, non-opaque envelopes, open table of random numbers or similar); or 'Unclear' (randomisation stated but no information on method used available).

#### 3. Blinding

Was knowledge of the allocated intervention adequately prevented during the study?

'Yes' (iron (intervention) and identical placebo (control) medication or similar); 'No' (tablets versus liquid or similar); or 'Unclear' (blinding stated but no information on method used available).

#### 4. Incomplete outcome data

Were incomplete data dealt with adequately by the researchers?

'Yes' (no missing outcome data, missing outcome data balanced in numbers across intervention groups, reasons for dropouts and withdrawals described or similar); 'No' (reason for missing outcome data likely to be related to true outcome or similar); or 'Unclear' (number of or reasons for dropouts and withdrawals not described).

#### 5. Selective outcome reporting

Were reports of the studies free of suggestion of selective outcome reporting?

'Yes' (study protocol available, published reports included all expected outcomes of frequency (number over time) or severity (loss of consciousness or convulsive movements) of breath-holding attacks or similar); 'No' (not all of the study's pre-specified primary outcomes were reported, one or more reported primary outcomes were not pre-specified or similar); or 'Unclear' (insufficient information to permit judgement of 'adequate' or 'inadequate').

Any other potential sources of bias (stopping the study early, extreme baseline imbalance or some other problem) were also explored.

### Measures of treatment effect

#### Binary data

For dichotomous outcomes (complete cessation of breath-holding attacks or no effect at all) the number of participants and incidence of events were recorded in each group of the trial. The risk of the outcome in the intervention group compared to the control group was expressed as an odds ratio (OR) with 95% confidence interval (CI).

### Continuous data

Where continuous scales of measurement were used to assess the effects of treatment (such as rate or degree of severity, as measured on a qualitative scale, of breath-holding episodes) we intended to make comparisons between the means of these scores. Where possible, the mean difference (MD) was to be calculated as the summary statistic in meta-analyses, with standardised mean difference (SMD) used if different scales or measures were used for the same outcome construct. Either final levels or changes in levels would be included in meta-analyses of continuous scales of measurement. When both measures were provided in a study, final levels would be included unless there was an important baseline difference between groups with regard to the outcome measure of interest. Where some studies reported data as change and others only reported final data, with SDs, these were to be plotted in separate subgroups in the meta-analyses.

As the two trials which were eligible to be included for this review reported their outcomes as binary data, our continuous data protocol was not used on this occasion.

### Unit of analysis issues

In order to preserve the effects of randomisation and obtain the practical impact of a treatment, we were to extract data according to the intention-to-treat principle and perform intention-to-treat analyses, where possible.

All included trials were assessed to determine the unit of randomisation and whether this unit was consistent with the unit of analysis. If cluster randomisation had occurred, an interclass correlation co-efficient (ICC) would have been extracted and used to modify the results. Where no ICC was given and a unit of analysis error appeared to exist, trial authors were to have been contacted and asked to provide an ICC or raw data to enable calculation of an ICC. Where no ICC was made available, we would have searched for similar studies from which an ICC could be imputed and apply a sensitivity analysis using a range of ICCs to assess the impact on treatment effect.

Where cross-over trials were found, means and standard errors of paired t-tests were to have been extracted and included in the meta-analyses using the generic inverse variance function.

The eligible papers for this review did not involve cluster randomisation or cross-over trials.

### Dealing with missing data

Where possible, authors of the included studies were contacted to obtain any missing data. Where missing data could not be obtained, we attempted a 'worst-case' 'best-case' sensitivity analysis (performed for binary data only).

### Assessment of heterogeneity

Since clinical and methodological diversity always occur in a meta-analysis, it is argued that statistical heterogeneity is inevitable (Higgins 2009). The  $I^2$  statistic has been developed to quantify inconsistency across studies with values increasing from zero to 100%, with higher values representing greater degrees of heterogeneity (Higgins 2009).

Clinical heterogeneity was assessed and agreed on by the review authors, based on the study participants, interventions and outcomes being sufficiently similar to warrant meta-analysis. The two trials which met the inclusion criteria for this review were very similar in their clinical and methodological characteristics; they used a similar baseline population, intervention and outcome criteria. We also examined the overlapping cut-off points for the study groups' confidence intervals (CIs) and visually inspected the forest plots as a further assessment of heterogeneity. We estimated heterogeneity to be extremely low ( $I^2 = 0$ ).

### Assessment of reporting biases

A sufficient number of studies was not found to perform assessment of reporting biases. Every attempt was made to obtain unpublished data and data from conference proceedings.

If a sufficient number of studies had been found, we would have drawn funnel plots to investigate any relationship between effect size and study precision (closely related to sample size). Such a relationship could be due to publication or related biases or due to systematic differences between small and large studies. If such a relationship was identified, clinical diversity of the studies would be further examined as a possible explanation (see also Egger 1997).

### Data synthesis

When two or more studies were suitable for inclusion, and those studies were considered to be sufficiently similar in their clinical and methodological characteristics, a meta-analysis was performed on the results. Both fixed-effect and random-effects analyses were performed as part of a sensitivity analysis.

For study results where the intervention was compared to different comparison groups (for example placebo, other drug intervention) we would have presented these comparisons separately. The studies which met the inclusion criteria for this review used similar comparators.

### Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be undertaken when clinically different interventions were identified or when there were clinically relevant differences between participant groups.

These clinical differences may include:

- dosage of intervention (iron);
- iron deficient or replete populations;
- age of participants;
- gender.

The two trials which met the inclusion criteria for this review were very similar in their clinical and methodological characteristics and were of low heterogeneity ( $I^2 = 0$ ). Both used a similar baseline population, intervention and outcome criteria.

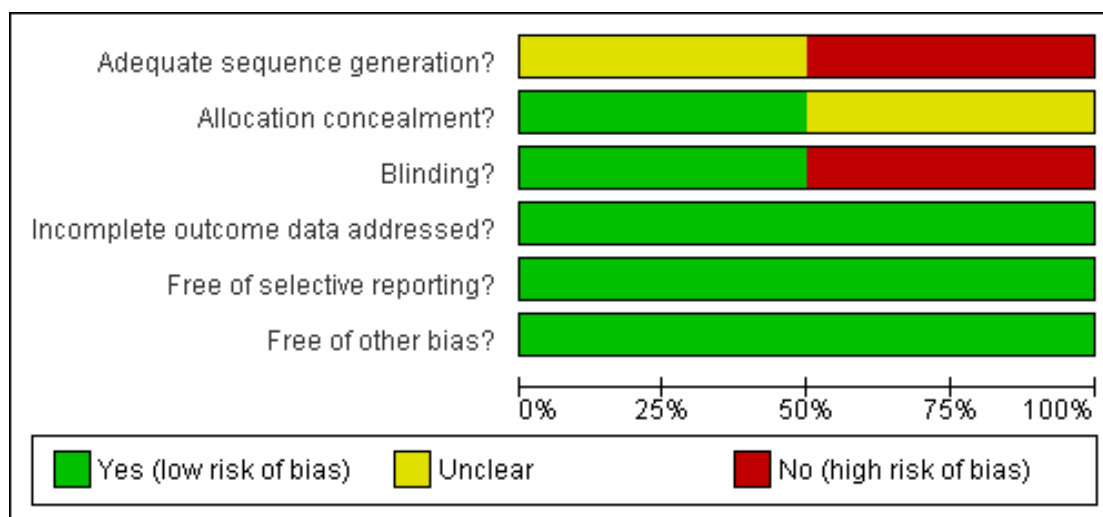
No additional data were received for us to conduct our own subgroup analysis, after attempting to contact each paper's authors.

### Sensitivity analysis

Sensitivity analysis was considered in order to assess the impact of risk of bias on the results of the meta-analyses. However, there were only two trials that met the inclusion criteria for this review. Both had no losses to follow up. We therefore did not test whether trials with high risk of bias, in particular high rates of loss to follow up, were more likely to show positive outcomes.

Methodological parameters impacting on risk of bias were assessed (Figure 2, Figure 3).

**Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**



**Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Daoud 1997	-	+	+	+	+	+
Paul 1969	?	?	-	+	+	+

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The two studies found were from the Middle East and the Indian subcontinent. See the tables [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### Results of the search

Our literature search yielded 41 articles. These were filtered to exclude 24 papers that were not relevant to clinical practice, breath-holding per se or children, leaving 17 papers pertaining to iron treatment for breath-holding attacks in children. The reference lists of each of these articles were reviewed to ascertain any further relevant papers. Each paper was independently critically appraised by the authors (AZ and NO). A total of six clinical studies were

found studying iron supplementation to treat breath-holding attacks in children. Applying our selection criterion of randomised controlled trials and quasi-randomised trials gave a final list of two papers (Daoud 1997; Paul 1969).

It is noted that there was insufficient information available about the Paul 1969 study to be certain whether it was eligible or ineligible for inclusion. To accurately estimate the risk of bias of the results, our decision was to include this study so that these issues could be presented and discussed.

Attempts were made to contact study authors (DiMario, Manchanda and Paul by NO) to ascertain if further unpublished papers exist. Two of the three authors replied, with no unpublished material being identified. The third (Dr Manchanda) is now deceased and no further information could be obtained regarding his paper. Pharmaceutical companies (Bayer, Sanofi-Aventis and AFT Pharmaceuticals) who manufacture oral iron preparations were contacted (by AZ) regarding unpublished trials or data. No further material was obtained.

### Included studies

See the [Characteristics of included studies](#) section for further details.

Daoud AS, Batiha A, Al-sheyyab M, Abuekteish F, Hijazi S. Effectiveness of iron therapy on breath-holding spells. *Journal of Pediatrics* 1997; 130: 547-50.

Paul R, Manchanda S. Breath-holding attacks. The role of psychological factors and iron therapy. *Indian Journal of Pediatrics* 1969; 36(259): 271-7.

### Excluded studies

See the [Characteristics of excluded studies](#) section for further details.

Ahmad Bhat M, Ali W, Mohidin K, Sultana M. Prospective study of severe breath holding spells and role of iron. *Journal of Pediatric Neurology* 2007; 5(1): 27-32.

Khalifa M, Aldoseky S, Shalaby H. Effectiveness of iron therapy on breath holding spells. *Neurosciences* 2004; 9(1): S8-S10.

Mocan H, Yildiran A, Orhan F, Erduran E. Breath holding spells in 91 children and response to treatment with iron. *Archives of Disease in Childhood* 1999; 81(3): 261-2.

Ziaullah Nawaz S, Shah S, Talaat A. Iron deficiency anemia as a cause of breath holding spells. *Journal of Postgraduate Medical Institute* 2005; 19(2): 171-4

## Risk of bias in included studies

### Randomisation

In [Daoud 1997](#), the allocation sequence was generated by alternating assignment, so the trial was quasi-randomised. Alternating assignment has the potential for bias as the sequence may be predicted and patients then allocated to groups through intention rather than randomisation. Baseline characteristics were comparable between the intervention (iron) and control (placebo) groups. There was a slightly greater degree of anaemia in the treatment group (mean haemoglobin level 89 g/L) than in the control group (mean 94 g/L) although this did not reach statistical significance ( $P = 0.07$ ). Having fewer than five attacks per month at baseline was more common in the treatment group (45%) compared with the placebo (32%) group though this difference was not significant ( $P = 0.52$ ).

[Paul 1969](#) reported that the trial population included children “picked up at random regardless of their age or sex”. Participants were then reported to be allocated to one of three groups according to their haemoglobin value. The treatment group had a haemoglobin below 10 g/dL and there were two control groups also differentiated by their haemoglobin status (below and above 10 g/dL respectively). There was no information available about the method of randomisation or the method of allocation to treatment or control groups.

### Allocation

Despite the absence of true randomisation, the allocation process in the [Daoud 1997](#) study was adequately concealed.

Whether allocation was concealed in the [Paul 1969](#) study is unknown.

### Blinding

In the [Daoud 1997](#) study both the guardian and treating physician were blinded to treatment and the solutions were provided in identical bottles. However, as iron usually leads to darker stools loss of blinding was possible for the guardians.

[Paul 1969](#) did not describe a blinding process and iron was given by intramuscular injection with no similar matched placebo in the non-intervention group. The control group was also given ‘vitamins’, so blinding would not have been possible.

### Incomplete outcome data

All patients who entered both trials were accounted for at the end ([Daoud 1997](#); [Paul 1969](#)) and there was no loss to follow up. Further, patients were analysed in the groups to which they were initially (quasi) randomised, in an intention-to-treat analysis.

### Selective reporting

The most important outcome, namely reduction of breath-holding episodes, was reported in a clinically relevant way. It was unlikely that there was selective outcome reporting. However, adverse events, which are quite common with administration of oral or intramuscular iron, were not reported so that risk benefit assessment was not possible.

### Other potential sources of bias

#### *Population and referral bias*

[Daoud 1997](#) enrolled children attending a tertiary children’s hospital in Jordan for breath-holding attacks over a three year period. This population may produce referral bias as more severely affected children are more likely to be referred, whilst milder cases of breath-holding attacks may be treated in a local, primary care setting. Before the trial was conducted, Daoud established exclusion criteria to omit children with: profound anaemia (haemoglobin < 70 g/L); a history of febrile convulsions or epilepsy; current treatment with anticonvulsant medications; a clinically identified neuromotor delay; growth parameters above or below 2 SD of standard references; and any other serious illness. All children seen were eligible for inclusion into the study. As the vast majority (67/74; 91%) of the eligible children were enrolled, the sample is felt to be representative of the population of children who had BHA and were seen at a tertiary children’s hospital. Milder cases of children with breath-holding attacks, seen in a community setting,

may never present to a tertiary children's hospital and this population was not represented here. Therefore, the applicability of the results of a tertiary children's hospital study must be considered when applied to a primary care community population.

The Paul 1969 population included children from a poor socio-economic status background in India, with one-third having a familial background of psychiatric and psychosomatic disorders. Because of the high rate of behavioural problems in addition to breath-holding attacks in the population, counselling was offered as a co-intervention and was applied across all groups. Like the Daoud 1997 study, these children attended a hospital's paediatric outpatient clinic.

### Effects of interventions

In the Daoud 1997 study, of the 33 children treated with iron 17 children had complete resolution of breath-holding attacks (BHA) and 12 displayed partial remission; iron had no effect on the frequency of breath holding in four children. Of the 34 children treated with placebo, only two had partial remission of BHAs. No child in the control group had complete remission of BHAs. Daoud 1997 found a 14-fold, significant reduction ( $P < 0.01$ ) in the frequency of BHAs (88%) in the treatment group compared with the 6% frequency in the placebo group. Iron supplementation was of particular benefit in children with BHAs who have iron deficiency anaemia, with the response being predicted by and correlating to improvements in haemoglobin values.

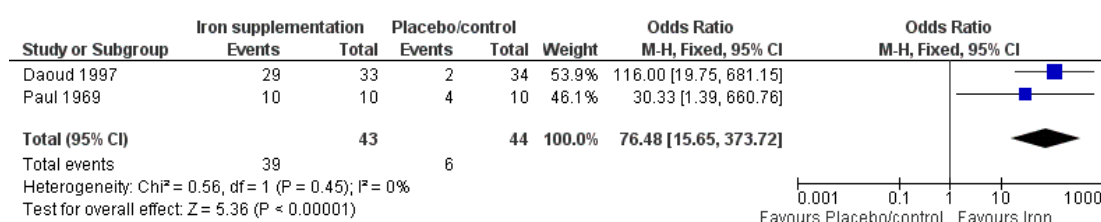
In the Paul 1969 study, all of the children treated with iron (10/

10) had complete (6) or partial (4) resolution of their BHAs. In comparison, of the 10 children in the control group none experienced complete and four had partial resolution of their BHAs. Paul 1969 also included a third group of 10 children who had a haemoglobin level  $> 10\text{g/dL}$ , were experiencing BHAs and received the control intervention (vitamins and counselling). Three children experienced complete resolution of BHAs, three partial resolution and four no effect. As this group differed from the other two studied by Paul 1969, which both have a haemoglobin level of  $< 10\text{g/dL}$ , we elected to omit this third group from our study to maintain standardised baseline population characteristics. Thus when considering Paul 1969, we used a population of 20 children with the same baseline haemoglobin level and who differed only in that one half received iron supplementation.

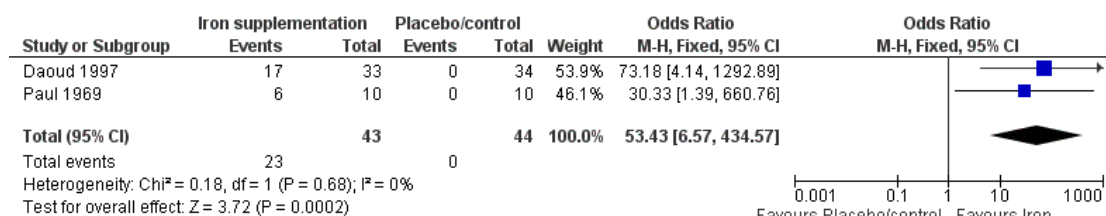
The population in Daoud 1997 had a similar baseline mean haemoglobin level (between 8.9 to 9.4 g/dL) to that of Paul 1969. Both studies used a similar outcome measure of BHA frequency: 'good' or complete cessation, 'fair' or partial cessation and 'poor' or no cessation. Daoud 1997 combined the complete and partial groups together and compared this result to the no effect result. To reduce heterogeneity between the studies we summated the 'good' and 'fair' results of the Paul 1969 study and compared this with the 'poor' result. In Daoud 1997 the intervention was conducted over 16 weeks, and it was conducted over three months in Paul 1969.

The absence of heterogeneity ( $I^2 = 0$ ) and the similar baseline populations and outcome assessment criteria used in both studies allowed us to perform meta-analyses (see Figure 4, Figure 5).

**Figure 4. Forest plot of comparison: I Iron supplementation versus placebo or control, outcome: I.I Resolution or reduction of breath-holding attacks.**



**Figure 5. Forest plot of comparison: I Iron supplementation versus placebo or control, outcome: I.2 Complete resolution of breath-holding attacks.**



Iron supplementation caused a significant reduction in the frequency of BHAs in children. Iron may either cause complete resolution (OR 53.43; 95% CI 6.57 to 434.57;  $P = 0.0002$ ) (Figure 5), or complete or partial resolution remission of BHAs (OR 76.48; 95% CI 15.65 to 373.72;  $P < 0.00001$ ) (Figure 4).

## DISCUSSION

### Summary of main results

Two trials involving 87 children fulfilled the inclusion criteria. Iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) reduced the frequency (number over time) or severity (measured as loss of consciousness or convulsive movements) of breath-holding attacks (BHAs) in children (OR 76.48; 95% CI 15.65 to 373.72;  $P < 0.00001$ ) (Figure 4).

A meta-analysis solely examining iron supplementation to cause complete resolution of breath-holding attacks maintained this significance (OR 53.43; 95% CI 6.57 to 434.57;  $P = 0.0002$ ) (Figure 5).

From the Daoud 1997 study, in particular, iron supplementation appears to be of particular benefit in children with breath-holding attacks who have iron deficiency anaemia. The response correlated with improvements in haemoglobin values.

Iron may still be of assistance in children who are not anaemic or who have low but normal haemoglobin levels.

No other outcome data (apart from complete resolution, partial remission or no effect on breath-holding attacks) was provided by these two studies.

Further high-quality randomised control trials of iron supplementation to treat breath-holding attacks in a non-iron deficient population of children are required to confidently recommend iron as an established treatment for breath-holding attacks in all children.

### Overall completeness and applicability of evidence

From our extensive search of the medical literature that was not limited by language or publication date and contacting prominent

study authors in this field as well as pharmaceutical companies that manufacture iron supplements, we feel that we have identified all of the existing relevant studies relating to the use of iron for breath-holding attacks in children.

No other outcome data apart from complete resolution, partial remission or no effect on breath-holding attacks was provided by the two included studies. No subgroup analysis or comments other than on the effect of iron supplementation on the frequency of breath-holding attacks in children can therefore be made. Future studies may aim to address areas of missing data.

Baseline characteristics of children were comparable between the intervention (iron) and control (placebo) groups in the Daoud 1997 study. There was a slightly greater degree of anaemia in the treatment group (mean Hb 89 g/L) than in the control group (mean 94 g/L) though this did not reach statistical significance ( $P = 0.07$ ). A larger proportion of children with less frequent attacks at baseline ( $< 5$  per month) was seen in the treatment group (45%) versus the placebo group (32%) though this difference was not significant ( $P = 0.52$ ).

Daoud 1997 undertook a post hoc analysis of the treatment group alone in order to identify factors that may have been associated with reduced breath-holding attacks. They found that those children who were anaemic tended to have more improvement in their breath-holding attacks than those who were not anaemic. The baseline mean haemoglobin level among those with a favourable response (complete or partial) was lower (86 g/L) than among children who responded poorly (106 g/L), and the difference was statistically significant ( $P = 0.004$ ). Total iron binding capacity at baseline was higher in children with a favourable response than in children with a poor response, and this difference was statistically significant ( $P = 0.05$ ). This information adds to the hypothesis that iron therapy for breath holding corrects an iron deficiency. However, caution is required because: the overall size of the trial was small; the number of children with a normal haemoglobin at baseline was even smaller; and the two children from the non-treatment group who had a partial response were not included in the analysis.

In Paul 1969, the control groups all received an oral vitamin sup-

plement which may have contained iron. It is unlikely that these differences could account for the positive effect of iron in this randomised controlled trial, as less frequent attacks in the treatment group (minimising the influence of regression to the mean in this group) and offering a therapy that may contain an 'effective' treatment would both tend to minimise the finding of an effect rather than creating a biased increase.

It is unclear if the intervention used was 5 mg/kg/day of ferrous sulphate or elemental iron. Ferrous sulphate contains only approximately 20% elemental iron (so the child may only have received elemental iron at a dosage of 1 mg/kg/day). However, from the increase in the haemoglobin parameters in the treated group it appears that a satisfactory dose of iron was used. Compliance with both treatments (iron or placebo) was assessed visually by the amount of solution remaining in the bottle at each clinic visit.

Paul 1969 used iron dosed according to 'Lahey's formula'. 'Lahey's formula' is  $\text{body weight (kg)} \times (13.5 - \text{Hb (g/dL)}) \times 2.5 = \text{mg elemental iron to give}$  (Lahey 1957). No haematological tests were undertaken after iron therapy to gauge a rise in iron indices though it was assumed that the dose was sufficient to do so.

No details of any adverse effects from iron therapy were provided in either study, such as allergic response (with parenteral iron) or gastrointestinal upset (with oral iron). Oral iron administration in therapeutic doses (as used in the studies) is generally well tolerated in children. As there were no adverse effects reported that necessitated the cessation of iron (an important outcome) we have inferred that iron was generally well tolerated in these studies.

In one paper (Daoud 1997) outcome measures appeared to have been objectively recorded (by a guardian record of the number of breath-holding attacks), which was then used to generate the average number of breath-holding attacks per month. The frequency was categorised into three levels of complete response (no more attacks), partial response ( $\geq 50\%$  reduction in the frequency but not complete disappearance of the attacks) and minimal or no response ( $< 50\%$  reduction in the frequency of the attacks). The first two categories (complete and partial response) were then combined and treated as one result.

Paul 1969 used a similar outcome reporting scale of 'good' (complete resolution of breath-holding attacks), 'fair' (decrease in attack frequency but not complete resolution) and 'poor' (no response to frequency of breath-holding attacks). 'Good' and 'fair' categories were not combined in the Paul 1969 study, however the original data was provided and we combined those subgroups such that the format of the outcome data was in keeping with the Daoud 1997 study.

From a meta-analysis of iron supplementation for complete resolution of breath-holding attacks versus no response, using the raw data from the Daoud 1997 and Paul 1969 trials, the significant effect of iron supplementation was maintained (Figure 5).

The expected benefit of iron is inferred to outweigh any potential risk of harm. Parenterally administered iron does not give a faster rise in haematological values in comparison to oral therapy. Oral

iron therapy is easier, more cost effective and has a safer profile than parenteral iron therapy, making it a suitable initial therapy for trial in treating breath-holding attacks. Parenteral iron treatment is usually only administered when iron deficiency is not correctable with oral treatment (in the case of intolerance or malabsorption). No studies examined children for breath-holding attacks beyond 16 weeks, nor if the beneficial effect of iron supplementation persisted after the iron therapy was ceased. Thus the optimum duration of therapy of iron therapy, how it should be withdrawn (weaned or ceased abruptly) and its duration of effect are unknown. These issues should be considered and be the focus of further trials of iron supplementation for breath-holding attacks in children.

As detailed above, Daoud 1997 may have introduced referral bias by enrolling only children attending a tertiary children's hospital. More severely affected children with breath-holding attacks are more likely to be referred to a tertiary centre. Milder cases (and the majority of children with breath-holding attacks) are instead treated in a local, primary care setting. The population of Paul 1969 included children from a poor socio-economic status background with a high rate of behavioural problems in addition to breath-holding attacks. Use of these sample populations reduces the general applicability of each trial's findings to an outpatient population of children in a developed Westernised community. Future trials conducted in this population may aim to address this.

## Quality of the evidence

After identifying all of the relevant studies examining the use of iron for breath-holding attacks in children, these studies were critically appraised to select high-quality methodological trials that were of the standard of a randomised (or quasi-randomised) controlled trial. Patient characteristics, the intervention and outcome criteria were analysed to ascertain if a high-quality meta-analysis could be formulated from the pooled data, and this was the case. When assessing the risk of bias in the Paul 1969 study many methodological details (for example allocation concealment, blinding) were not present, which reduces confidence in his study. The author was unavailable for contact as he was deceased. However, tables of raw data were listed in the Paul 1969 paper, which we have used.

Both papers have low power but each produced statistically significant, positive effects because of the large effect size of iron treatment.

## Potential biases in the review process

There were no potential biases in the review process. Nor was there any conflict of interest. Two authors (AZ and NO) independently reviewed and selected the papers for inclusion in the systematic review. There was also an independent, unanimous decision made on the selection of the excluded studies. Other authors (KW and



AB) also independently reviewed a shortlist of papers to ensure their inclusion or exclusion and readily came to the same decisions.

### Agreements and disagreements with other studies or reviews

Our systematic review is the first in the field of iron supplementation for the treatment of breath-holding attacks in children. The results of our meta-analysis are in keeping with the trends and findings from all of our included and excluded (case-series, retrospective and uncontrolled prospective) studies, however now with a significant high-quality quantifiable result.

## AUTHORS' CONCLUSIONS

### Implications for practice

Breath-holding attacks are a common, debilitating neuro-behavioural condition of childhood that provokes parental stress and presentation of the children to healthcare facilities (Zehetner 2010). As it is low cost and generally well-tolerated, iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks. This is likely to be of particular benefit in children with iron deficiency anaemia, with preliminary data showing a

trend towards greater improvement with breath-holding episodes linked to improvements in haemoglobin values. Iron may still be of assistance in children who are not anaemic or who have low but normal haemoglobin levels, but this has not yet been proven in subgroup analysis as only pooled data has been collected to date.

### Implications for research

Further high-quality randomised controlled trials of iron supplementation to treat breath-holding attacks in children are required. In particular, studies in populations of children who are not iron-deficient, seen in non-tertiary settings, live in developed communities and receive oral iron supplementation as the sole intervention (in a standardised dose of 5 mg/kg/day of elemental iron) are needed. To ascertain the treatment effect of iron in further detail, trials involving longer follow up and assessing the effect of iron cessation (after a positive response on breath-holding attacks) should be conducted.

## ACKNOWLEDGEMENTS

Geraldine Macdonald (Review Group Coordinator), Jane Dennis (former Review Group Coordinator) and Joanne Abbott (Trial Search Coordinator) at the Cochrane Developmental, Psychosocial and Learning Problems Group, School for Policy Studies, University of Bristol.

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\* Paul R, Manchanda S. Breath-holding attacks. The role of psychological factors and iron therapy. *Indian Journal of Pediatrics* 1969;**36**(259):271–7.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Daoud 1997

Methods	Quasi-randomised controlled trial
Participants	All children with breath-holding attacks from June 1992 to June 1995 attending a tertiary children's hospital in Jordan 67 children (33 treatment group, 34 placebo group) Haemoglobin > 70 g/dL Generally an anaemic population (baseline Hb 89-94 g/L) Parental consent No convulsions, growth $\pm$ 2 standard deviations, neuromotor delay
Interventions	Ferrous sulphate 5 mg/kg/day for 16 weeks (intervention) Placebo (control)
Outcomes	Complete, partial ( $\geq$ 50% reduction) or nil remission of breath-holding attacks
Notes	There was a trend for children from consanguineous parents to respond to treatment but this was not statistically significant (P = 0.07) Treatment group responders had significantly lower Hb and higher TIBC than non-responders

#### *Risk of bias*

Item	Authors' judgement	Description
Adequate sequence generation?	No	Via alternating assignment
Allocation concealment?	Yes	Stated to be "adequately concealed"
Blinding? All outcomes	Yes	"Parents and physicians blinded"
Incomplete outcome data addressed? All outcomes	Yes	No loss to follow up Data treated and analysed in groups originally assigned to
Free of selective reporting?	Yes	Most important clinically relevant outcome (reduction of breath holding episodes) reported
Free of other bias?	Yes	Potential for referral bias (tertiary children's hospital population). However, all children seen in this setting were eligible for inclusion into the study (91% were)

**Paul 1969**

Methods	Prospective study (possibly a controlled trial but randomisation uncertain)
Participants	30 outpatient children (21 boys, 9 girls) attending a hospital paediatric outpatient clinic in India No epilepsy or mental retardation
Interventions	Intervention group (Hb < 100 g/L): Iron dose according to 'Lahey's formula': body weight (kg) x (13.5 - Hb (g/dL)) x 2.5 = mg elemental iron to give (Lahey 1957). Iron administered by intramuscular (IM) injection, not oral route. Counselling provided (co-intervention) Control group (Hb < 100 g/L): not given iron. Given 'vitamins' & counselling (co-interventions). Matched control group with similar baseline haemoglobin values Control group (Hb > 100 g/L): not given iron or counselling. Given 'vitamins' (co-intervention). This group was not included in our systematic review due to the different baseline haemoglobin values to the intervention group (unmatched controls)
Outcomes	Follow up at 3 months Decrease in breath-holding attack frequency: 'good' - complete cessation 'fair' - partial reduction 'poor' - no response
Notes	The first two groups (included in our systematic review) received counselling (co-intervention). The control groups received 'vitamins' which may contain iron Minimal study details provided

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Picked at random regardless of age or sex"
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	No	IM iron not blinded or placebo-controlled. Control group given "vitamins" so blinding not possible
Incomplete outcome data addressed? All outcomes	Yes	No loss to follow up Data treated and analysed in groups originally assigned to
Free of selective reporting?	Yes	Most important clinically relevant outcome (reduction of breath holding episodes) reported
Free of other bias?	Yes	Potential for referral bias (poor socio-economic status population with 1/3 familial

Paul 1969 (Continued)

		background of psychiatric and psychosomatic disorders). However, counselling was applied across both intervention and control groups to counteract any potential effects from the population's high rate of behavioural problems
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**Characteristics of excluded studies** [ordered by study ID]

Ahmad Bhat 2007	Prospective study (India) Iron only given to anaemic children. Non-anaemic children acted as controls Tendency to younger age of BHA peak frequency in anaemic (treatment) group
Khalifa 2004	Retrospective study (Saudi Arabia) Iron only given to anaemic children
Mocan 1999	Case series (Turkey) Iron only given to anaemic children 10 children had febrile convulsions (6 in iron treatment group)
Ziaullah 2005	Prospective study (Pakistan) No comparison group Combined mild and moderate anaemia groups for outcome

## DATA AND ANALYSES

### Comparison 1. Iron supplementation versus placebo or control

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution/Reduction of Breath-holding Attacks	2	87	Odds Ratio (M-H, Fixed, 95% CI)	76.48 [15.65, 373.72]
2 Complete resolution of Breath-holding Attacks	2	87	Odds Ratio (M-H, Fixed, 95% CI)	53.43 [6.57, 434.57]

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## FEEDBACK

### Comments on review by Paul Garner, 26 May 2010

#### Summary

I read this review with interest, in particular the conclusion: "As it is low cost and generally well-tolerated, iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks". This amounts to a recommendation. However, the evidence is based on less than 100 patients, with a "soft" outcome, in two studies of low quality. One (Paul) is probably not randomised, and the other study is alternate allocation (so not randomised, and also, by definition, not concealed). The size of the effect is massive: 29/33 with resolution (any or all) compared with 2/33 in the control group, which strongly suggests a poor quality study. I do not think the authors can recommend iron on the basis of this evidence and think they need to express a LACK of reliable information, rather than this providing evidence of an effect.

Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Name: Paul Garner

Email Address: pgarner@liv.ac.uk

Personal Description: Occupation PROFESSOR

## Reply

Dear Prof Garner,

Thank you for your comments regarding our recent systematic review examining iron supplementation to treat breath-holding attacks in children[1]. We have addressed each point you have raised as follows.

*I read this review with interest, in particular the conclusion: "As it is low cost and generally well-tolerated, iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks". This amounts to a recommendation.*

This sentence should not be read in isolation, rather in the context of the whole conclusion and the recommendations that follow.

*However, the evidence is based on less than 100 patients, with a "soft" outcome, in two studies of low quality.*

We do not agree that resolution of breath-holding attacks is a soft outcome. Witnesses of breath-holding attacks invariably report such events as distressing and frightening in nature, causing much concern and presentation to medical services. Such attacks may occur multiple times each day and confer great morbidity to all involved. The spectacular presentation of breath-holding attacks is unlikely to be missed by parents and therefore the outcome, although parent reported, is relatively objective and robust, similar to an outcome of reported seizures. The number of high quality studies available is of concern and is dealt with elsewhere in the review and the recommendations. The high prevalence and distressing nature of these episodes, as well as the availability, low cost and widespread use of iron in children in this age group (without significant harmful side effects), have all been taken in to consideration in coming to our conclusions based on the balance of relatively few, lower quality studies.

*One (Paul) is probably not randomised, and the other study is alternate allocation (so not randomised, and also, by definition, not concealed). The size of the effect is massive: 29/33 with resolution (any or all) compared with 2/33 in the control group, which strongly suggests a poor quality study.*

Effect size is often largest in earlier reported lower quality studies. However, effect size can also be large because a treatment is very effective. The nature of which category this large finding falls into awaits further evidence.

*I do not think the authors can recommend iron on the basis of this evidence and think they need to express a LACK of reliable information, rather than this providing evidence of an effect.*

We stand by our statement that "iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks" and that "supplementation is of particular benefit in children with iron deficiency anaemia." In children who are not anaemic or have low normal range haemoglobin levels, iron may still be of assistance but this has not yet been proven in subgroup analysis (as only pooled data has been collected to date). Further trials are needed to address the insufficiency of data of an adequate quality to recommend the use of iron in children with breath holding attacks that are iron replete. Currently we would not recommend its use outside of a trial setting.

*Dr Anthony Zehetner*

*Dr Nigel Orr*

*A/Prof Adam Buckmaster*

*A/Prof Katrina Williams*

*Dr Danielle Wheeler*

## Reference

1. Zehetner AA, Orr N, Buckmaster A, Williams KJ, Wheeler DM. Iron supplementation for breath-holding attacks in children [Systematic Review]. Cochrane Database of Systematic Reviews 2010, Issue 5. Art. No.: CD008132. DOI: 10.1002/14651858.CD008132.pub2.

## Contributors

This feedback was prepared by Jane Dennis, feedback editor for CDPLPG, in consultation with the submitter, the authors, the Coordinating Editor and the Managing Editor.



## WHAT'S NEW

Last assessed as up-to-date: 14 October 2009.

2 June 2010	Feedback has been incorporated	Feedback has been received on this review and addressed by authors. A summary and response appear below.
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## HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 5, 2010

## CONTRIBUTIONS OF AUTHORS

AZ: trials searching, data extraction, data analysis, development of the protocol and writing up the review

NO: trials searching, data extraction, data analysis, development of the protocol and writing up the review

AB: protocol guidance, clinical opinion, arbitration for inclusion and exclusion disagreements, data analysis and writing up the review

KW: protocol guidance and development, arbitration for inclusion and exclusion disagreements, clinical opinion, data analysis and writing up the review

DW: protocol guidance and development, arbitration for data extraction disagreements and data analysis

## DECLARATIONS OF INTEREST

None known

## INDEX TERMS

### Medical Subject Headings (MeSH)

Adolescent; Infant, Newborn; Iron, Dietary [\*therapeutic use]; Randomized Controlled Trials as Topic; Respiration Disorders [\*drug therapy]

### MeSH check words

Child; Child, Preschool; Humans; Infant