Monosodium glutamate avoidance for chronic asthma in adults and children (Review)

Zhou Y, Yang M, Dong BR

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[Intervention Review]

Monosodium glutamate avoidance for chronic asthma in adults and children

Yan Zhou[1], Ming Yang[2], Bi Rong Dong[2]

[1]Department of Geriatrics, West China Hospital, Sichuan University, Chengdu, China. [2]Center of Geriatrics and Gerontology, West China Hospital, Sichuan University, Chengdu, China

Contact address: Yan Zhou, Department of Geriatrics, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China. hxzhouyan@hotmail.com.

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ABSTRACT

Background

Monosodium glutamate (MSG) is the sodium salt of the non-essential amino acid, glutamic acid, and is used as a flavour enhancer. It has been implicated in causing adverse reactions, which have been referred to as "Chinese restaurant syndrome". Over the last two decades there have been a number of studies investigating whether MSG ingestion induces an asthmatic response, and several reviews have been published (ILSI 1991; Stevenson 2000; Woods 2001), but no meta-analysis or Cochrane systematic review has been performed.

Objectives

The objectives of this review are to: 1) identify randomised controlled trials (RCTs) of MSG ingestion and asthma response in adults and children older than two years of age with asthma; 2) assess the methodological quality of these trials; and 3) determine the effect of MSG ingestion on asthma outcomes.

Search methods

We searched the Cochrane Airways group's Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and bibliographies of existing trials. Searches were current up to May 2012.

Selection criteria

We included RCTs that investigated the effect of MSG on chronic asthma in adults and children.

Data collection and analysis

Two authors independently extracted, entered and analysed data from included studies. We contacted study authors for additional information.

Main results

Only two cross-over studies involving 24 adults met the eligibility criteria; the challenge dosages of MSG were 1 g, 5 g and 25 mg/kg. They reported the number of subjects who had a maximum fall in forced expiratory volume in the first second (FEV_1) greater than 15% or 200 mL after MSG or the control challenge. The pooled data found no statistically significant difference between MSG and placebo. One trial reported the mean change at four hours and maximum fall in FEV_1 over four hours after MSG or the placebo

challenge, but found no statistically significant difference between interventions. There were no differences in symptom scores, non-specific bronchial hyper-responsiveness (BHR), eosinophil cationic protein (ECP) or tryptase levels in peripheral blood between MSG and control, although we were unable to perform meta-analyses.

Authors' conclusions

The limited evidence available (n = 24) found no significant difference between MSG or the control challenge for the number of subjects who had a maximum fall in FEV_1 greater than 15% or 200 mL. There is no evidence to support the avoidance of MSG in adults with chronic asthma, but as data were limited, this review cannot provide a reliable evidence base for determining whether MSG avoidance is a worthwhile strategy. We could not find any studies conducted on the effect of MSG in children with chronic asthma. There is therefore, a need for further RCTs to investigate any relationship between MSG and asthma, especially in children.

PLAIN LANGUAGE SUMMARY

Monosodium glutamate (MSG) avoidance for chronic asthma in adults and children

Monosodium glutamate (MSG) is used as a flavour enhancer and has been implicated in "Chinese Restaurant Syndrome", causing tightness, burning or numbness in the face, neck and upper chest (although there is no evidence to prove this syndrome). It has also been proposed that asthmatics may react badly to MSG. In two randomised controlled trials (RCTs), involving 24 adult asthmatics, there was no evidence that MSG worsened asthma when compared to control ingestion. Further RCTs are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Monosoium glutamate (MSG) avoidance for chronic asthma

Patient or population: adults and children with asthma
Settings: community
Intervention: monosodium glutamate (MSG) capsule
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk MSG capsule				
Lung function	See comment	See comment	See comment	See comment	⊕◯◯◯ **very low**[1,2,3]	We were unable to pool the two small trials on 24 people. The participants are different in each trial (Schwartzstein 1987: 12 people with chronic asthma and Woods 1998: 12 people who perceived themselves MSG-intolerant) and we would not expect the same effect in these two trials
Hospital admissions	See comment	See comment	See comment	See comment	⊕◯◯◯ **very low**[1,2,3]	See above

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. (-1 limitations) we were uncertain of methods for randomisation
2. (-1 indirectness) participants are different in each trial (Schwartzstein 1987: chronic asthma and Woods 1998: people who perceived themselves MSG-intolerant) and we would not expect the same treatment effect in these two trials (unless the treatment is ineffective)
3. (-1 imprecision) small trials with few events

BACKGROUND

Monosodium glutamate (MSG), a flavour enhancer, is the sodium salt of the non-essential amino acid, glutamic acid. Glutamate is present in almost all proteins, and it plays an essential role in human metabolism as a key component of metabolic cycles (Filer 1994). Because there is no chemical difference between the MSG we find in foods and the MSG manufactured through fermentation by micro-organisms, the effects of MSG on the body are the same.

Kwok 1968 originally noted that MSG may cause adverse reactions; he wrote a letter to the New England Journal of Medicine to explain how he felt after eating MSG in a Chinese restaurant. The symptoms were tightness, burning or numbness in the face, neck and upper chest. This syndrome was named "Chinese Restaurant Syndrome". Kwok hypothesised that this syndrome could be due to MSG, sodium or some other unidentified substance. In 1981, Allen and Baker reported two cases of asthma and proposed an association between asthma and MSG (Allen 1981). Over the last two decades there have been a number of studies investigating whether MSG ingestion can induce an asthmatic response, but results are conflicting.

Although there are hypotheses about the mechanisms of MSG-induced asthma, for example, mediated by immunoglobulin E (IgE; a class of antibody found in mammals) or acetylcholine, findings are inconclusive. Yoneda 2011 investigated the effects of MSG on bronchial inflammation; they measured cytological, histological and functional changes in an ovalbumin-induced asthma mouse model, but found no acute effects on lung inflammation or airway hyper-responsiveness.

Although there are several narrative reviews on this topic (ILSI 1991; Stevenson 2000; Woods 2001), no meta-analyses have been performed.

OBJECTIVES

The objectives of this review were to:

1. identify randomised controlled trials (RCTs) of monosodium glutamate (MSG) ingestion and asthma response in adults and children older than two years of age with asthma;

2. assess the methodological quality of these trials; and

3. determine the effect of MSG ingestion on asthma outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs only, with either parallel or cross-over design. We preferred double-blind trials, but we also reviewed single-blind and open studies for possible inclusion. We did not limit inclusion of trials by their duration.

Types of participants

We included adults and children older than two years with a diagnosis of asthma. We accepted trialist-defined asthma and recorded both the definition of asthma and the entry criteria used for each trial. We excluded studies on patients with acute asthma or exercise-induced bronchospasm because it is difficult to identify whether the attack of asthma is caused by MSG. We considered studies which included patients with other conditions only if the results for subjects with asthma could be identified separately. We excluded studies in children less than two years of age.

Types of interventions

We included studies involving either a challenge of MSG to the diet, manipulation of dietary intake of MSG, or both. We considered only the oral route of administration (for example, capsule or liquid etc). We included placebo and untreated control groups.

Types of outcome measures

We anticipated that not all studies would have results pertaining to the entire outcome measures listed below, but included all outcomes that were reported or available through contact with the authors.

Primary outcomes

1. Lung function measurements, such as forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF) or forced vital capacity (FVC)
2. Hospital admissions

Secondary outcomes

1. Asthma symptom scores
2. Bronchial hyper-responsiveness (BHR)
3. Soluble inflammatory markers, such as eosinophil cationic protein (ECP) and/or tryptase
4. Asthma medication usage

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways group "Asthma and Wheez* RCT" ProCite Specialised Register, with no language restrictions. We performed the latest search in May 2012.
We used the following search terms:
MSG or "monosodium glutamate*" or monoglutamate or monosodiumglutamate or *sodium or sodium* or glutam* or Glutavene or L-glutamic or L-glu or accent or vestin or (food* and (salt* or additive* or flavour* or flavor*)).

Searching other resources

We searched bibliographies of existing trials and approached primary authors of eligible trials and MSG manufacturing companies to ask if they were aware of any other published or unpublished trials. We also searched trial registries for current or recently completed trials.

Data collection and analysis

Selection of studies

Two review authors (YZ, MY) reviewed the title and abstract of references returned by the searches to identify potentially relevant trials for full review. Then we independently read the abstract and methods sections of the papers to select the trials for inclusion in this review. We resolved differences between reviewer authors by consensus.

Data extraction and management

Two review authors (YZ, MY) independently extracted data for inclusion in the Characteristics of included studies tables. We contacted the principal investigators of included studies, when necessary, to request additional data or confirm methodological aspects of their study. We combined trials using Review Manager 5.1 software (RevMan 2011).

Assessment of risk of bias in included studies

We assessed the risk of bias in the included studies as either 'high', 'low' or 'unclear' using the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011a) under the following headings: 1) sequence generation; 2) allocation concealment; 3) blinding; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other potential bias.

Measures of treatment effect

Lung function measurements included the forced expiratory volume in one second (FEV_1), the peak expiratory flow (PEF) and the forced vital capacity (FVC). Hospital admissions included the total number of admissions, the number of participants admitted to hospital and hospital admission rates. Asthma symptom scores included both validated and simple (for example, visual analogue scales) scores. Bronchial hyper-responsiveness (BHR) to a range of non-specific provocants were included, either measured as the provocation concentration or provocation dose of the provocant. Soluble inflammatory markers included eosinophil cationic protein (ECP), tryptase, or both. Asthma medication usage was recorded as number of puffs of inhaled therapy over specific time periods.

Unit of analysis issues

We planned to combine data from cross-over studies using generic inverse variance in Review Manager 5.1 software (RevMan 2011).

Dealing with missing data

We requested information from the trial authors when sufficient details were not available in the published reports to conduct analyses.
For binary outcomes, we used data from intention-to-treat analyses. If intention-to-treat data were not available in the publications, we used 'on-treatment' data (i.e. the data of those who complete the trial) and indicated it as such.

Assessment of heterogeneity

We had planned to measure statistical variation between studies using the I^2 statistic (Higgins 2011b). If we had found significant heterogeneity we had planned to investigate this further using sensitivity analyses as indicated below.

Assessment of reporting biases

We had planned to visually inspected funnel plots to test for publication bias if we had found sufficient trials on a single meta-analysis.

Data synthesis

We had planned to combine data in Review Manager 5.1 (RevMan 2011) using a fixed-effect mean difference (MD) and the 95% confidence intervals (CIs) for continuous variables measured on the same scale. We would have calculated the standardised mean difference (SMD) and 95% CIs for variables measured on different scales. We had planned to use a fixed-effect odds ratio (OR) for dichotomous variables. We had planned to compare random-effects and fixed-effect models; if we found a major difference in the pooled effect sizes and their 95% CIs, we would have opted for the random-effect model.

Subgroup analysis and investigation of heterogeneity

We had planned to perform the following subgroup analyses if we had found sufficient data:

1. MSG versus placebo:
2. MSG versus no treatment;
3. low dose versus high dose; and
4. adults versus children.

Sensitivity analysis

We had planned to perform sensitivity analyses if we had found sufficient included trials to explore the influence of the:

- risk of bias for allocation concealment; and
- risk of bias for outcome evaluation.

RESULTS

Description of studies

Results of the search

From the preliminary searches (latest search May 2012) we found a total of 86 references. By searching bibliographies of existing trials, we identified five additional studies. After removing 15 duplicate references from the searches, we identified 76 studies as potentially relevant; only two of these studies met the entry criteria and we included them in this review.

Included studies

Both studies that met the inclusion criteria were double-blind, randomised, cross-over trials that recruited adult participants (Schwartzstein 1987; Woods 1998). Full details of these included studies can be found in the Characteristics of included studies section.

The purpose of the Schwartzstein 1987 trial was to study the effect of oral MSG on airway function in 12 subjects with a history of chronic asthma (diagnosed using criteria from the American Thoracic Society). Participants had a history of food sensitivity, or not, and they were clinically stable. Clincal stability was defined as: 1) no increase in symptoms requiring medical attention within the past month; 2) no participants receiving corticosteroid therapy for at least one month; and 3) being able to discontinue medications for at least 12 hours without adverse effects. The article did not report how the participants were recruited. The participants (eight men and four women) were 22 to 44 years old (mean 28 years), and the mean duration of asthma was 16 years (3 to 30 years). None of the participants used bronchodilators within 12 hours of the challenges. Two participants had a history of milk sensitivity, and only one subject believed that she was MSG-sensitive. Six subjects were receiving bronchodilator therapy on a daily basis. The interventions were MSG (25 mg/kg) versus sodium chloride (equimolar to MSG), given in identical capsules. Subjects fasted for at least six hours prior to study visits. The forced expiratory volume in the first second ($FEV_{1)}$ and forced vital capacity (FVC) were measured before and after the challenge for two hours, with a 15-minute interval, and then they were measured every 30 minutes for a further two hours. If at the end of four hours observation, the FEV_1 had declined by 10% or more from baseline, measurement of pulmonary function continued at 30-minute intervals for an additional two hours. At the end, subjects were asked whether they had experienced any side effects, 24 to 48 hours after each study day.

The main purpose of the Woods 1998 trial was to determine if MSG would induce bronchoconstriction in adults with asthma who perceived they were MSG-sensitive. Twelve participants were recruited through The Alfred Hospital Asthma and Allergy Clinic, from patients registered on a computer database, between March 1995 and September 1996. The participants were aged between 19 and 57 years (mean 35.3 years), and seven (58%) of them were female. All of the participants had a history of reversible airway obstruction, however, they had been clinically stable without any change in their regular asthma medications in the past four weeks before the study. The study exclusion criteria were: 1) a previous life-threatening attack of asthma; 2) life-threatening anaphylaxis; 3) females who were pregnant or lactating or 4) a baseline FEV_1 greater than 60% predicted or less than 1.5 L. An elimination diet was commenced after the baseline visit. Subjects continued with their regular inhaled bronchodilators and anti-inflammatory asthma medications during the study period, but they were instructed to withhold their short-acting $beta_2$- agonist bronchodilator medication for at least four hours before attending the laboratory on each of the control days**.** The amount of relief medication and the time it was taken, if required on the control day, was duplicated on the subsequent control and challenge days. The participants received MSG (1 g), MSG (5 g), and placebo (5 g lactose) challenges as single doses on an empty stomach. Subjects received the lower dose (1 g) of MSG before the higher dose (5 g), with the placebo randomly interspersed on separate study days. Spirometry was conducted every 15 minutes, commencing 45 minutes before the challenge. The participants continued to monitor their peak expiratory flow (PEF) and FEV_1 at 15, 30, and 45 minutes and regular intervals after each challenge until 12 hours. Symptoms, symptom scores, non-specific bronchial hyperresponsiveness (BHR) and soluble inflammatory marker activity (tryptase and eosinophil cationic protein (ECP)) were also measured.

Excluded studies

We excluded 74 references for the following reasons.

1. The studies did not examine the relationship between MSG and asthma (N = 45).
2. They were review articles (N = 10), rather than trials.
3. The studies were not randomised (N = 9).
4. The studies involved subjects with diseases other than asthma (N = 10).

Full details can be found in the Characteristics of excluded studies table.

Risk of bias in included studies

We judged risk of bias in included studies as unclear using the Cochrane Collaboration's 'Risk of bias' tool (see Figure 1, Figure 2). Our judgement of each risk of bias can be found in Characteristics of included studies.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

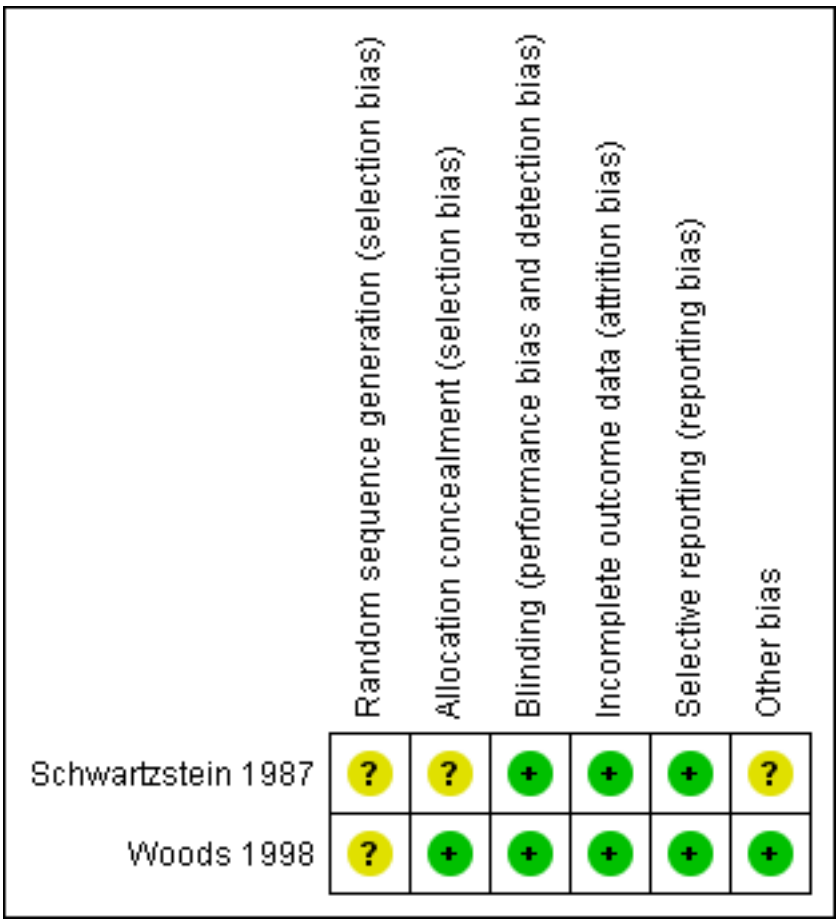
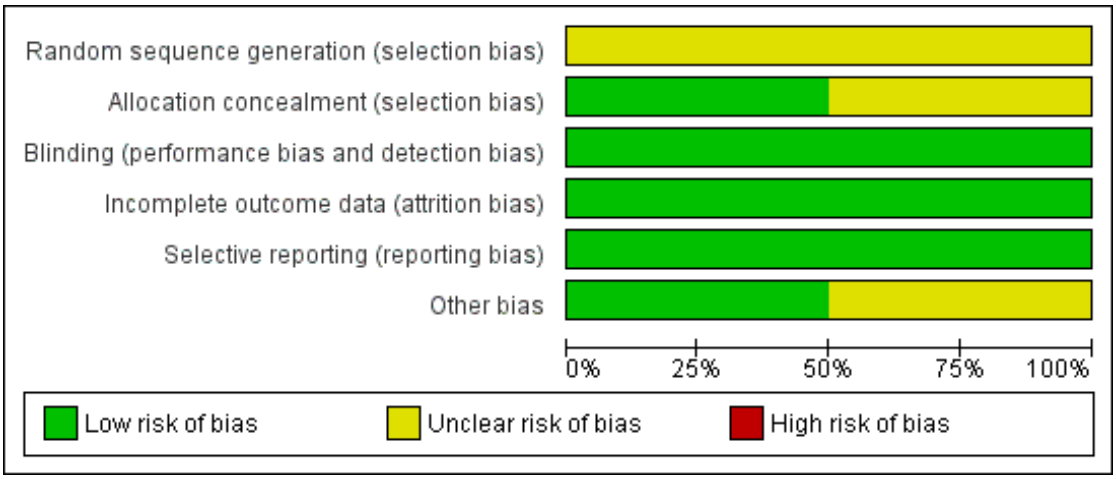


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Both studies (Schwartzstein 1987; Woods 1998) were reported as randomised, but gave no information of the methods used, and we therefore judged them to be at unclear risk of bias. Schwartzstein 1987 did not describe the allocation concealment, but there was reference to personnel carrying-out the randomisation in Woods 1998, and so we judged the latter as low risk of bias. Subjects and investigators were blinded as to the identity of the medications. Because of the unique flavour of MSG, capsules were used in both studies so that participants were unable to tell the difference between a capsule containing MSG and one containing placebo. All of the outcomes were reported according to the protocol. Schwartzstein 1987 was supported in part by the International Glutamate Technical Committee, and we are unsure if such sponsorship would influence the result.

Effects of interventions

See: **Summary of findings for the main comparison**

Two cross-over trials involving a total of 24 subjects were included, with all subjects being exposed to MSG and control interventions. Both reported changes in FEV_1 after MSG and placebo challenges (Schwartzstein 1987; Woods 1998). Woods 1998 reported other outcomes, including non-specific BHR, ECP levels in peripheral blood and symptom scores.

We were unable to perform meta-analyses because of the heterogeneity of the studies. The participants in included studies were different; Schwartzstein 1987 included people with chronic asthma, with or without a history of food sensitivity, and Woods 1998 included people with clinically documented asthma and who perceived themselves MSG-intolerant). Furthermore, to be able to combine dichotomous data from cross-over studies, we would need to know the number of participants who form discordant pairs, but this information was not reported in Schwartzstein 1987. Hence, we presented the results in narrative form.

Primary outcome: lung function

In Woods 1998, eight out of 12 people experienced a fall in FEV_1, PEF, or both of greater than 15% of their pre-challenge spirometry after receiving an MSG challenge (each received two separate challenges of 1 g and 5 g). Two participants experienced a fall in lung function measurement after placebo only, three after both active and placebo treatment, and two to the 1 g MSG challenge only, but not the 5 g MSG challenge. One subject had a greater than 15% fall in spirometry to both high and low doses of MSG, but the change was not statistically significant and the trialists interpreted this as a negative effect. All participants except one experienced a drop of 20% or more of their pre-challenge spirometry measurement, so the authors stated that they "did not find any conclusive evidence of true MSG-induced asthma by using this rigorous method of analysis" (Woods 1998).

Schwartzstein 1987 gave only one MSG challenge of 25 mg/kg. Schwartzstein 1987 reported the mean FEV_1 change at four hours post-challenge and the difference between these values was not statistically significant.

In summary, there was no statistically significant difference between MSG and placebo for a positive FEV_1 response at any of the doses studied.

Secondary outcomes

Symptom scores

Woods 1998 reported that there were no statistically significant differences in daytime or night time symptom scores between

placebo and 1 g MSG challenges (P = 0.5 and P = 1.0, respectively), placebo and 5 g MSG challenges (P = 1.0 and P = 1.0, respectively), or 1 g and 5 g MSG challenges (P = 0.25 and P = 1.0, respectively). Schwartzstein 1987 reported the number of participants who had unusual sensations (two in the MSG group and two in the placebo group), but did not score the symptoms.

Non-specific bronchial hyper-responsiveness

Woods 1998 found that there was no evidence of MSG affecting non-specific BHR.

Eosinophil cationic protein levels in peripheral blood

Woods 1998 reported that five participants had elevated ECP levels following the MSG challenge, however, baseline ECP levels were elevated in four participants. In the fifth subject, the ECP level was raised after both the 1 g and 5 g MSG challenge (the level was higher after the 1 g than the 5 g MSG challenge), but was normal after the placebo challenge.

Tryptase levels in peripheral blood

Woods 1998 found that the only elevated tryptase level occurred on a baseline sample.

DISCUSSION

This review summarises evidence from two small clinical trials assessing the effects of the MSG challenge on short-term physiological, symptomatic and biomarker outcomes. Long-term dietary avoidance has not been addressed in any clinical trials involving asthma patients to date. The evidence from this review, which found no difference in outcomes following MSG or control exposure, does not provide a reliable basis for recommendations on avoidance of MSG.

There are two reasons for this. First of all, only two small trials met the eligibility criteria of the review. The sample sizes of both studies were small and identical in number (n = 12), and the quality of one study was poor. As data from the included studies were limited, no firm conclusions can be drawn from this review regarding the effects of MSG in asthma. Secondly, the participants recruited had been clinically stable; those with a baseline FEV_1 of less than 60% predicted were excluded. Therefore, these results cannot be applied to people with severe or unstable asthma, nor children, since both trials recruited only adult patients.

The dose of MSG in studies is reasonable. The average daily MSG intake in Western countries is 0.3 g to 1 g, but it may be as high as 4 g to 6 g in a highly seasoned restaurant meal (Allen 1987). The doses in the studies were 0.3 g to 7.5 g (0.3, 1, 2.5, 5, 6, 7.5) (Raiten 1995), and the dosage used most frequently was 2.5 g. The doses used in challenges in the included studies are similar to quantities in meals, which means that it is unlikely that the absence of effect is due to under dosing.

Another limitation of this review is the lack of numerical outcome data on clinical scores such as symptoms, for which we were unable to extract raw data from trials assessing these outcomes.

We did not find any RCTs assessing the effects of MSG in children, so were unable to explore the relationship between childhood asthma and MSG.

Our result is consistent with most clinical (Freeman 2006; Stevenson 2000; Williams 2009) and mechanical (Yoneda 2011) studies, and it is difficult to draw a firm conclusion.

AUTHORS' CONCLUSIONS

Implications for practice

Limited evidence from people with stable chronic asthma did not provide any evidence that MSG could pose a risk. However, this review has not been able to establish the effect of MSG exposure on people with stable chronic asthma, as data were limited by small sample sizes. Because of the lack of data, these results cannot be applied to people with severe or unstable asthma, nor children since both trials recruited only adult patients.

Implications for research

There is a need for large, placebo-controlled randomised trials that would address as many MSG-related symptoms as possible, and researchers should pay attention to other aspects such as psychological factors. There is a need for further studies in children.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Schwartzstein 1987

Methods	Double-blind, randomised, cross-over trial
Participants	12 patients (male = 8, female = 4) with chronic stable asthma Mean age 28 years (22 to 44) Mean duration of asthma 16 years (3 to 30)
Interventions	1. MSG (25 mg/kg) 2. Sodium chloride (equimolar to MSG) Treatments administered in identical capsules
Outcomes	FEV_1 and FVC collected at: 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240 minutes If FEV_1 declined $\geq$ 10%, FEV_1 and FVC were also measured at 270, 300, 330, 360 minutes Symptoms: 24, 48 hours
Notes	Diagnostic criteria: American Thoracic Society This study was supported in part by the International Glutamate Technical Committee

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The order in which the test substances were given was randomly assigned" Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"both subjects and investigators were blinded as to the identity of the medications being given." The drugs were administered in identical capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results of all the subjects were reported
Selective reporting (reporting bias)	Low risk	All the results described in method chapter were reported
Other bias	Unclear risk	"This study was supported in part by the International Glutamate Technical Committee"

Schwartzstein 1987 (*Continued*)

		Comment: we are not certain whether it would influence the result

Woods 1998

Methods	Double-blind, randomised, cross-over, placebo-controlled trial
Participants	12 patients (male = 5, female = 7) who believed they had previously had reactions to MSG Mean age 35.3 years (19 to 57)
Interventions	1. MSG 1 g 2. MSG 5 g 3. Placebo (lactose)
Outcomes	FEV_1, PEF at -15, -30, -45, 0, 15, 30, 45 minutes; 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours on 15 days , 18 days, 20 days (challenge visit 6, 7, 8 days) Soluble inflammatory marker activity (ECP and tryptase)(2 days, 6 days, 7 days, 8 days) Non-specific BHR to methacholine (1 day, 5 days, 9 days)
Notes	Diagnostic criteria: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"This study was conducted as a randomised, cross-over, double-blind, placebo-controlled trial" "We thank Ms. Anne James, Pharmacist, for the preparation of the challenge capsules and Ms. Pam Liakakis, Respiratory Scientist, for the randomisation and administration of the capsules" Comment: Not described
Allocation concealment (selection bias)	Low risk	"We thank Ms. Anne James, Pharmacist, for the preparation of the challenge capsules and Ms. Pam Liakakis, Respiratory Scientist, for the randomisation and administration of the capsules"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Each challenge dose comprised 10 size 00 opaque capsules, which were manufactured with a capsule machine filler (Sandell, Switzerland) by a pharmacist not otherwise involved in the study. All capsules were wiped clean after filling and rolled in lac-

Woods 1998 (*Continued*)

		tose powder to prevent any MSG being detected on the outside of the capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results of all the subjects were reported
Selective reporting (reporting bias)	Low risk	All the results described in the method chapter were reported
Other bias	Low risk	"The participants had a diet that was low in other chemicals perceived to cause asthma symptoms" Comment: it minimised the influence of other materials

BHR: bronchial hyper-responsiveness
FEV_1: forced expiratory volume in the first second
FVC: forced vital capacity
MSG: monosodium glutamate
PEF: peak expiratory flow

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

Study	Reason for exclusion
Allen 1987	Not randomised
Bernstein 1978	Not focused on the relationship between MSG and asthma
Briese 1987	Not focused on the relationship between MSG and asthma
Businco 1990	Not focused on the relationship between MSG and asthma
D'Elia 1972	Not randomised
Dahl 1978	Not focused on the relationship between MSG and asthma
Daniliak 1995	Not focused on the relationship between MSG and asthma
Demissie 1996	Not focused on the relationship between MSG and asthma
Doeglas 1975	Involved subjects with other diseases, such as urticaria, rather than asthma
Fiocchi 1995	Involved subjects with other diseases, such as urticaria, rather than asthma

(*Continued*)

FSA 1998	Involved subjects with other diseases, such as urticaria, rather than asthma
Fuchs 1998	Not focused on the relationship between MSG and asthma
Fuglsang 1994	Not focused on the relationship between MSG and asthma
Germano 1991	Not randomised
Harries 1978	Not focused on the relationship between MSG and asthma
Hodge 1996	Not randomised
James 1999	Review
Novembre 1988	Review
Onorato 1986	Not randomised
Pacor 1992	Not randomised
Patil 1997	Not focused on the relationship between MSG and asthma
Prieto 1988	Not focused on the relationship between MSG and asthma
Raiten 1995	Review
Reinert 1991	Involved subjects with other diseases, such as urticaria, rather than asthma
Sabbah 1990	Review
Stenius 1976	Not focused on the relationship between MSG and asthma
Stevenson 1997	Not randomised
Stevenson 2000	Review
Tarlo 1982	Not focused on the relationship between MSG and asthma
Walker 1999	Review
William 1997	Not focused on the relationship between MSG and asthma
Wilson N 1989	Not focused on the relationship between MSG and asthma
Woessner 1999	Not randomised
Yang 1997	Involved subjects with other diseases, such as urticaria, rather than asthma

MSG: monosodium glutamate

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 2 May 2012.

Date	Event	Description
4 June 2014	Amended	PLS title amended

CONTRIBUTIONS OF AUTHORS

Yan Zhou selected the trials, extracted data, performed analyses, and wrote the review.

Ming Yang selected the trials.

Birong Dong gave advice on methodology.

Richard Wood-Baker edited the review and revised text.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Chinese Cochrane Centre, China.

INDEX TERMS

Medical Subject Headings (MeSH)

Asthma [*chemically induced; physiopathology]; Cross-Over Studies; Food Additives [*adverse effects]; Forced Expiratory Volume [*drug effects]; Sodium Glutamate [*adverse effects]

MeSH check words

Adult; Humans