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Dietary sodium manipulation and asthma (Review)

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[Intervention Review]

Dietary sodium manipulation and asthma

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ABSTRACT

Background

There is a wide geographical variation in the prevalence of asthma and observational studies have suggested that dietary sodium may play a role.

Objectives

To assess the effect of dietary sodium manipulation on asthma control.

Search methods

We carried out a search using the Cochrane Airways Group asthma register. We searched the bibliographies of included randomised controlled trials (RCTs) for additional studies. We carried out the most recent search in November 2010.

Selection criteria

We considered only RCTs that involved dietary sodium reduction or increased sodium intake in patients with asthma.

Data collection and analysis

Both review authors assessed study and extracted data. We conducted data analyses in RevMan 5 using mean differences and random effects.

Main results

We identified a total of nine studies in relation to sodium manipulation and asthma, of which five were in people with asthma (318 participants), and four in people with exercise-induced asthma (63 participants). There were no significant benefits of salt restriction on the control of asthma. There was some evidence from the exercise-induced asthma studies that a low sodium diet may improve lung function after exercise and possibly baseline lung function, but this is based on findings from a very small numbers of participants.

Authors' conclusions

This review did not find any evidence that dietary sodium reduction significantly improves asthma control. Although dietary sodium reduction may result in improvements in lung function in exercise-induced asthma, the clinical significance of this effect is unclear.

PLAIN LANGUAGE SUMMARY

Does reducing the amount of salt in a diet improve asthma symptoms?

A review of the current literature suggests that reduction in the amount of dietary sodium consumed has no significant effect on the symptoms of asthma but may be associated with improvements in some lung function measurements in exercise-induced asthma.

BACKGROUND

Asthma prevalence

Asthma is a respiratory disease which is characterised by increased airway responsiveness to a wide variety of stimuli and causes variable airflow obstruction (Tattersfield 2002). Asthma prevalence has been increasing over recent decades, with 300 million individuals globally reporting asthma symptoms and worldwide. Reports indicate that 255,000 individuals died of asthma in 2005 (Masoli 2004; WHO, 2006). The prevalence of asthma and atopy (a tendency to experience allergic reactions) is higher in developed countries (Anderson 1994; Peat 1994; Shaw 1990) than in developing or less affluent countries (Keeley 1991; Van Niekerk 1979; Yemaneberhan 1997). Some of this difference may be a consequence of differential methods of diagnosing asthma, but there is evidence that asthma appears to be associated with the economic development of a country. One suggestion that might explain the difference in asthma prevalence between countries is that diet is important in the aetiology of asthma (Fogarty 2000; McKeever 2004), and one of the characteristics of developed countries is a higher level of dietary sodium intake (Gleibermann 1973; Page 1974). This has led to the hypothesis that sodium has a role in the aetiology of asthma (Burney 1987).

Epidemiological and cross-sectional studies

The first studies of the relationship of dietary sodium and asthma were by Peter Burney in the late 1980s (Burney 1986; Burney 1987a). An ecological study (Burney 1987a) investigated the relationship between the standardised mortality ratio for each area of England and Wales and the amount of table salt purchased. The table salt purchases were estimated by a Ministry of Agriculture, Fisheries and Food survey. This showed that table salt purchases were strongly and significantly related to asthma mortality. However, this relationship was observed in men (15 to 64 years old, $r = 0.80$, $P < 0.05$) and children (5 to 14 years old, $r = 0.82$. $P < 0.05$), but not in women ($r = 0.40$, $P > 0.05$). In addition, Burney 1986 investigated the relationship between sodium intake and bronchial reactivity. Questionnaires were sent to adults enquiring about symptoms of asthma and bronchial reactivity. Individuals with symptoms and 20% of responders without symptoms had a bronchial histamine challenge and skin prick test performed. Participants also provided 24-hour urinary sodium excretion samples. There was a significant increase in bronchial reactivity ($\log_{10}PD_{20}$ -histamine) with an increase in 24-hour urinary sodium concentration. There was on average a 10-fold difference in reactivity over the 95% range of sodium excretion recorded in the study. However, a large study (Britton 1994) failed to demonstrate any relationship between sodium and bronchial reactivity in 1,702 adults who were randomly selected from a population-based sample. Participants provided data on a methacholine challenge and a 24-hour urinary sodium sample collection was performed. There was no relationship found between 24-hour urinary sodium excretion and methacholine challenge after adjustment for age, smoking and gender.

There have been several cross-sectional studies in different populations throughout the world. These studies have used different definitions of asthma such as patient questionnaires, physicians' diagnosis or bronchial reactivity. The measurement of dietary sodium consumption varies between studies. Some studies used food frequency questionnaires, others used three-day food recall and some used 24-hour urinary sodium which is the most accurate for daily intake. Some of the studies suggest a relationship between dietary sodium and asthma or bronchial reactivity (Demissie 1996; Mohamed 1995; Pistelli 1993; Schwartz 1990; Tribe 1994), whereas other studies have not demonstrated any relationship (Devereux 1995; Sparrow 1991; Sausenthaler 2005; Zoia 1995;). Therefore, it is unclear at a population level what the role of dietary sodium is on asthma control. Interventional randomised controlled trials are a more robust method to assess the role of dietary sodium on asthma.

OBJECTIVES

To assess the effect of dietary sodium manipulation on asthma control.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised, placebo-controlled trials (RCTs). We included double blind, single blind and open studies.

Types of participants

We included trials that involved adults or children with asthma as defined by the American, British Thoracic Society criteria, physician diagnosis or by objective measurements such as bronchial reactivity. Exercise-induced asthma was defined as a drop greater than 10% in forced expiratory volume (FEV_1) after exercise.

Types of interventions

We included studies that involved modification of dietary sodium with either an increase or decrease in dietary sodium.

Types of outcome measures

Primary outcomes

The primary outcomes for people with asthma were bronchial hyper-responsiveness (Lewis 2001) and asthma quality of life. For people with exercise-induced asthma, the primary outcomes were baseline and five-minute post-exercise FEV_1 (ATS 2000) and asthma quality of life score. We chose these outcomes as they best reflect the severity of, and patients' experience of, the disease.

Secondary outcomes

In subjects with asthma, we examined the following secondary outcomes:

- forced expiratory volume in one second (FEV_1);
- ratio of forced expiratory volume in one second divided by forced volume capacity (FEV_1/FVC);
- peak flow (PEFR);
- bronchodilator use (puffs/day);
- 24-hour sodium secretion (mmol/24 hours).

In subjects with exercised induced asthma, we examined the following outcomes:

- baseline forced vital capacity (FVC) (pre-exercise challenge);
- baseline FEV_1/FVC (pre-exercise challenge);

- five-minute post-exercise challenge FVC;
- five-minute post-exercise challenge FEV_1/FVC;
- 24-hour sodium secretion (mmol/24 hours).

Search methods for identification of studies

Electronic searches

We conducted a search using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group search methods for further details). We searched all records in the Specialised Register coded as 'asthma' using the following terms:

salt or nacl OR (sodium* and (chloride or diet* or intake or restriction*))*

We carried out the search on 11 November 2010.

Searching other resources

We searched bibliographies of all selected RCTs for additional studies that might have contained further RCTs. We contacted authors of identified RCTs where necessary to clarify any data which were unclear.

Data collection and analysis

Selection of studies

Both review authors independently examined the results of the search, selected trials for inclusion in the review and assessed the full text of all trials that appeared potentially relevant. We reached complete agreement on the inclusion and exclusion of all studies. The authors of the previous version of this review contacted the study authors for further information. However, to date only one author (Gotshall 2000) has replied with additional information. In addition, we obtained information on randomisation and blinding from one author during the editorial process of the review update (Mickleborough 2000; Mickleborough 2001; Mickleborough 2005). We had access to data from Pogson 2008 and we re-analysed the data to allow for comparison with data from the other studies.

Data extraction and management

We designed a data collection form for the review and we independently collected the following items:

- publication details;
- patient population, inclusion/exclusion criteria;
- randomisation/allocation concealment;
- details of blinding measures;
- description of the intervention;
- results;
- potential source of bias;
- funding/conflict of interest.

We resolved all disagreements by discussion until we reached a consensus.

Assessment of risk of bias in included studies

Both review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We assessed the risk of bias according to the following domains.

1. Allocation sequence generation.
2. Concealment of allocation.
3. Blinding of participants and investigators.
4. Incomplete outcome data.
5. Selective outcome reporting.

We graded each potential source of bias as yes, no or unclear, relating to whether the potential for bias was low, high or unknown respectively.

Measures of treatment effect

We entered data as mean differences and pooled results using a random-effects model. We entered data for high versus low dose sodium diets.

Data synthesis

All but one of the trials was designed as a cross-over trial. For the parallel group study, the data in the analysis was the difference in the change in baseline in the two groups. For the cross-over trials, where possible we extracted and used the paired mean difference with the 95% confidence intervals (CI) and/or the exact P values. If only summary measure were presented (mean, standard error (SE) or standard deviation (SD)) for the two groups, we entered the data into Review Manager (RevMan 5) as if the results were a parallel group study and the mean difference (MD) and SE were estimated. We adjusted the SE to match the significance in the research paper, where this was reported. We entered the actual or derived mean difference and SE for each of the studies in RevMan 5 using the generic inverse variance method. We pooled the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We did not plan any subgroup analysis to investigate heterogeneity.

RESULTS

Description of studies

Results of the search

We identified 263 references from the electronic search. Both review authors screened the references and we excluded 250 on the basis of the title and abstract. We retrieved 13 full-text papers relating to 11 studies for further scrutiny. We included nine studies and excluded two studies.

Included studies

We included nine studies with a combined total of 381 participants. We found five studies with a total of 318 patients with asthma and four studies with 63 participants with exercise-induced asthma. The studies that included people with asthma ranged in size from 17 to 220 participants and the size of the studies with participants who had exercise-induced asthma ranged from 8 to 24. All the studies were cross-over trials which ranged from two to five weeks in each arm, except for the study by Pogson 2008 which was a parallel

group study of six weeks. The majority of studies placed individuals on a low sodium diet and then intervened with either sodium or placebo tablets. The amount of additional sodium differed between the studies, with supplementation being aimed at producing a sodium consumption similar to the average consumption in the UK (Burney 1989; Lieberman 1992; Medici 1993; Pogson 2008) or a high supplementation (Carey 1993; Gotshall 2004; Mickleborough 2000; Mickleborough 2001; Mickleborough 2005). We have provided a full description of all the studies in Table 1.

A number of other outcomes were presented in the asthma papers including PD_{10}, forced vital capacity, skin prick tests, blood pressure, asthma symptom scores, PEFR (morning and evening) and the number of asthma attacks. Other outcomes presented for exercise-induced asthma included pre-exercise PEFR, pre-exercise forced expiratory flow (FEF) 25% to 50%, post-exercise lung function measurements at 1, 10, 15, 20, 45, 75, 90, 105, and 120 minutes, diffusing capacity of the lung for carbon monoxide (DLco), carbon monoxide transfer coefficient (Kco), alveolar volume (V_a), intrinsic diffusing capacity of the alveolar capillary membrane (DMco), pulmonary capillary blood volume (V_c), and ratio of V_a/V_c. In addition, Mickleborough 2005 collected induced sputum for a total cell count, eosinophils, neutrophils, lymphocytes, macrophages, bronchial epithelial cells, interleukin 8, mean leukotriene b_4, cysteinyl leukotriene, and PGD2-methoxine. These samples were collected pre-exercise and 1, 6 and 24 hours post-exercise.

One study only recruited men (Carey 1993) and one study presented separate results for men and women (Burney 1989). Three studies recruited the participants from a university population (Gotshall 2000; Mickleborough 2000; Mickleborough 2001). Patients in two studies were told to stop their regular medications and take their medications on an as-needed basis and this could limit the applicability of the results, as it would have potentially affected the patients' asthma control during the trial (Medici 1993; Mickleborough 2005).

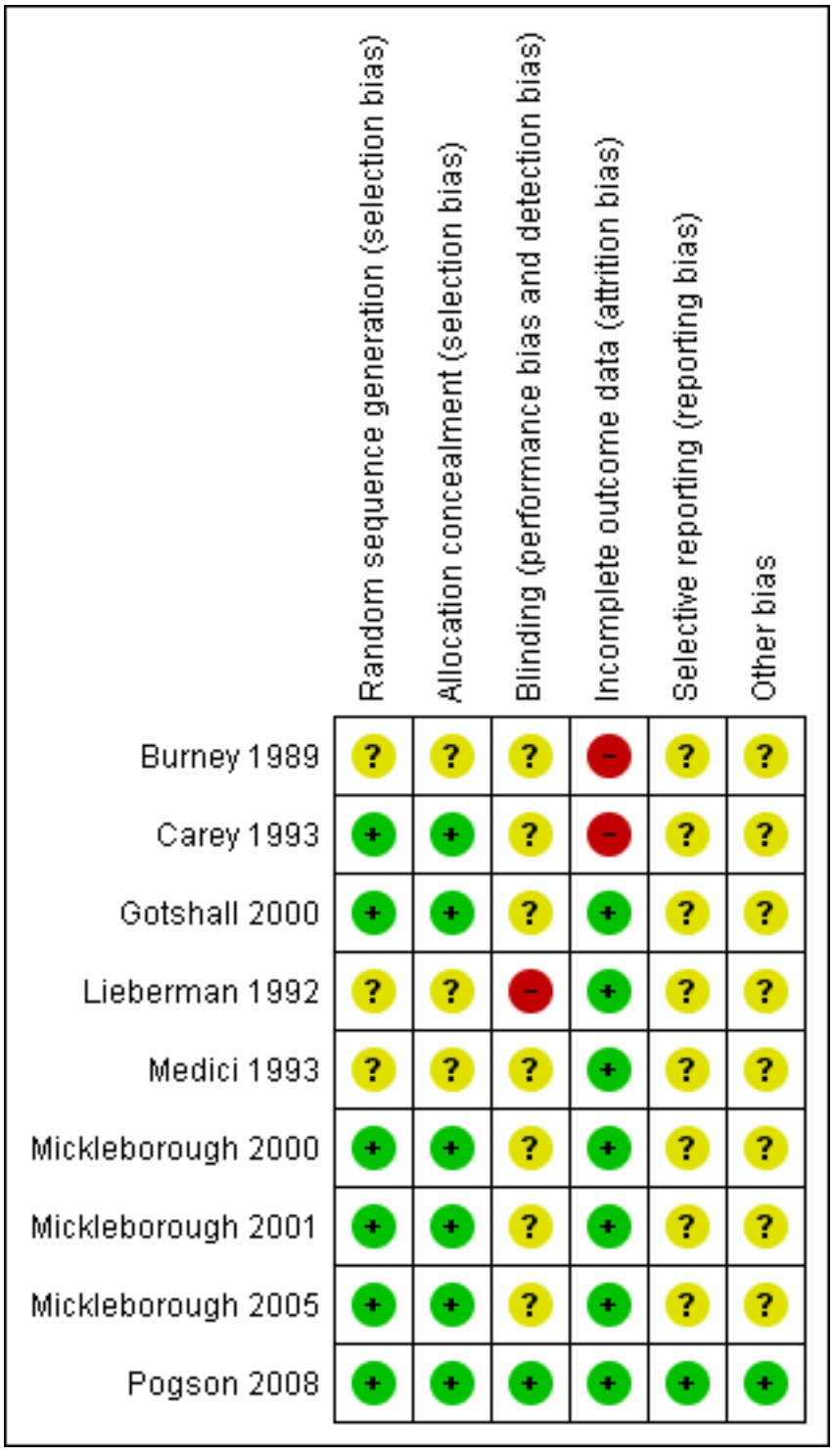
Excluded studies

We excluded two studies at the full text stage as neither were RCTs (Gotshall 2004; Javaid 1988).

Risk of bias in included studies

We have provided full details of the risk of bias for each study in Characteristics of included studies. See Figure 1 for a summary of the risk of bias.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies were described as randomised. Pogson 2008 randomised subjects in blocks of eight; Carey 1993 used random numbers and Gotshall 2000 drew lots and therefore we judged all three to have a low risk of bias for sequence generation. In Mickleborough 2000, Mickleborough 2001 and Mickleborough 2005, an independent investigator having no contact with the subjects and no involvement in data collection or analysis used a computerised random number generator to create the randomisation sequence. We judged these studies to have a low risk of bias for sequence generation. Carey 1993 and Pogson 2008 both used sealed envelopes, therefore we considered these studies to be at a low risk of bias for allocation concealment, but the rest of the studies gave no detail of allocation concealment and were therefore at unclear risk of bias.

Blinding

Lieberman 1992 was the only study which was not blinded and we judged it to have a high risk of bias. Pogson 2008 states the clinicians and subjects were blinded and the code was not broken until primary analysis had been completed and therefore had the lowest risk of bias. The rest of studies were described as blinded but gave no information on blinding; however in one study, Medici 1993, the amount of salt was altered due to side effects of salt loading. In addition, salt does have a distinctive and known taste so it would be possible for participants to become aware of their treatment.

Incomplete outcome data

We judged six studies to be at a low risk of bias for incomplete outcome data as there were no drop-outs (Gotshall 2000; Lieberman 1992; Medici 1993; Mickleborough 2000; Mickleborough 2001; Mickleborough 2005). Pogson 2008 used intention-to-treat analysis to address incomplete outcome data and we therefore considered this study to have a low risk of bias. Burney 1989 and Carey 1993 excluded drop-outs from their analysis and therefore did not address incomplete data. We considered both of these studies to be at a high risk of bias, although the number of drop-outs in these studies was small.

Selective reporting

Pogson 2008 stated all the outcomes at the beginning of study so was at low risk of bias, but the rest of the studies did not and so it was not clear if they were free from selective reporting. Although this does not seem likely, we judged these studies to be at unclear risk of bias.

Other potential sources of bias

In most of the studies there were areas where bias might have affected the results. Only Pogson 2008 reported a power calculation and clear primary and secondary outcomes. Mickleborough 2005 had a power calculation but it was not clearly or fully described as the primary outcomes of the study were not stated. All the studies except Pogson 2008 were cross-over in design. Only Gotshall 2000; Mickleborough 2005 and Mickleborough 2001 examined for cross-over effects and there was no wash-out period in four studies (Burney 1989; Carey 1993; Lieberman 1992; Medici 1993). In Medici 1993, participants experienced heartburn (the number who experienced it was not stated in the paper) when taking sodium tablets, which may indicate that the study was unblinded.

Effects of interventions

Asthma

For the primary objective outcome, bronchial hyper-reactivity, none of the data from the three included studies could be combined due to different substances being used for provocation and differences in the presentation of the data (Burney 1989; Medici 1993; Pogson 2008).The first of these studies found a significant mean change in the provoking dose in men (n = 11) but not for women (n = 20) (Burney 1989). The second study, in 14 individuals, found no differences between a low sodium and higher sodium diet and PD_{20} (Medici 1993). Finally, in the parallel group study there was no difference in mean change from baseline of doubling doses of PD_{20} between individuals on a low sodium and higher sodium diet (n = 220) (Pogson 2008).

Only one study reported data on change in asthma quality of life and it found no difference in asthma quality of life between the low sodium and higher sodium intake (P = 0.49) (Pogson 2008).

None of the secondary outcomes FEV_1, FEV_1/FVC, PEFR or bronchodilator usage demonstrated any significant differences between lower sodium and higher sodium diets (Analysis 1.1, (n = 265); Analysis 1.2 (n = 238); Analysis 1.3 (n = 255); Analysis 1.4, (n = 255) respectively) despite significant changes in urinary sodium between different diets. The differences in urinary sodium concentration indicates that diet manipulation and the different interventions did impact sodium intake (Analysis 1.5, (n = 282)).

Exercise-induced Asthma

The primary outcome of five-minute post-exercise FEV_1 (MD 0.46; 95% CI 0.01 to 0.91; (n = 23); Figure 2) was significantly better in the low sodium diet as compared with the high sodium diet, although the difference was borderline. None of the studies reported on asthma quality of life. There were borderline significant results (P = 0.05) for baseline FEV_1 (MD 0.15; 95% CI -0.00 to 0.30; (n = 47); Figure 3) and baseline FVC (MD 0.13 L; 95% CI -0.00 to 0.26, (n = 47); Figure 4). A low sodium diet was associated with significantly better five-minute post-exercise FVC (MD 0.86; 95% CI 0.04 to 1.68, (n = 23); Figure 5). However differences in diet did not effect FEV_1/FVC at baseline (Figure 6, n = 47) or five minutes post-exercise (Figure 7, n = 23). There were large significant changes in urinary sodium (MD -236.00; 95% CI -281.56 to -190.44; (n = 23); Analysis 2.7).

Figure 2. Forest plot of comparison: 2 Exercise induced asthma - low sodium diet vs high sodium diet, outcome: 2.4 5-minute post-exercise FEV1 (litres).

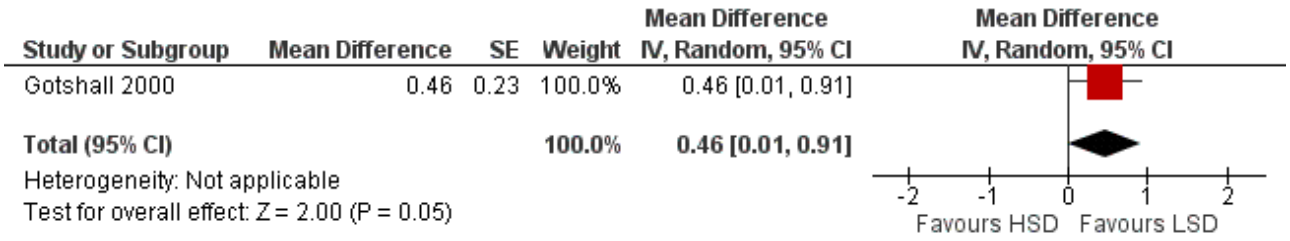


Figure 3. Forest plot of comparison: 2 Exercise induced asthma - low sodium diet vs high sodium diet, outcome: 2.1 Baseline FEV1 (litres).

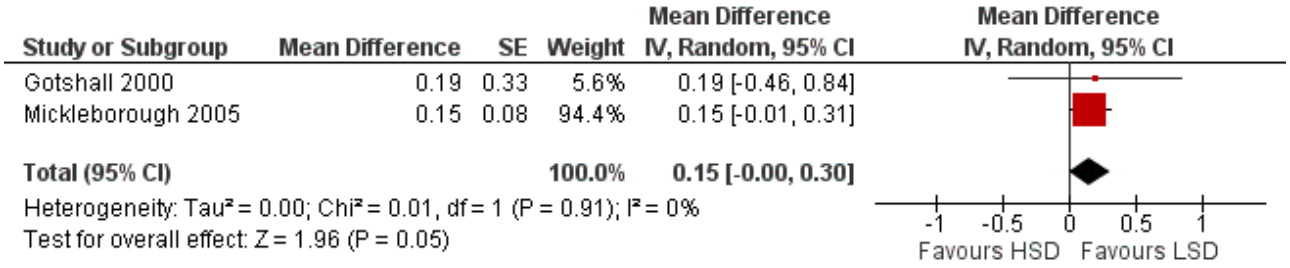


Figure 4. Forest plot of comparison: 2 Exercise induced asthma - low sodium diet vs high sodium diet, outcome: 2.2 Baseline FVC (litres).

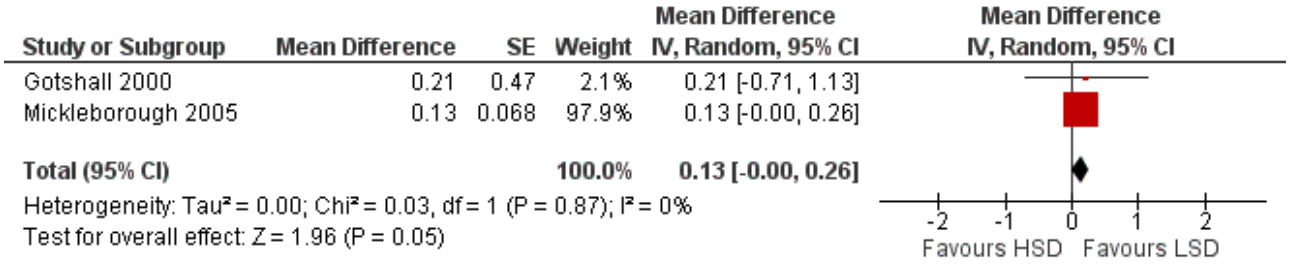


Figure 5. Forest plot of comparison: 2 Exercise induced asthma - low sodium diet vs high sodium diet, outcome: 2.5 5-minute post-exercise FVC (litres).

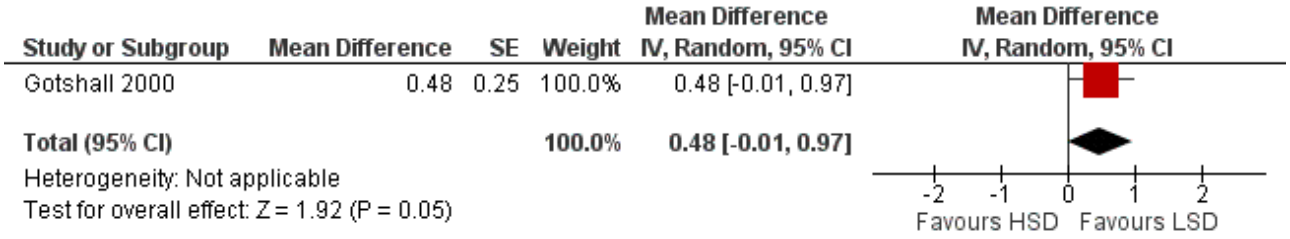


Figure 6. Forest plot of comparison: 2 Exercise induced asthma - low sodium diet vs high sodium diet, outcome: 2.3 Baseline FEV1/FVC (%).

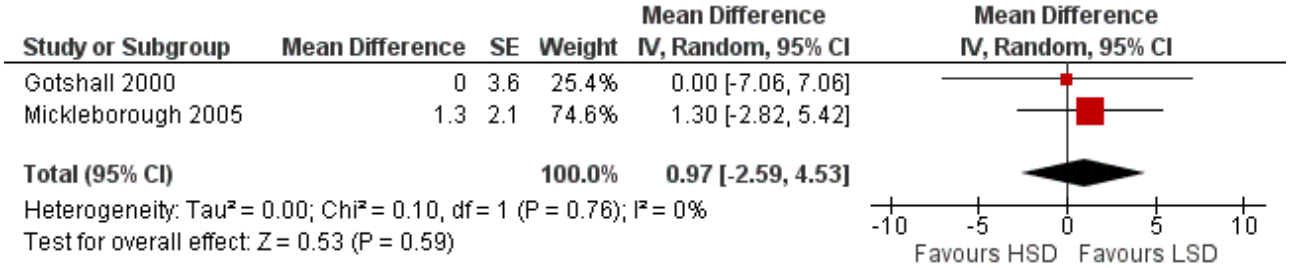
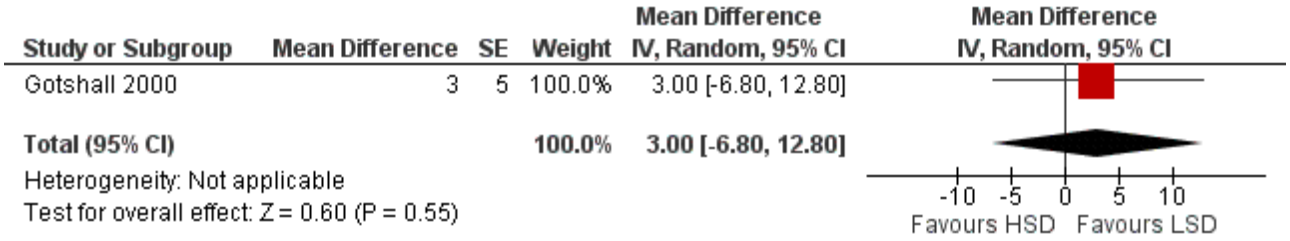


Figure 7. Forest plot of comparison: 2 Exercise induced asthma - low sodium diet vs high sodium diet, outcome: 2.6 5-minute post-exercise FEV1/FVC (%).



DISCUSSION

This review investigated the effect of sodium manipulation in people with either asthma or exercise-induced asthma. Most of the lung function outcomes improved for people with exercise-induced asthma who were consuming a low sodium diet.

We were able to pool data from only four studies in patients with asthma and these were mostly studies on small numbers of participants. One included study was larger and involved 220 participants. This large study also demonstrated the lowest risk of potential bias in the design and conduct of the study. The analyses used six different measures of asthma control and the number of participants in each analysis varied from 14 to 239. The only outcome affected by sodium manipulation was the FEV_1/FVC ratio. All other measures were negative despite a significant change in urinary sodium. However, it must be recognised that there was a wide difference in the amount of change in urinary sodium between the different studies depending on the intervention. In addition, patients did not benefit from an improvement in quality of life, however only one study reported on this outcome.

The four studies in exercise-induced asthma had a small number of participants with between 23 and 59 participants in each analysis. This review found that some lung function parameters for exercise-induced asthma were improved by reducing sodium intake. There were improvements in FEV_1 and FVC at baseline for individuals when a low sodium diet was compared with a high sodium diet; however these differences in lung function were not demonstrated in the asthma population. The five-minute post-exercise lung function suggests that a low sodium diet may be beneficial for people with exercise-induced asthma, with a large reduction of FEV_1 of 630 mL and FVC of 860 mL. It should be noted that the changes of dietary sodium intake within the exercise-induced asthmatic population were extreme. In 2004 the UK consumption of sodium was estimated as 165 mmol (Dietary and Nutritional Survey 2004) but the high sodium diet group were consuming at least 230 mmol and had changes in urinary sodium of 270 mmol/L between comparison groups. Therefore these changes might only be possible in a RCT environment. Another limitation of the analyses of the exercise-induced asthma is that the mean difference (MD) and standard error (SE) were all derived from the summary data given and therefore did not take account of the paired data. It is also possible that the people with exercise-induced asthma who were predominantly recruited from university students may not represent the general population of people with exercise-induced asthma and therefore the results may not be generalisable to the wider population of people with exercise-induced asthma.

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests that people with asthma may not benefit significantly from altering their dietary sodium intake in order to improve their asthma control. People with exercise-induced asthma might benefit from a reduction of dietary sodium; however the change in dietary sodium needed is extremely large and the clinical significance of this effect is unclear. The effects seen were unique to the exercise-induced asthma population, possibly due to having a different phenotype of asthma and possibly because of the large changes in the sodium consumption they achieved. Therefore these findings could be limited to a small number of people with exercise-induced asthma and the change in sodium may be difficult to achieve and sustain outside a clinical trial environment.

Implications for research

This review demonstrates that dietary sodium reduction did not have a significant effect on asthma control within a population of people with asthma. Therefore, no further research in this area is recommended. There appears to be an effect of dietary sodium manipulation on some outcomes of lung function in people with exercise-induced asthma. This could potentially be further investigated in larger studies in order to determine the clinical relevancy of these changes as the changes were inconsistent across different markers of lung functions. In addition, it is not known if these changes persist longer than two weeks.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Burney 1989

Methods	Randomised placebo-controlled cross-over study. .
Participants	36 participants (14 men, 22 women) with moderately severe asthma were included in the study. Age range 18 to 53 years. 9 current smokers, 10 ex-smokers and 17 never smoked. 35 subjects on inhaled bronchodilators and 12 using inhaled steroids.
Interventions	After one week run-in, subjects were put on a low sodium diet and asked to take either slow sodium tablets (80 mmol/day) or placebo. After a 2-week period the subjects were crossed over (no wash-out period). Study measurements were performed after the run-in period, 2 weeks after first intervention and 2 weeks after the secondary intervention. Exclusion criteria: none stated in the paper.
Outcomes	FEV_1, FVC, PD_{20}, PD_{10}, skin prick tests and blood pressure.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given in paper.
Allocation concealment (selection bias)	Unclear risk	Described as randomised; no other information available.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blinded; no other information available.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 subjects were excluded but not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Not clear from the information presented.
Other bias	Unclear risk	The significant results are only present in men and has no calculation of power described. There was no wash-out period.

Carey 1993

Methods	Randomised placebo-controlled cross-over study.

Carey 1993 *(Continued)*

Participants	27 male patients (5 dropped out - 1 due to exacerbation and 4 due to poor compliance), age range 12 to 68 years with stable asthma. All had been previously given a diagnosis of asthma and were currently on medication (all on beta 2 agonists, 12 inhaled corticosteroids, 4 inhaled cromoglycate, 3 oral theophyllines). No subjects were using oral beta agonists, antihistamines or steroids at the time of the study. None were current smokers, only one had previously smoked. Exclusion criteria: history, clinical or laboratory evidence of renal, hepatic, cardiovascular disease, hypertension or electrolyte imbalance. In addition participants could not take diuretic therapy.
Interventions	All participants placed on low sodium diet (80 mmol daily) and then randomised to receive either slow sodium (200 mmol daily) or placebo (placebo tablets) for 5 weeks and then crossed over (no wash-out period).
Outcomes	PD_{20}, PEFR (morning and evening), symptom score, bronchodilator requirements and FEV_1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coded random numbers used for treatment allocation.
Allocation concealment (selection bias)	Low risk	Treatment given in sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blind; no other information given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Subjects who dropped out were not included in analysis.
Selective reporting (reporting bias)	Unclear risk	Not clear from the information presented.
Other bias	Unclear risk	5 drop-out not included in analysis. No washout period. Only men included in this paper. No calculation of power described.

Gotshall 2000

Methods	Randomised placebo-controlled cross-over study.
Participants	8 (1 male and 7 female) participants with objectively diagnosed exercise-induced asthma (> 10% drop in FEV_1 after exercise). Mean age 23 years. All subjects used short-acting rescue medications and none were on maintenance medications. Control group were 8 (4 male and 4 female) non-asthmatics. Exclusion criteria: no participants had atopic asthma.
Interventions	All participants entered the study on their normal sodium diet for 1 week. Participants then consumed a low sodium diet (65 mmol of sodium a day by means of a meal plan) and randomly assigned to either high sodium limb or low sodium limb for 2 weeks. Thereafter, a 1-week wash-out period on a normal sodium diet followed, then all patients followed alternative diet for 2 weeks (crossover). In the low

Gotshall 2000 *(Continued)*

	sodium limb participants consumed a low sodium diet and placebo tablets and participants in the high sodium limb consumed a low sodium diet (174 mmol of sodium/day).
Outcomes	FEV_1, FVC, FEV_1/FVC and PEFR pre-exercise test and 1,5,10,15 minutes post-exercise tests.
Notes	Author reply received (03/02/01) further information provided on allocation (drawing lots)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation of treatment was done by drawing lots.
Allocation concealment (selection bias)	Low risk	Treatments were drawn by lots so both participants and investigators blinded to the randomisation sequence.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blinded; no other information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not clear from information presented.
Other bias	Unclear risk	Population recruited from an university population only. No calculation of power described.

Lieberman 1992

Methods	Randomised open placebo-controlled cross-over study.
Participants	17 patients with mild asthma (9 men, 8 women) recruited from pulmonary outpatient clinic. Mean age 43 (range 27 to 62) years. All patients had a history of intermittent wheezing and greater than 15% change in FEV_1. All used beta 2 agonists, 5 used inhaled corticosteroids, 10 used oral theophyllines. Exclusion criteria: hypertensive patients and smokers.
Interventions	3 regimens of diet were tested for 2 weeks each with no wash-out period in-between: normal diet (regular diet with no deliberate change in sodium intake), low sodium (used for hypertensive patients) and high sodium (eat as much sodium as possible and consuming 34 mmol of sodium/day)
Outcomes	PEFR (3 times daily), daily asthma medication requirements.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given.

Lieberman 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Described as randomised; no other information available.
Blinding (performance bias and detection bias) All outcomes	High risk	The study was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not clear from the information given.
Other bias	Unclear risk	No wash-out period and no calculation of power described.

Medici 1993

Methods	Randomised placebo-controlled cross-over study. .
Participants	18 patients recruited (4 excluded during run-in due to poor compliance). Study group 14(9 men, 5 women). Age range 20 to 65 years. They had stable atopic asthma and fulfilled the ATS criteria for the diagnosis of asthma. Exclusion criteria: instability of asthma, therapy with oral steroids, cromoglycan or diuretics, cardiac insufficiency, arrhythmias, liver diseases, kidney diseases, diabetes mellitus, smoking and pregnancy.
Interventions	After 2 weeks on a low sodium diet (86 to 103 mmol/day), given 157 mmol of sodium daily (in the form of sodium chloride) or placebo for 3 weeks. Then the 2 groups were crossed over for a second 3-week treatment period (sodium citrate with 154 sodium mmol). There was no washout period.
Outcomes	PD_{20}, FEV_1, FVC, PEFR x 3 a day, inhaler bronchodilator and corticosteroids sprays, number of asthma attacks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	Described as randomised; no information given.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blind, however the papers states that due to side effects when on the salt tablets, less than intended amount was used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	

Medici 1993 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not clear from information given.
Other bias	Unclear risk	Subjects had heartburn on the sodium tablets and so could have been unblinded. Subjects changed medication from regular to prn and there was no wash-out period. No calculation of power described.

Mickleborough 2000

Methods	Randomised placebo-controlled cross-over study.
Participants	15 participants (age range 18 to 36 years) with exercise-induced asthma (10% drop of FEV_1 with exercise). Participants were recruited from university population. Exclusion criteria: none stated.
Interventions	All participants had a 1-week run-in on normal sodium diet. All participants then started a low sodium diet (65 mmol of sodium a day by a meal plan) and then randomised to high sodium limb (174 mmol of sodium tablets) or low sodium limb (placebo tablets). After 2 weeks a 1-week washout period took place on a normal sodium diet and then subjects consumed the other limb for 2 weeks.
Outcomes	Pre-exercise, 1 minute and 5 minutes post-exercise FEV_1, FVC, FEV_1/FVC, PEFR, FEF 25-75%. VE and VO_2 at 1 minute.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent investigator had no contact with the subjects and no involvement in data collection or analysis used a computerized random number generator to create the randomisation sequence.
Allocation concealment (selection bias)	Low risk	Randomised study with independent investigator generating the sequence.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blinded; no other information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not clear from information given.
Other bias	Unclear risk	Subjects were from a university population.

Mickleborough 2001

Methods	Randomised placebo-controlled cross-over study.

Mickleborough 2001 *(Continued)*

Participants	16 participants. 8 participants with exercise-induced asthma (mean age 22 years and all using short beta agonists) and 8 controls (mean age 23 years). The population was recruited from a university population. Exclusion criteria: none of the participants had atopic asthma.
Interventions	All participants entered the study on a normal sodium diet and were started a low sodium diet (65 mmol of sodium using a meal plan). All participants were randomised to a low sodium limb (placebo tablets) or high sodium low chloride limb (174 mmol of sodium a day as sodium bicarbonate) for 2 weeks. After this a 1-week wash-out period followed and then participants switched to the alternative diet.
Outcomes	FEV_1,FVC, FEV_1/FVC pre-exercise and post-exercise measurement at 1, 5, 10 and 15 minutes.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent investigator had no contact with the subjects and no involvement in data collection or analysis used a computerised random number generator to create the randomisation sequence.
Allocation concealment (selection bias)	Low risk	Randomised study with independent investigator generating the sequence.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blinded; no other information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not clear from information given.
Other bias	Unclear risk	Participants recruited from a university population. No calculation of power.

Mickleborough 2005

Methods	Randomised placebo-controlled cross-over study.
Participants	24 participants (mean age 24 years) were recruited from a university population and local community. 14 participants were on inhaled short beta 2 agonists and 12 participants on inhaled corticosteroids. All had documented exercise-induced asthma - wheezing, shortness of breath and chest tightness after exercise and atopic asthma. Exclusion criteria: pregnancy, hypertension, hyperlipidaemia, diabetes, bleeding disorders, delayed clotting time or taking aspirin.
Interventions	All participants had a run-in period of 1 week on a normal sodium diet; after this all participants consumed a low sodium diet (65 mmol of sodium a day as meal plan). Participants were then randomised to either high sodium limb (sodium tablets 174 mmol of sodium a day) or low sodium limb (placebo

Mickleborough 2005 *(Continued)*

	tablets). After 2 weeks there was a wash-out period on a normal sodium diet for one week. Finally participants had two weeks on the different limb.
Outcomes	Pre- and post-exercise FEV_1, FVC, FEV_1/FVC, FEF25-50%, DL_{CO}, K_{CO}, V_a, DM_{C0}, VL, V_C/V_A. Post-exercise measures were 1, 5, 20, 45, 75, 90, 105, 120 minutes. In addition inhaled sputum was collected for total cell count, neutrophils, lymphocytes, macrophages, epithelial cells, interleukin 8, mean leukotriene b_4, cysteinyl leukotriene, PGD2-methoxine. This was collected pre-exercise, 1 hour, 6 hours and 24 hours post-exercise.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent investigator had no contact with the subjects and no involvement in data collection or analysis used a computerised random number generator to create the randomisation sequence.
Allocation concealment (selection bias)	Low risk	Randomised study with independent investigator generating the sequence.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as blinded; no other information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not clear from information given.
Other bias	Unclear risk	Subjects had to stop maintenance medication during the study. The study was controlled for cross-over effect. Power calculation was not fully described.

Pogson 2008

Methods	Randomised double-blind placebo-controlled parallel group study.
Participants	220 participants (mean age 44 years) with GP diagnosis of asthma and bronchial reactivity. Population recruited from general practice. All participants used short acting beta 2 agonists, 74% used inhaled corticosteroids and 38% used long acting beta 2 agonists. Exclusion criteria: oral steroids or change in asthma medication in the last 4 weeks, smoking history over 10 pack year, use of diuretics or angiotension converting enzyme inhibitors, pregnancy or planned pregnancy.
Interventions	All participants consumed a low sodium diet for six weeks and half of participants were randomised to placebo tablets and half of participants were randomised to sodium chloride tablets (80 mmol of sodium).
Outcomes	PD_{20}, FEV_1,FVC, PEFR-morning and evening, twice daily symptoms score, twice daily bronchodilator use, atopic status and Juniper asthma quality of life questionnaire.

Pogson 2008 *(Continued)*

Notes	Data was re-analysed in order for it to be combined with other data, as it is presented in the paper as mean change from baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in permuted block of 8 and stratified by the presence or absence of inhaler corticosteroid use.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes (author stated).
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, clinicians and outcome assessor blind and code not broken until end of the study and primary analyses completed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat analysis.
Selective reporting (reporting bias)	Low risk	All outcomes stated at the beginning of the study.
Other bias	Low risk	

DL_{CO}:diffusing capacity of the lung for carbon monoxide
DMCO: intrinsic diffusing capacity of the alveolar capillary membrane
FEF: forced expiratory flow
FEV_1: forced expiratory volume
FVC: forced volume capacity
K_{CO}: carbon monoxide transfer coefficient PEFR: peak flow
PD10: provocative dose of ventilation causing a 10% fall in FEV1
PD20: provocative dose of ventilation causing a 20% fall in FEV1
PGD2: prostaglandin D2
V_a: alveolar volume
V_C/V_A: Alveolar volume / Pulmonary capillary blood volume
V_C: Pulmonary capillary blood volume
vo_2: volume of oxygen uptake

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gotshall 2004	This is not a randomised controlled trial.
Javaid 1988	This is not a randomised controlled trial.

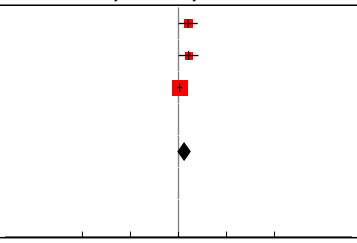
DATA AND ANALYSES

Comparison 1. Asthma - low sodium diet (LSD) vs higher sodium diet (HSD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (litres)	3		Mean Difference (Random, 95% CI)	0.12 [-0.02, 0.26]
2 FEV1/FVC (%)	2		Mean Difference (Random, 95% CI)	0.62 [-2.98, 4.21]
3 PEFR (litres/min)	3		Mean Difference (Random, 95% CI)	11.01 [-12.67, 34.70]
4 Bronchodilator usage (puffs/day)	3		Mean Difference (Random, 95% CI)	-0.03 [-0.18, 0.12]
5 Sodium excretion (mmol/L)	4		Mean Difference (Random, 95% CI)	Totals not selected

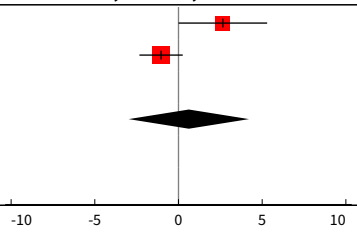
Analysis 1.1. Comparison 1 Asthma - low sodium diet (LSD) vs higher sodium diet (HSD), Outcome 1 FEV1 (litres).

Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Medici 1993	0	0	0.2 (0.101)		25.9%	0.2[0,0.4]
Carey 1993	0	0	0.2 (0.105)		24.88%	0.21[0,0.42]
Pogson 2008	0	0	0 (0.026)		49.23%	0.03[-0.03,0.08]
Total (95% CI)					**100%**	**0.12[-0.02,0.26]**
Heterogeneity: Tau^2=0.01; Chi^2=5.41, df=2(P=0.07); I^2=63.01%						
Test for overall effect: Z=1.61(P=0.11)						



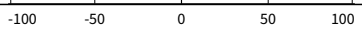
Analysis 1.2. Comparison 1 Asthma - low sodium diet (LSD) vs higher sodium diet (HSD), Outcome 2 FEV1/FVC (%).

Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Medici 1993	0	0	2.7 (1.35)		44.91%	2.65[0,5.3]
Pogson 2008	0	0	-1 (0.66)		55.09%	-1.04[-2.33,0.25]
Total (95% CI)					**100%**	**0.62[-2.98,4.21]**
Heterogeneity: Tau^2=5.68; Chi^2=6.03, df=1(P=0.01); I^2=83.42%						
Test for overall effect: Z=0.34(P=0.74)						



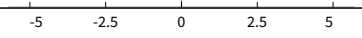
Analysis 1.3. Comparison 1 Asthma - low sodium diet (LSD) vs higher sodium diet (HSD), Outcome 3 PEFR (litres/min).

Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Lieberman 1992	0	0	-4.2 (25.72)		15.9%	-4.18[-54.59,46.23]
Medici 1993	0	0	34.8 (14.5)		31.27%	34.8[6.38,63.22]
Pogson 2008	0	0	1.5 (4.44)		52.82%	1.5[-7.2,10.2]
Total (95% CI)					**100%**	**11.01[-12.67,34.7]**
Heterogeneity: Tau^2=256.73; Chi^2=4.93, df=2(P=0.09); I^2=59.43%						
Test for overall effect: Z=0.91(P=0.36)						



Analysis 1.4. Comparison 1 Asthma - low sodium diet (LSD) vs higher sodium diet (HSD), Outcome 4 Bronchodilator usage (puffs/day).

Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Lieberman 1992	0	0	-0.3 (1.39)		0.31%	-0.33[-3.05,2.39]
Medici 1993	0	0	-0.4 (0.358)		4.74%	-0.4[-1.1,0.3]
Pogson 2008	0	0	-0 (0.08)		94.94%	-0.01[-0.17,0.15]
Total (95% CI)					**100%**	**-0.03[-0.18,0.12]**
Heterogeneity: Tau^2=0; Chi^2=1.18, df=2(P=0.56); I^2=0%						
Test for overall effect: Z=0.38(P=0.71)						



Analysis 1.5. Comparison 1 Asthma - low sodium diet (LSD) vs higher sodium diet (HSD), Outcome 5 Sodium excretion (mmol/L).

Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Carey 1993	0	0	-204 (9.35)		-204[-222.33,-185.67]
Lieberman 1992	0	0	-117 (19.33)		-117[-154.89,-79.11]
Medici 1993	0	0	-58 (15.74)		-58[-88.85,-27.15]
Pogson 2008	0	0	-51.2 (10)		-51.2[-70.8,-31.6]

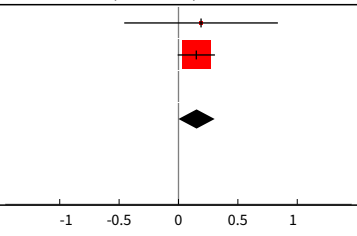
Comparison 2. Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Baseline FEV1 (litres)	2		Mean Difference (Random, 95% CI)	0.15 [-0.00, 0.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Baseline FVC (litres)	2		Mean Difference (Random, 95% CI)	0.13 [-0.00, 0.26]
3 Baseline FEV1/FVC (%)	2		Mean Difference (Random, 95% CI)	0.97 [-2.59, 4.53]
4 5-minute post-exercise FEV1 (litres)	1		Mean Difference (Random, 95% CI)	0.46 [0.01, 0.91]
5 5-minute post-exercise FVC (litres)	1		Mean Difference (Random, 95% CI)	0.48 [-0.01, 0.97]
6 5-minute post-exercise FEV1/FVC (%)	1		Mean Difference (Random, 95% CI)	3.0 [-6.80, 12.80]
7 Sodium excretion (mmol/l)	2		Mean Difference (Random, 95% CI)	-236.0 [-281.56, -190.44]

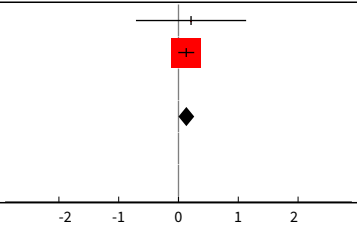
Analysis 2.1. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 1 Baseline FEV1 (litres).

Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Gotshall 2000	0	0	0.2 (0.33)		5.55%	0.19[-0.46,0.84]
Mickleborough 2005	0	0	0.2 (0.08)		94.45%	0.15[-0.01,0.31]
Total (95% CI)					**100%**	**0.15[-0,0.3]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%						
Test for overall effect: Z=1.96(P=0.05)						

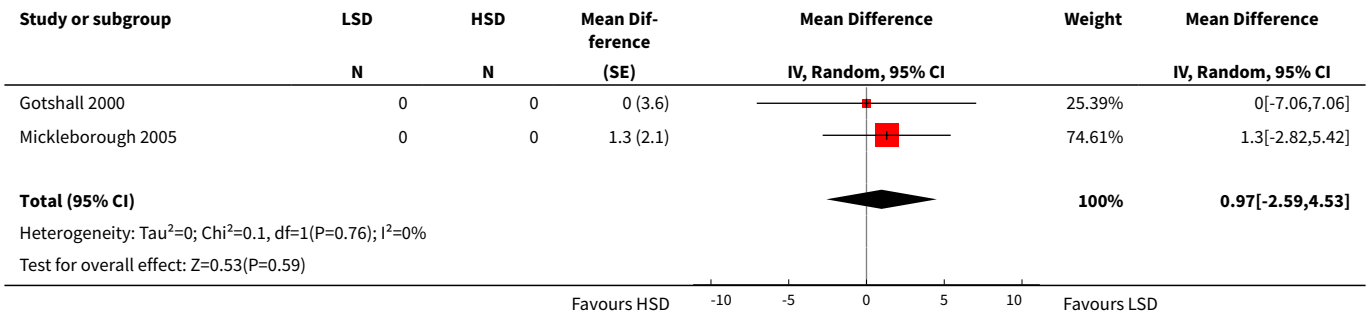


Analysis 2.2. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 2 Baseline FVC (litres).

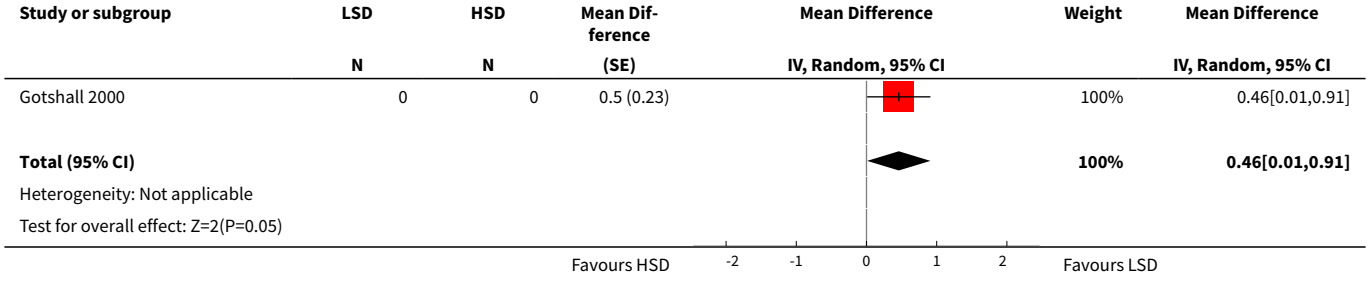
Study or subgroup	LSD N	HSD N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Gotshall 2000	0	0	0.2 (0.47)		2.05%	0.21[-0.71,1.13]
Mickleborough 2005	0	0	0.1 (0.068)		97.95%	0.13[-0,0.26]
Total (95% CI)					**100%**	**0.13[-0,0.26]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%						
Test for overall effect: Z=1.96(P=0.05)						



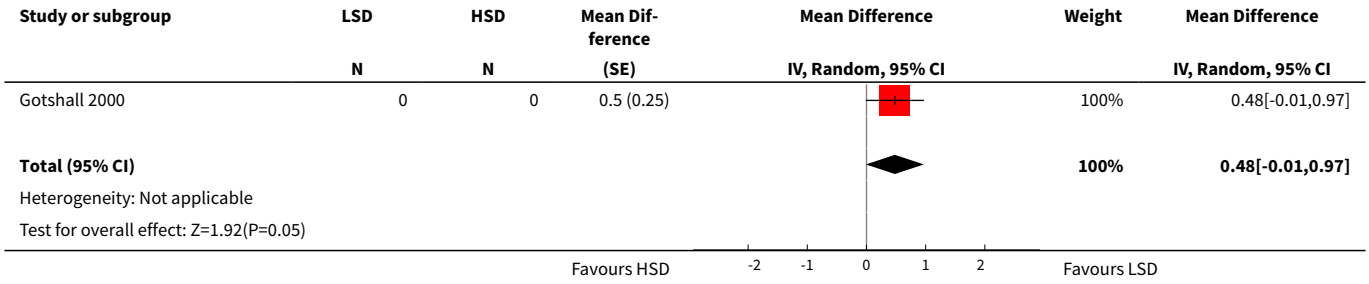
Analysis 2.3. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 3 Baseline FEV1/FVC (%).



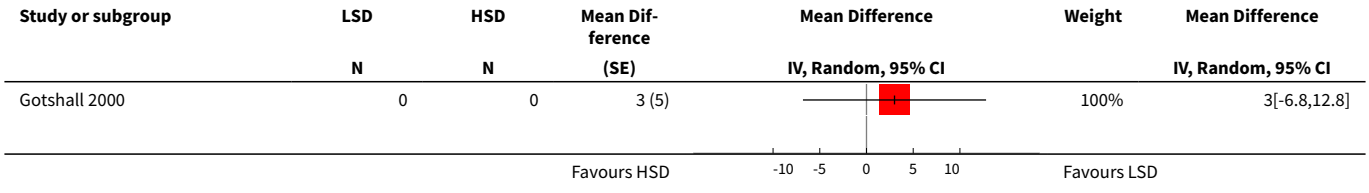
Analysis 2.4. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 4 5-minute post-exercise FEV1 (litres).

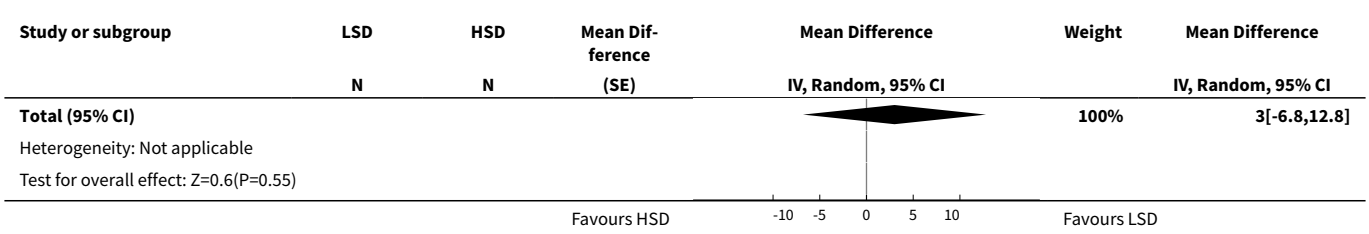


Analysis 2.5. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 5 5-minute post-exercise FVC (litres).

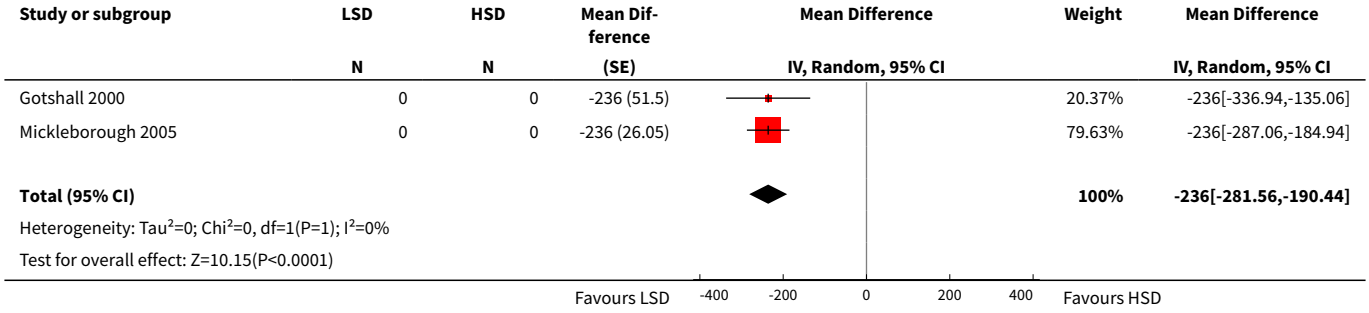


Analysis 2.6. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 6 5-minute post-exercise FEV1/FVC (%).





Analysis 2.7. Comparison 2 Exercise induced asthma - low sodium diet (LSD) vs high sodium diet (HSD), Outcome 7 Sodium excretion (mmol/l).



ADDITIONAL TABLES

Table 1. Details of included studies

Study	Number of Participants	Initial Diet Requirements	Interventions		Intervention period
			Low sodium diet	High sodium diet	
Asthma studies					
Burney 1989	36	Low sodium diet	Low sodium diet and placebo tablets	Low sodium diet and 80 mmol of sodium a day	Cross-over 2 weeks each limb
Lieberman 1992	17	Low sodium diet used for hypertension	Low sodium diet	Add sodium to diet and consuming 34 mmol of sodium a day	Cross-over 2 weeks each limb
Carey 1993	27	Low sodium diet aiming for 80 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 200 mmol of sodium a day	Cross-over 5 weeks each limb
Medici 1993	18	Low sodium diet aiming for 86 to 103 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 154 mmol of sodium a day	Cross-over 3 weeks each limb

Table 1. Details of included studies *(Continued)*

Pogson 2008	220	Low sodium diet aiming for 80 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 80 mmol of sodium a day	Parallel group 6 weeks intervention period
Exercise- induced asthma studies					
Mickleborough 2000	15	Meal plan aiming for 65 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 174 mmol of sodium a day	Cross-over 2 weeks each limb
Mickleborough 2001b	16	Meal plan aiming for 65 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 174 mmol of sodium a day (sodium bicarbonate)	Cross-over 2 weeks each limb
Gotshall 2000	8	Meal plan aiming for 65 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 174 mmol of sodium a day	Cross-over 2 weeks each limb
Mickleborough 2005	24	Meal plan aiming for 65 mmol of sodium a day	Low sodium diet and placebo tablets	Low sodium diet and 174 mmol of sodium a day	Cross-over 2 weeks each limb

WHAT'S NEW

Date	Event	Description
4 June 2014	Amended	PLS title amended

HISTORY

Protocol first published: Issue 3, 1996
Review first published: Issue 1, 2000

Date	Event	Description
13 January 2011	New search has been performed	New literature search carried out, review updated with three new studies.
13 January 2011	New citation required but conclusions have not changed	The author team has changed. The review has been rewritten from a new protocol and the title has changed.
18 February 2004	New citation required and conclusions have changed	Updated March 2004 by FR with the inclusion of another RCT (Mickleborough 2001) however, this did not alter the conclusion of the review.

CONTRIBUTIONS OF AUTHORS

ZP and TM conducted all of the work for this review with help from various people as listed in the acknowledgment section.

DECLARATIONS OF INTEREST

ZP and TM were both involved with the largest study reported in this review (Pogson 2008).

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK.

External sources

- No external support, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This was an update of a previous review. This previous review did not have a protocol and a review of the data only was performed.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet, Sodium-Restricted; Asthma [*prevention & control]; Asthma, Exercise-Induced [prevention & control]; Randomized Controlled Trials as Topic; Sodium Chloride, Dietary [*administration & dosage]

MeSH check words

Humans