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[Intervention Review]

Interventions for managing taste disturbances

Sumanth Kumbargere Nagraj[1], Renjith P George[2], Naresh Shetty[3], David Levenson[4], Debra M Ferraiolo[4], Ashish Shrestha[5]

[1]Department of Oral Medicine and Oral Radiology, Faculty of Dentistry, Melaka-Manipal Medical College, Melaka, Malaysia. [2]Department of Oral Pathology, Faculty Of Dentistry, Melaka-Manipal Medical College, Melaka, Malaysia. [3]School of Dentistry Oral & Maxillofacial Surgery, International Medical University - IMU, Bukit Jalil, Malaysia. [4]Department of Oral and Maxillofacial Pathology, Radiology and Medicine, New York University College of Dentistry, New York, New York, USA. [5]Community Dentistry, College of Dentistry, BP Koirala Institute of Health Sciences, Dharan, Nepal

Contact address: Sumanth Kumbargere Nagraj, Department of Oral Medicine and Oral Radiology, Faculty of Dentistry, Melaka-Manipal Medical College, Jalan Batu Hampar, Bukit Baru, Melaka, 75150, Malaysia. sumikn@rediffmail.com, sumikn@yahoo.co.in.

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ABSTRACT

Background

The sense of taste is very much essential to the overall health of an individual. It is a necessary component to enjoy one's food, which in turn provides nutrition to an individual. Any disturbance in taste perception can hamper quality of life in such patients by influencing their appetite, body weight and psychological well-being. Taste disorders have been treated using different modalities of treatment and there is no consensus for the best intervention. Hence this Cochrane Review was undertaken. This is an update of the Cochrane Review first published in November 2014.

Objectives

To assess the effects of interventions for the management of patients with taste disturbances.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 4 July 2017); the Cochrane Central Register of Controlled Trials (CENTRAL; 2017 Issue 6) in the Cochrane Library (searched 4 July 2017); MEDLINE Ovid (1946 to 4 July 2017); Embase Ovid (1980 to 4 July 2017); CINAHL EBSCO (1937 to 4 July 2017); and AMED Ovid (1985 to 4 July 2017). The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for trials. Abstracts from scientific meetings and conferences were searched on 25 September 2017. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

We included all randomised controlled trials (RCTs) comparing any pharmacological agent with a control intervention or any non-pharmacological agent with a control intervention. We also included cross-over trials in the review.

Data collection and analysis

Two pairs of review authors independently, and in duplicate, assessed the quality of trials and extracted data. Wherever possible, we contacted trial authors for additional information. We collected adverse events information from the trials.

Main results

We included 10 trials (581 participants), nine of which we were able to include in the quantitative analyses (566 participants). We assessed three trials (30%) as having a low risk of bias, four trials (40%) at high risk of bias and three trials (30%) as having an unclear risk of bias. We only included studies on taste disorders in this review that were either idiopathic, or resulting from zinc deficiency or chronic renal failure.

Of these, nine trials with 544 people compared zinc supplements to placebo for patients with taste disorders. The participants in two trials were children and adolescents with respective mean ages of 10 and 11.2 years and the other seven trials had adult participants. Out of these nine, two trials assessed the patient-reported outcome for improvement in taste acuity using zinc supplements (risk ratio (RR) 1.40, 95% confidence interval (CI) 0.94 to 2.09; 119 participants, very low-quality evidence). We meta-analysed for taste acuity improvement using objective outcome (continuous data) in idiopathic and zinc-deficient taste disorder patients (standardised mean difference (SMD) 0.44, 95% CI 0.23 to 0.65; 366 participants, three trials, very low-quality evidence). We also analysed one cross-over trial separately using the first half of the results for taste detection (mean difference (MD) 2.50, 95% CI 0.93 to 4.07; 14 participants, very low-quality evidence), and taste recognition (MD 3.00, 95% CI 0.66 to 5.34; 14 participants, very low-quality evidence). We meta-analysed taste acuity improvement using objective outcome (dichotomous data) in idiopathic and zinc-deficient taste disorder patients (RR 1.42, 95% 1.09 to 1.84; 292 participants, two trials, very low-quality evidence). Out of the nine trials using zinc supplementation, four reported adverse events like eczema, nausea, abdominal pain, diarrhoea, constipation, decrease in blood iron, increase in blood alkaline phosphatase, and minor increase in blood triglycerides.

One trial tested taste discrimination using acupuncture (MD 2.80, 95% CI -1.18 to 6.78; 37 participants, very low-quality evidence). No adverse events were reported in the acupuncture trial.

None of the included trials could be included in the meta-analysis for health-related quality of life in taste disorder patients.

Authors' conclusions

We found very low-quality evidence that was insufficient to conclude on the role of zinc supplements to improve taste acuity reported by patients and very low-quality evidence that zinc supplements improve taste acuity in patients with zinc deficiency/idiopathic taste disorders. We did not find any evidence to conclude the role of zinc supplements for improving taste discrimination, or any evidence addressing health-related quality of life due to taste disorders.

We found very low-quality evidence that is not sufficient to conclude on the role of acupuncture for improving taste discrimination in cases of idiopathic dysgeusia (distortion of taste) and hypogeusia (reduced ability to taste). We were unable to draw any conclusions regarding the superiority of zinc supplements or acupuncture as none of the trials compared these interventions.

PLAIN LANGUAGE SUMMARY

Interventions for managing taste disturbances

What is the aim of this review?

The aim of this Cochrane Review was to find out what is the best method for the management of zinc-deficient/idiopathic (of unknown cause) taste disorders and taste disorders secondary to chronic renal failure in children and adults.

Key messages

Giving zinc supplements or acupuncture may have some benefit in treating taste disorders. However, we still need more high-quality studies to ascertain the role of zinc supplements and acupuncture in treating taste disorders.

What was studied in the review?

The sense of taste is essential to the health and psychological well-being of an individual. Taste disorders can range from lack of taste, to distortion of taste, to reduced ability to taste. Any disorder in taste perception can lead to conditions like malnutrition and consumption of poisonous food substances. The cause may be due to disease, drugs, radiation treatment, or ageing; or it may result from unknown causes.

Various treatment methods have been used to improve taste sensation. These include the use of zinc compounds, pilocarpine, alpha lipoic acid, transcranial magnetic stimulation, ginkgo biloba and acupuncture.

What are the main results of the review?

We collected and analysed all relevant studies to answer this question and found 10 trials in which a total of 581 subjects received different treatments. Nine trials assessed the benefits of zinc compounds and one trial assessed the effects of acupuncture. We only included studies on taste disorders in this review that were either idiopathic, or resulting from zinc deficiency or chronic renal failure.

Two trials were from Germany, three from Japan, two from the UK, and three from the US. These studies compared zinc with placebo or acupuncture with sham procedure for patients with taste disorders. Two were government funded, three were privately funded, two were funded by a pharmaceutical company and three trials did not mention funding details.

When patients with taste disorders are given zinc, compared to placebo:

- we found very low-quality evidence that was insufficient to conclude on the role of zinc supplements to improve taste acuity reported by patients and very low-quality evidence that zinc supplements improve taste acuity in patients with zinc deficiency/idiopathic taste disorders;
- zinc supplementation showed adverse events like eczema, nausea, abdominal pain, diarrhoea, constipation, decrease in blood iron, increase in blood alkaline phosphatase and minor increase in blood triglycerides;
- no studies were found that looked at improvement in taste discrimination or quality of life.

When patients with taste disorders are given acupuncture, compared to sham procedure:

- we found very low-quality evidence that is not sufficient to conclude on the role of acupuncture for improving taste discrimination in cases of idiopathic dysgeusia (distortion of taste) and hypogeusia (reduced ability to taste);
- acupuncture trial did not show adverse events;
- no studies were found that looked at improvement in taste acuity or quality of life.

We were unable to draw any conclusions regarding the superiority of zinc supplements or acupuncture as none of the trials compared these interventions.

How up-to-date is this review?

We searched for studies that had been published up to 4 July 2017.

Summary of findings for the main comparison. Zinc compared to placebo for the management of taste disturbances

Zinc compared to placebo for the management of taste disturbances						
Patient or population: patients with taste disturbances **Setting:** secondary and tertiary hospitals **Intervention:** zinc **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with zinc**				
Taste acuity improvement (patient-reported outcome) assessed with VAS/questionnaire where improvement in dysgeusia is defined as more than 5% improvement in the VAS scores for a mean follow-up period of 3 months	Study population - zinc-deficient/idiopathic taste disorder 407 per 1000	569 per 1000 (382 to 850)	1.40 (0.94 to 2.09)	119 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[1, 2, 3]	There is a 40% relative increase in taste acuity improvement (patient-reported outcome) in patients taking zinc when compared to placebo with a CI of 6% decrease to 109% increase of taste acuity
Taste acuity improvement (objective outcome - continuous data) assessed with filter paper strip and filter paper disk methods for a mean follow-up period of 3 months	-	SMD 0.44 higher (0.23 higher to 0.65 higher)	-	366 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[3, 4, 5]	The standardised mean difference for taste acuity improvement in the zinc intervention group is 0.44 higher than the placebo group
Taste acuity improvement (objective outcome - dichotomous data) assessed with filter paper disk and Henkin's 3-drop stimulus method for a mean follow-up period of 3 months	Study population - zinc-deficient/idiopathic taste disorder 435 per 1000	618 per 1000 (475 to 801)	RR 1.42 (1.09 to 1.84)	292 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[3, 6, 7]	There is a 42% relative improvement in taste acuity in patients taking zinc when compared to placebo with a CI of 9% to 84% increase of taste acuity
Cross-over trial - taste detection assessed with Henkin's method for a follow-up period of 6 months	The mean taste detection was 7.5	MD 2.50 higher (0.93 higher to 4.07 higher)	-	14 (1 RCT)	⊕⊖⊖⊖ VERY LOW[3, 7, 8]	The mean difference for taste detection in the intervention group is 2.50 higher than the placebo group
Cross-over trial - taste recognition assessed with Henkin's method for a follow-up period of 6 months	The mean taste recogni-	MD 3.00 higher (0.66 higher to 5.34 higher)	-	14 (1 RCT)	⊕⊖⊖⊖ VERY LOW[3, 7, 8]	The mean difference for taste recognition in the intervention group is 3.00 higher than placebo group

	tion was 16				
Adverse events - follow-up range 12 weeks to 18 weeks	Study population - zinc-deficient/idiopathic taste disorder and taste disorder secondary to chronic renal failure	5.20 (0.90 to 30.19)	335 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[3, 7, 8]	Risk of 1 per 1000 assumed in placebo group (as it was 0) There is 420% relative increase in the adverse events in patients taking zinc compared to placebo with 95% CI of 10% decrease to 2919% increase in adverse events
	6 per 1000 — 31 per 1000 (5 to 180)				

*__The risk in the intervention group__ (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; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMD:** standardised mean difference; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Unclear randomisation and high risk of bias due to attrition in Sakai 2002. Downgraded by 1 level.
[2]The confidence interval of the effect estimate indicates no difference as well as appreciable benefit with zinc. Downgraded by 1 level.
[3]We know a trial with unpublished results which was not shared by the investigators. Hence we suspect publication bias and have downgraded by 1 level.
[4]Unclear selection bias in two trials (Ikeda 2013; Sakagami 2009). Downgraded by 1 level.
[5]Wide confidence intervals in all 3 included trials (Heckmann 2005; Ikeda 2013; Sakagami 2009). Downgraded by 1 level.
[6]High risk of bias in Sakai 2002 due to attrition bias. Downgraded by 1 level.
[7]Wide confidence intervals in the trial. Downgraded by 1 level.
[8]High risk of bias due to incomplete outcome data and other reasons explained in other bias. Downgraded by 1 level.

Summary of findings 2. Acupuncture compared to sham control for the management of taste disturbances

Acupuncture compared to sham control for the management of taste disturbances

Patient or population: idiopathic dysgeusia combined with hypogeusia
Setting: tertiary healthcare centre (university clinic)
Intervention: acupuncture
Comparison: sham control

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	Comments

	Risk with sham (control)	Risk with acupuncture	(95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	
Taste discrimination assessed with 32 taste strips with a follow-up of 8 weeks	The mean taste discrimination was 14.7	MD 2.80 higher (1.18 lower to 6.78 higher)	-	37 (1 RCT)	⊕⊕⊖⊖ VERY LOW[1, 2]	The mean difference for taste discrimination in the acupuncture group is 2.80 higher than the sham group

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Brandt 2008 is a single-blind trial with high risk of performance bias. Downgraded by 2 levels.
[2]The confidence interval of the effect estimate indicates no difference as well as appreciable benefit with acupuncture. Downgraded by 1 level.

BACKGROUND

The sense of taste is important for health and quality of life, yet it is often taken for granted. More than 200,000 people/ year visit a physician for chemosensory problems such as taste disorders. Many more taste disorders go unreported (NIDCD 2010). Approximately 240,000 people in Japan have an altered taste sensation and present to health professionals for evaluation (Ikeda 2005). Alterations in taste can lead to loss of appetite, resulting in malnutrition, affecting both physical and psychological well-being (NIDCD 2009). The US National Health and Nutrition Examination Survey (NHANES) published the results of a survey from 2011 to 2012 where prevalence and risk factors were assessed based on individuals' self-reported responses to chemosensory alterations. Survey results reflected prevalence of taste alterations were 19% including dysgeusia at 5%, with rates increasing with age (> 80 years of age = 27%) (Rawal 2016).

The basic tastes are salty, sour, bitter, sweet and umami (taste of meaty/ savoury substances, found in glutamates). It has also been suggested that fatty taste may be recognised as another basic taste quality (Mattes 2009). In humans, there are approximately 5000 taste buds in the oral cavity, situated on the superior surface of the tongue, on the palate, and on the epiglottis (Miller 1995). Taste receptor signalling is not limited to taste buds, but occurs in a variety of tissues like chemosensory cells of the alimentary tract, pancreas, brain and airway epithelium (Kinnamon 2012).

It is important to understand how our taste buds function, both as an organ and in conjunction with other factors, especially our sense of smell. Taste buds are onion-shaped aggregates of approximately 50 to 100 elongated cells, with a life span of 10 to 11 days (Porter 2010). Due to such a fast turnover rate, the taste cells used for breakfast may be different from those used for lunch (Spielman 1992). They extend from the basal lamina to the surface of the tongue, where their apical microvilli extend through an opening in the epithelium to contact sapid chemicals in the oral cavity. Salts and acids utilise apically located ion channels for transduction, while bitter, sweet and umami stimuli utilise G-protein-coupled receptors (GPCRs) and second-messenger signalling mechanisms (Kinnamon 2012). These taste cells receive tastant from the apical pore and transduce the signal to gustatory nerves that innervate taste buds (Iwatsuki 2012). Taste-related impulses are then transmitted via the facial, glossopharyngeal and vagus nerves to the nucleus of the solitary tract, and thereafter to the thalamus and upwards to the postcentral gyrus-facial area and olfactory area of the cortex (Porter 2010). There are super tasters who experience the sense of taste with far greater intensity than average due to an increased number of fungiform papillae, and have extreme sensitivity to n-propylthiouracil (Bartoshuk 1994).

As important as taste is to food enjoyment, flavour is even more important. It is the distinctive quality of a particular food or drink. Flavour tells us whether we are eating a pear or an apple. In order to perceive flavour, the brain interprets not only taste stimuli, but also olfactory, thermal and tactile sensations. With spicy food, the brain will perceive pain as one aspect of flavour. When one cannot 'taste' food due to the common cold, in reality it is the inability to smell that is affecting the 'flavour' of the food and not the basic tastes of the food. It is important to understand the mechanism by which taste and smell work together. When one chews food, aromas are released that enter the nose through a retronasal passage connecting the roof of the mouth with the nose. Nerve endings in the olfactory bulb in the nose send these smell stimuli to the brain. It is the aroma, when combined with the stimuli of taste, temperature and texture that give the food a 'flavour'. It is the integration of these stimuli by the brain that distinguishes between, for example, eating an apple rather than a pear. Many studies have shown a significant relationship between smell disorders and taste disorders; loss of flavour can increase the salt intake in hyposmia patients (Henkin 2014), as smell loss severity decreased, salivary cAMP and cGMP levels increased consistently with each stepwise change of clinical loss severity (Henkin 2009), and decreased cAMP and cGMP levels in parotid saliva and nasal mucosal secretions of patients diagnosed with taste and smell disorders (Henkin 2007; Henkin 2013).

With the growing population of elderly people globally, and the effects of drugs and other treatment forms of modern medicine at any age, peoples' senses of taste and smell will continue to be adversely affected. The sense of smell is more impaired by aging compared with the sense of taste (Winkler 1999). Both anatomical investigations and human taste threshold studies indicate that age-related differences in the gustatory system are not as substantial as investigators have suggested in the past (Mistretta 1984). Nutrition surveys have shown that the elderly population with taste loss consume more sweet and salty food (Sergi 2017). A Japanese study has shown that taste hyposensitivity is present even in children (Ohnuki 2014).

Taste and smell protect against malnutrition, depression and their concomitant diseases. The taste or smell of rancid food telling us to avoid it, or perhaps the odour of gas alerting us to danger, are lost or diminished without these senses. Simple pleasures like delicious foods and their aroma enable an individual to enjoy quality of life.

People who suffer from dysgeusia (distortion of taste) are also forced to manage the impact that the disorder has on their quality of life. An altered taste has effects on food choice and intake, and can lead to weight loss, malnutrition, impaired immunity, and a decline in health (Bromley 2000). Patients diagnosed with dysgeusia must use caution when adding sugar and salt to food and must be sure not to over-compensate for their lack of taste with excess amounts. Since the elderly are often on multiple medications, they are at risk for taste disturbances increasing the chances of developing depression, loss of appetite, and extreme weight loss. This is cause for an evaluation and management of their dysgeusia. In patients undergoing chemotherapy, taste distortions can often be severe and make compliance with cancer treatment difficult. Other problems that may arise include anorexia and behavioural changes that can be misinterpreted as psychiatric delusions regarding food. Symptoms including paranoia, amnesia, cerebellar malfunction and lethargy can also manifest when undergoing histidine treatment. This makes it critical that these patients' dysgeusia is either treated or managed in order to improve their quality of life (Padala 2006).

Description of the condition

The symptoms of taste impairment may vary depending on the cause. Patients may experience a reduced ability to taste (hypogeusia), a distortion of taste (dysgeusia), the total lack of taste (ageusia), or all three. However, the following terms have been used in literature to describe taste abnormalities (Hawkes 2002).

- Ageusia: absence of taste sense.
- Hypo or microgeusia: reduction of taste sense.
- Dysgeusia: distortion of taste sense.
- Parageusia: distortion due to a specific stimulus.
- Phantogeusia: distortion when there is no external stimulus.
- Cacogeusia: unpleasant type of distortion.
- Torquegeusia: burning type of distortion.
- Hypergeusia: increased sensitivity to common taste.
- Gustatophobia: dislike of certain tastes.
- Heterogeusia: all food and drink taste the same.
- Presbygeusia: decline of taste sense with age.
- Type 1 hypogeusia: inability to recognise stimulus with varying degrees of detection.
- Type 2 hypogeusia: decreased detection or recognition.
- Type 3 hypogeusia: reduced intensity ability with normal detection and recognition.

The most common causes of taste disorders are drug use (21.7%), zinc deficiency (14.5%), and oral and systemic diseases (7.4% and 6.4%, respectively) (Imoscopi 2012). Anything that negatively affects either the physical make-up of the taste buds or their cells, saliva production, the nerve pathway, or brain can cause a taste disorder. Therefore, in addition to the normal aging process, a host of other factors such as smoking, infection, nerve diseases, tumours, radiation treatment, drugs, chemicals, head injury, zinc deficiency, dry mouth and poor oral hygiene can also affect the ability to taste.

Taste impairment may be caused not only by an altered threshold of taste and sensory pathway but also by various mental and physical disorders, including depression, taste bud or mucosal lesions, gum disease, dry mouth, gastrointestinal diseases, zinc deficiency and medication. Therefore the symptoms of taste impairment may vary depending on the cause. Subnormal taste often induces appetite loss, which results in malnutrition and impairs quality of life (Kashihara 2011).

Taste disorders are classified based on two principles: type and site of the lesion. Based on the type of lesion, taste disorders are grouped as quantitative dysgeusias (ageusia, hypogeusia and hypergeusia), and qualitative dysgeusias (parageusia, pseudogeusia, phantogeusia, cacogeusia and agnogeusia). Based on the site of the lesion, taste disorders are classified as epithelial, neural and central dysgeusias (Fikentscher 1987). Systemic disorders like renal disorders (Mahajan 1980), alcoholic cirrhosis (Russell 1980), regional enteritis (Solomons 1974), and iatrogenic causes like postradiation therapy (Mossman 1978; Silverman 1983), or chemotherapy (Wickham 1999) can lead to taste disorders. Xerostomia was the strongest risk factor for taste disorder (Rawal 2016).

Description of the intervention

Various treatment modalities have been used to improve taste disorders. These include the use of zinc (Heckmann 2005; Sakai 2002), transcranial magnetic stimulation (Henkin 2011a), alpha lipoic acid (Femiano 2002), ginkgo biloba (Mattes 2004), pilocarpine (Aframian 2007), and acupuncture (Brandt 2008). The ability to manage taste disorders varies with each intervention.

Diminished taste acuity resulting in malnutrition in haemodialysis patients was studied in Mahajan 1980. The subjects were tested for taste acuity related to plasma zinc concentration. This double-blinded trial was instituted using a zinc supplement (zinc acetate) and a placebo. The same authors studied the effect of zinc supplements on patients undergoing regular haemodialysis (Mahajan 1982). Treatment of taste abnormalities with zinc sulphate was tried in patients receiving external beam radiation therapy (ERT) for head and neck cancers (Halyard 2007; Ripamonti 1998). In a double-blind, placebo-controlled trial, the efficacy of zinc picolinate and zinc gluconate were studied in idiopathic zinc deficiency taste disorders (Sakai 2002). Zinc gluconate was tested in patients with drug-induced taste disorders in Yoshida 1991. Zinc supplements were also tried in taste disorders due to head trauma and malignant tumours of head and neck in Henkin 1976.

Dosage of zinc varied drastically in different trials: capsules containing 22.6 mg of zinc (Barrie 1987); 29 mg of zinc three times a day for three months (Sakai 2002); 45 mg of zinc sulphate three times a day (Ripamonti 1998); and 50 mg of elementary zinc (as zinc acetate) per day (Mahajan 1980).

- In an open cross-over trial on idiopathic dysgeusia patients, considering idiopathic dysgeusia as a neuropathy similar to burning mouth syndrome, an alpha lipoic acid intervention was studied (Femiano 2002).
- Gingko biloba extracts were tried to enhance cognitive, taste and smell functions in dementia patients (Mattes 2004).
- Repetitive transcranial magnetic stimulation (rTMS) was used in patients with smell and taste disorders (Henkin 2010; Henkin 2011a).
- Intranasal theophylline was used for the management of patients with smell and taste disorders (Henkin 2012).

Other than these interventional studies, many individual case reports/pilot studies on management of taste disorders are found in the literature. They are:

- high dose biotin (Greenway 2011);
- application of glutamate (Sasano 2010);
- branched-chain amino acid-enriched supplementation (Aminofeel) (Nagao 2010);
- transient cooling of the mouth by using ice cubes (Fujiyama 2010);
- thioridazine/haloperidol to inhibit phantogeusia (Henkin 2000);
- miracle fruit (Synsepalum dulcificum) (Wilken 2012).

How the intervention might work

Zinc is an important element in both the maintenance and repair of taste buds. Zinc influences the synthesis of the protein gustin, which is linked to the production of taste buds. A decrease in the salivary gustin/carbonic anhydrase VI is associated with taste and smell disorders and can be effectively treated with zinc supplementation (Henkin 1999). Zinc has also been shown to increase calcium concentration in saliva. Taste buds rely on calcium receptors to work properly (Heckmann 2005). Finally, zinc is an important cofactor for alkaline phosphatase, the most important enzyme in taste bud membranes (Bicknell 1988). Zinc supplementation has shown to be effective in treating taste disorders. It can also be found in natural foods such as meat, cereals, beans and oysters.

Alpha lipoic acid (ALA) is an antioxidant that is produced naturally in human cells. Among its functions, it has an important role in the Krebs cycle assisting in the production of nerve growth factor. Research in animals has shown that ALA can improve nerve induction velocity. However, there are contradictory opinions about the efficacy of ALA in treating burning mouth syndrome and dysgeusia (de Moraes 2012; Femiano 2002).

Ginkgo biloba, an herbal extract, may have three effects on the human body: improvement in blood flow to most tissues and organs; protection against oxidative cell damage from free radicals; and blockage of many platelet-activating factors (aggregation and blood clotting). These anticlotting characteristics may be of help with circulatory problems attributed to aging. It is being used to treat memory loss, and the impact to the brain and circulation may make it helpful in treating taste disorders (Mattes 2004). However, there is no evidence for its clinically significant benefits in dementia patients (Birks 2009).

Transcranial magnetic stimulation (TMS) uses electromagnetic induction to induce weak electric currents stimulating activity in specific parts of the brain with minimal discomfort. A variant of TMS, called repetitive TMS, was used to treat various neurological and psychiatric disorders including migraines, Parkinson's disease, tinnitus, stroke, depression (Henkin 2011a), and phantogeusia (unpleasant taste sensation in the absence of food or drink) (Henkin 2011b).

Research has found that saliva contains specific proteins that are growth factors (nerve growth factor, epidermal growth factor) that make taste buds develop and mature. Without these growth factors, taste buds degenerate (Gardiner 2008). Pilocarpine, by increasing saliva production, gives taste buds greater access to food molecules and may be responsible for maintenance of taste buds. Studies have shown that treatment with pilocarpine enhances taste (Aframian 2007; Leek 2002).

Acupunture is the stimulation of specific acupoints along the skin of the body involving various methods such as the application of heat, pressure or laser or penetration of thin needles. It is a key component of traditional Chinese medicine which aims to treat a range of conditions including dysgeusia. According to traditional Chinese medicine, stimulating specific acupuncture points corrects imbalances in the flow of *qi* through channels known as meridians. This seeks to re-establish an equilibrium of forces in the diseased body between the energies of yin and yang (contrary energies such as fire and water, hot and cold), which are distorted in the diseased body (Vent 2010).

Why it is important to do this review

Taste disturbances are not uncommon, have a range of causes and result in significant reduction in quality of life. A systematic review is necessary to summarise the evidence of the effects of the many interventions available to treat taste disturbances and to provide evidence to guide decision-making. This is an update of the Cochrane Review first published in 2014 (Kumbargere 2014).

OBJECTIVES

To assess the effects of interventions for the management of patients with taste disturbances.

METHODS

Criteria for considering studies for this review

Types of studies

We included only parallel and cross-over randomised controlled trials (RCTs) with either a pharmacological or non-pharmacological intervention in this review.

Types of participants

We included patients with taste disorders diagnosed clinically as dysgeusia, parageusia, ageusia, hypogeusia or phantogeusia regardless of their age, gender, race, profession or residential location. It is a well established fact that many treatment procedures like surgery, radiation therapy and chemotherapy can cause taste perception problems. Once the effect of these treatment procedures diminishes, the taste perception slowly reverts back to normal. Considering these variations, we agreed upon the following exclusion criteria. We excluded the following types of patients in our review.

- Demolitive surgery of tongue, palate or oropharynx.
- Presence of oral lesions such as ulcers, stomatitis, candidiasis and necrosis.
- Cerebral lesions or surgical damage to the nervous system.
- Endocrinal and neurological disorders known to affect taste, or smell sensitivity, or both.
- Patients undergoing treatment with drugs known to affect taste perception (e.g. chemotherapy).
- Patients who underwent treatment affecting salivary function (e.g. radiotherapy).
- Patients experiencing hyposalivation.

Types of interventions

- Any intervention versus placebo or no treatment.
- Any direct comparisons between two active interventions, e.g. drug A versus drug B, or between two doses of the same drug e.g. drug A dose X versus drug A dose Y.
- We included all routes of drug administration or modes of application.

Types of outcome measures

We considered improvement in taste acuity to at least one quality of taste by subjective/objective assessment scales as the most important outcome. It could be any one of the following.

- Sip and spit method (traditional method): in this method, a solution of a known concentration of a sweet, salty, bitter, or sour substance is gargled and sloshed in the mouth and then discarded. The patient is asked to identify the taste substance, and the concentration can be varied to determine threshold sensitivity. It is an easy test to administer but assumes severe taste loss. Regional damage (e.g. on the front or tip of the tongue) would be masked by stimulation of the remaining taste cells elsewhere in the mouth.
- Filter paper disk method (Tomita 1986): in this test, filter paper or a dissolvable strip is impregnated with a known concentration of a sweet, salty, bitter, or sour substance, and the filter paper or strip is placed on a specific part of the tongue or

palate. The patient is asked to identify the taste substance. The concentration can be varied to determine threshold sensitivity. This test is also easy to administer. The goal is to activate major regions of taste cells to determine whether the individual has partial taste deficit or damage.

- Electrogustometry (Tomita 1986): the measurement of taste threshold by passing a controlled anodal current through the tongue. When the current passes through the tongue a unique and distinct metallic taste is perceived.
- Three stimulus drop technique (Henkin 1963): testing involves a three-stimuli forced choice drop technique given in a type of staircase technique. The subject is given three drops of liquid, which are placed successively onto the lingual surface. Out of three, two drops are water and one drop is water with a solute, either NaCl (salt), sucrose (sweet), hydrogen chloride (HCl) (sour) or urea (bitter).
- Edible taste strips (Smutzer 2008): prepared from pullulan hydroxypropyl methylcellulose solutions that are dried to a thin film. The maximal amount of a tastant that could be incorporated in a 2.54 cm × 2.54 cm taste strip is 5% for each class of tastant (sweet, sour, salty, bitter and umami) during strip formation.
- Filter paper strips method (Mueller 2003): all four of five taste qualities, sweet, sour, salty and bitter are tested using filter paper strips coated with four different concentrations for each taste quality. This is tested randomly on the right and left side of the anterior two-thirds of the tongue, and the subject is asked to identify the taste from a list of four descriptors.
- Visual analogue scale (VAS) (traditional method).
- Self-reporting questionnaire method (Soter 2008).
- Spatial taste test (Gondivkar 2009).
- Clinical bitterness masking test for phantogeusia (Ishimaru 2001).

Primary outcomes

- Taste acuity improvement - we considered improvement in taste acuity to at least one quality of taste by subjective/objective assessment scales as the most important outcome.
- Taste discrimination improvement.

Taste acuity includes taste detection and recognition, whereas taste discrimination is the ability to distinguish one taste from the other.

Secondary outcomes

- Adverse events related to the interventions.
- Health-related quality of life.

Search methods for identification of studies

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions.

Electronic searches

The following databases were searched:

- Cochrane Oral Health's Trials Register (searched 4 July 2017) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 6) in the Cochrane Library (searched 4 July 2017) (Appendix 2);
- MEDLINE Ovid (1946 to 4 July 2017) (Appendix 3);
- Embase Ovid (1980 to 4 July 2017) (Appendix 4);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 4 July 2017) (Appendix 5);
- AMED Ovid (Allied and Complementary Medicine; from 1985 to 4 July 2017) (Appendix 6).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

The following databases were searched for ongoing trials:

- the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 4 July 2017) (Appendix 7);
- the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; searched 4 July 2017) (Appendix 8).

We searched abstracts from scientific meetings and conferences for appropriate studies through the websites of the following organisations:

- International Association for Dental Research/American Association for Dental Research Conference Proceedings (to 25 September 2017) (Appendix 9);
- Association for Research in Otolaryngology Conference Proceedings (to 25 September 2017) (Appendix 10).

The previous version of this review included searches of the metaRegister of Controlled Trials (to 5 March 2014) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Clinical Trials Portal (to 5 March 2014). However, these sources are no longer available (see Appendix 11).

We checked reference lists of included studies to identify any further additional studies. We contacted authors of the included studies for relevant unpublished material.

Data collection and analysis

Selection of studies

Two pairs of review authors (Renjith P George (RPG) and Naresh Shetty (NS), and David Levenson (DL) and Debra M Ferraiolo (DMF)) screened the titles and abstracts of all the obtained reports for eligibility, independently and in duplicate. Full papers of relevant RCTs (based on the inclusion and exclusion criteria) were obtained and screened independently and in duplicate by two review authors (Sumanth Kumbargere Nagraj (SKN) and RPG). Any disagreements on eligibility were resolved by discussion. When resolution was not possible, we consulted an arbiter (Adinegara Lutfi Abas). We recorded studies excluded at this point in the Characteristics of excluded studies tables along with reasons for

exclusion. We did not mention non-RCTs or quasi-RCTs in the Characteristics of excluded studies tables.

Data extraction and management

Two review authors (SKN and RPG) extracted the data independently and in duplicate, using a data extraction form specifically designed for this review. Any disagreements were resolved by discussions. For two studies, we could not resolve the disagreement, and a third review author was asked to do the data extraction independently, and this was deemed final. We entered all of the trial details in the Characteristics of included studies tables in Review Manager 5 (Review Manager 2014).

We recorded the following details for each trial.

- Publication details like year of publication and language.
- Demographic details of the report.
- Inclusion and exclusion criteria.
- Sample size, method of randomisation, allocation concealment, blinding, type of trial, method of assessing the outcome, and dropouts, if any.
- Type of intervention.
- Details of the outcome reported.
- Duration of follow-up.
- Results of the intervention.
- Funding details.

We contacted the author/s of included/excluded studies via email if clarification of any details or additional data were required.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies using Cochrane's 'Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We completed a 'Risk of bias' table for each included trial. Within each table, we assessed the following domains of risk of bias: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. For each domain, we described what was reported to have happened, using quotes from the trial, followed by a judgement of 'low risk', 'high risk' or 'unclear risk' of bias. We contacted the trial authors for clarification where necessary, quoting their responses in the risk of bias table. We resolved any disagreements on risk of bias by consulting a third review author (arbiter).

Summarising risk of bias

Studies have been grouped into the following categories.

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

We summarised risk of bias graphically using the plots available in Review Manager 5 (Review Manager 2014).

Measures of treatment effect

For dichotomous data, we expressed the estimates of effect of an intervention as risk ratios (RRs) together with 95% confidence intervals (CIs). For continuous data, we used standardised mean difference, as the included studies used different taste scales to measure the same primary outcome (e.g. improvement in taste acuity). For continuous data which were measured using same scales were expressed the estimates of effect as mean difference.

Unit of analysis issues

Cross-over studies

We had two cross-over trials in our review. One trial (Eggert 1982) presented the data in graphs and we separately analysed only the data before cross-over. The other trial (Watson 1983) gave the data in median value and we could not use this in the meta-analysis of outcomes; however, we used the adverse events data in the meta-analysis.

Studies with multiple intervention arms

One trial (Sakagami 2009) had three treatment arms. We combined the data using the method described in Section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We contacted trial authors to obtain missing data whenever possible. If we could not get the missing data, we used per protocol analyses for missing data and assessed the data at a high risk of bias in the 'Risk of bias' tables.

If both mean and standard deviations were reported as graphs, we derived the data from the graphs by magnifying them and approximating the measures of mean and standard deviation.

If the data were described in the form of ordinal outcome, we converted the shorter ordinal scales into dichotomous data by combining relevant adjacent categories.

Assessment of heterogeneity

We assessed heterogeneity of the studies by examining the forest plots, with poor overlap of the confidence intervals indicating the presence of heterogeneity. We used the Chi^2 test to assess whether heterogeneity was present and quantified it using the I^2 statistic. We used the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* to interpret the I^2 statistic: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% indicates considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

According to our protocol we intended to do a test of asymmetry to assess reporting bias, but we did not do this test as we had less than 10 trials included in our meta-analysis.

Data synthesis

We analysed the data using Review Manager 5 software (Review Manager 2014). We used the data available from the trials with similar comparisons and outcomes in the meta-analysis. We combined RRs for dichotomous data and standardised mean differences for continuous data (as the trials used different scales), and used a random-effects model in the meta-analysis. We used the first-phase data from one cross-over trial (Eggert 1982), although we did not pool these data with other studies in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses whenever there was heterogeneity.

To identify the reasons for clinical or methodological heterogeneity in meta-analyses, we carried out subgroup analyses, based on:

- population: idiopathic dysgeusia/hypogeusia, and dysgeusia and hypogeusia secondary to chronic renal failure; and
- outcome: patient-reported outcome (VAS scale, questionnaire), and objective outcome (taste strips or filter paper disks).

Sensitivity analysis

Wherever feasible, we undertook sensitivity analyses to assess the robustness of our findings by excluding studies with high risk of bias.

Summarising and interpreting results

We used the GRADE approach to interpret findings. We used the GRADEpro GDT software (GRADEpro GDT 2015), and imported the data from Review Manager 5 to create 'Summary of findings' tables for each comparison included in this review. We assessed the outcomes with reference to the overall risk of bias of the included studies, the inconsistency of the results, the directness of the evidence, the precision of the estimates, and the risk of publication bias. We categorised the quality of the body of evidence for each assessable outcome as no reason to downgrade the quality of evidence, serious reason (downgraded by one) or very serious reason (downgraded by two). These tables provide the information concerning the overall quality of the evidence from the trials, the magnitude of effect of the interventions examined and the sum of available data on the primary outcome and secondary outcomes. We selected the outcomes of improvement in taste acuity, adverse events and taste discrimination, for inclusion in these tables (Summary of findings for the main comparison; Summary of findings 2).

RESULTS

Description of studies

Results of the search

The electronic search identified 5728 records from English and other language databases.

We used keywords "taste", "dysgeusia" and "chemosensory" to search for related abstracts, and identified 70 abstracts from the International Association for Dental Research conference proceedings (as of 25 September 2017) and 19 trials from the Association of Research in Otolaryngology conference proceedings (as of 25 September 2017).

The metaRegister of Controlled Trials (mRCT) and the IFPMA trials registry were searched for the original version of this review, but these resources no longer exist. The electronic search of these databases resulted in 21 trials from IFPMA (as on 5 March 2014) and nine trials from mRCT (as on 5 March 2014). Only four trials were related to interventions in patients with taste disorders, and of these, two trials were ongoing (IFPMA, NCT01143285 (excluded) and JapicCTI-121907 (awaiting classification)) and two trials were completed (clinicaltrials.gov/show/NCT00316563 and JPRN-C000000401 (awaiting classification)). The completed trial (NCT00316563) is published and we excluded the trial from our review (Brisbois 2011).

At the end of our search, we had 4724 records after removing duplicates, out of which we discarded 4644 and we requested full-text copies of 80 references. Two pairs of review authors (Renjith P George (RPG) and Naresh Shetty (NS), and David Levenson (DL) and Debra M Ferraiolo (DMF)), independently and in duplicate assessed these papers to determine their eligibility. We identified 10 studies (12 references) which met the inclusion criteria and included them in this review, and 24 were excluded (Figure 1). For details of the studies examined and reasons for inclusion or exclusion, see the Characteristics of included studies and Characteristics of excluded studies tables. Six trials are awaiting classification and one is ongoing. So we will consider them in a future update of the review.

Figure 1. Study flow diagram.

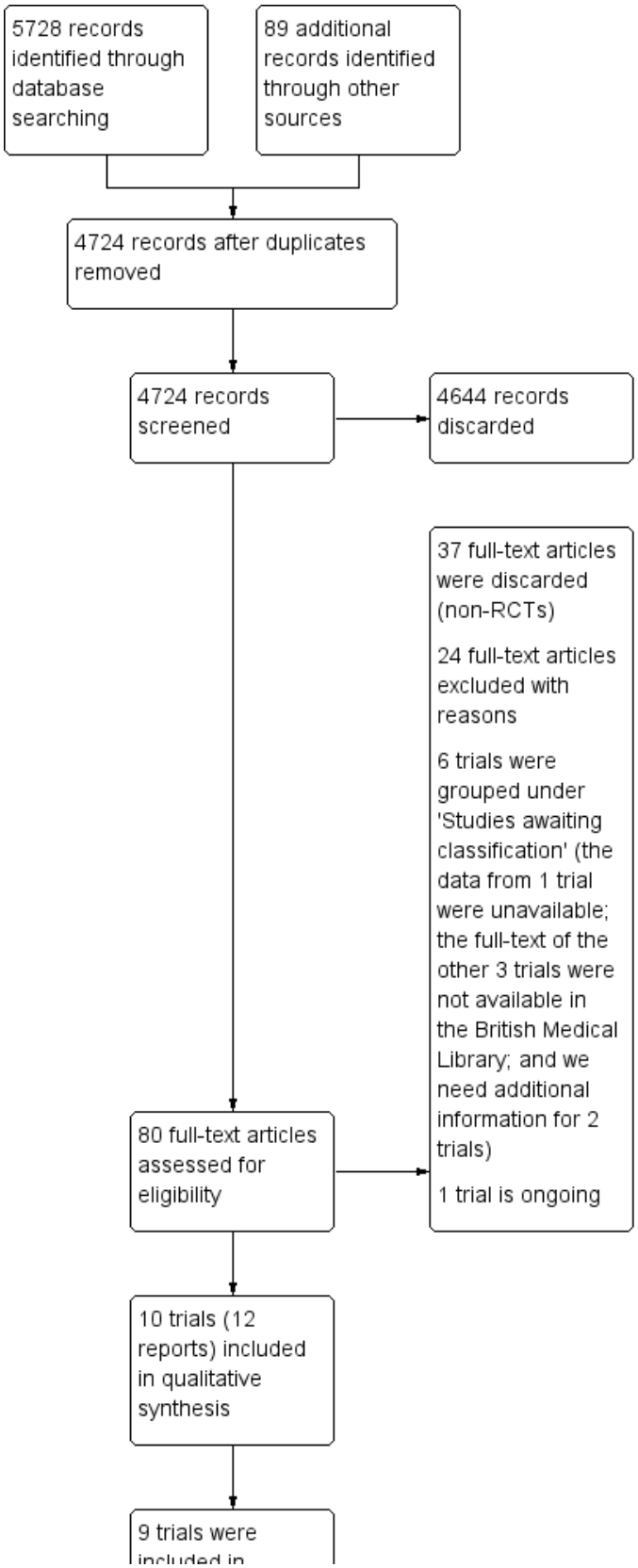
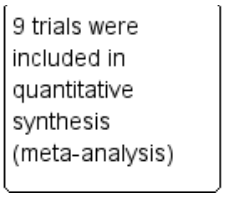


Figure 1. (Continued)



We contacted authors of six included trials and we received clarifications for only four trials. We could not contact authors of three trials due to non-availability of recent address/email address. One trial did not have any missing data and hence the authors were not contacted (see Characteristics of included studies). We also contacted the authors of two unpublished clinical trials and one of them refused to share the details of the trial (see Characteristics of studies awaiting classification).

Included studies

See Characteristics of included studies table.

Characteristics of the trial settings and investigators

We included 10 randomised controlled trials (RCTs) in the review. Out of these, eight were in the English language, one was in German (Brandt 2008), and one was in Japanese (Ikeda 2013). The countries of origin for the included studies were: two from Germany (Brandt 2008; Heckmann 2005), three from Japan (Ikeda 2013; Sakagami 2009; Sakai 2002), two from the UK (Matson 2003; Watson 1983), and three from the US (Eggert 1982; Mahajan 1980; Mahajan 1982).

Eight trials were parallel-design trials and two were cross-over trials (Eggert 1982; Watson 1983).

Out of 10 trials, seven provided grant information and out of these seven, two were government funded (Mahajan 1980; Mahajan 1982), three were privately funded (Brandt 2008; Eggert 1982; Heckmann 2005), one was funded by a pharmaceutical company (Ikeda 2013), one had the intervention drug sponsored by a pharmaceutical company (Sakagami 2009). Three trials did not mention funding details (Matson 2003; Sakai 2002; Watson 1983).

Two of the trials were multicentric (Ikeda 2013; Sakagami 2009) and others were carried out in either one or two centres.

Only one trial (Brandt 2008) studied taste discrimination as the trial outcome; eight trials tested for taste acuity (detection, recognition, or both), and one trial (Matson 2003) studied both taste acuity and taste discrimination as the trial outcome. Two trials (Brandt 2008; Heckmann 2005) have reported the data related to improvement in the mood scale and depression inventory. In addition to these, Brandt 2008 also reported the assessment of 'quality of life' using a visual analogue scale.

Characteristics of the participants

Eight out of 10 trials included only adult patients (Brandt 2008; Heckmann 2005; Ikeda 2013; Mahajan 1980; Mahajan 1982; Matson 2003; Sakagami 2009; Sakai 2002); and two were trials on children (Eggert 1982; Watson 1983). Seven trials included both genders in their trial, one trial included only males (Mahajan 1982), and two trials did not report on the gender distribution (Eggert 1982; Mahajan 1980). The minimum age included in the trials was 0.5 years (Eggert 1982) and the maximum age included in the trials was 83 years (Brandt 2008). The minimum sample size was 15 (Matson 2003) and the maximum sample size was 219 (Ikeda 2013) with an average of 62.4.

Five trials were on renal failure-induced hypogeusia (Eggert 1982; Mahajan 1980; Mahajan 1982; Matson 2003; Watson 1983), three were on idiopathic dysgeusia/hypogeusia (Brandt 2008; Heckmann 2005; Sakagami 2009), and two were on idiopathic dysgeusia and zinc deficiency-induced hypogeusia (Ikeda 2013; Sakai 2002).

Characteristics of the interventions

We included one non-pharmacological intervention (needle acupuncture) in our review (Brandt 2008); the remaining nine trials had zinc (Zn) compounds as the intervention drug. Three trials studied zinc sulphate (Eggert 1982; Matson 2003; Watson 1983) and two used polaprezinc (Ikeda 2013; Sakagami 2009). Zinc acetate was used in two trials (Mahajan 1980; Mahajan 1982), zinc gluconate in one (Heckmann 2005), and zinc picolinate in one trial (Sakai 2002).

Zinc supplement

Zinc sulphate

Two cross-over trials and one parallel-group trial studied the effects of zinc sulphate on taste disorders in chronic renal failure patients (Eggert 1982; Matson 2003; Watson 1983). Zinc sulphate was given at the dosage of 0.5 mg/Zn/kg/day to 0.75 mg/Zn/kg/day to all the children included in the trial for six months (Eggert 1982). Zinc sulphate was given at a dose equivalent to 15 mg elemental zinc for children and 50 mg elemental zinc for adults, for a period of six weeks (Watson 1983). In Matson 2003 trial, 220 mg per day (45 mg elemental zinc) was given for a period of six weeks.

Zinc acetate

Two trials studied the effects of zinc acetate on taste disorders in chronic renal failure patients (Mahajan 1980; Mahajan 1982). Both trials tested 25 mg elemental zinc, twice a day in zinc acetate form.

Polaprezinc

Two trials studied the efficacy of polaprezinc on taste disorders (Ikeda 2013; Sakagami 2009). In the trial by Sakagami 2009, polaprezinc was tested in three different dosages, 75 mg, 150 mg, and 300 mg, which was equivalent to 17 mg, 34 mg, and 68 mg of elemental zinc, respectively for 12 weeks. In the trial by Ikeda 2013, polaprezinc was administered as 75 mg (17 mg elemental zinc), twice a day for 12 weeks. Additional to this, the daily intake of dietary zinc was standardised in both the experimental and control groups (Additional Table 1; Additional Table 2; Additional Table 3; Additional Table 4).

Zinc picolinate

One trial studied the effects of zinc picolinate on taste disorders at the dosage of 28.9 mg, three times a day for three months (Sakai 2002). No dietary instructions to increase dietary zinc were given to either of the groups in this trial (Additional Table 5).

Zinc gluconate

One trial studied the effects of zinc gluconate on taste disorders at the dosage of 140 mg/day (equivalent to 20 mg elemental zinc) for three months (Heckmann 2005) (Additional Table 6; Additional Table 7).

Acupuncture

We included one trial that studied the effects of 15 acupuncture treatments on taste disorders over a period of eight weeks (Brandt 2008). Two patients did not require further acupuncture treatment after 10 treatments. De-activated laser acupuncture was used as a sham control (Additional Table 8).

Excluded studies

See Characteristics of excluded studies tables for further details.

We excluded 37 non-RCTs and quasi-RCTs without any explanation. We procured 24 full-text articles and excluded these with reasons (Characteristics of excluded studies).

Four trials included patients with taste disorders under medications which might affect taste perception (Brisbois 2011; Green 2013; Lyckholm 2012; UMIN000027177).

Ten trials reported the intervention effects on either normal volunteers or subjects without taste disorders (Atkin-Thor 1978; Dahl 1984; Deniz 2016; Hartman-Petrycka 2016; Kamphuis 2003; Mahajan 1992; Ohno 2003; Stewart-Knox 2008; Tupe 2009; Treldal 2016).

Six trials were aimed at prevention of taste disorders in patients undergoing chemotherapy or radiotherapy (Halyard 2007; Jham 2009; Najafizade 2013; NCT01143285; Ripamonti 1998; Strasser 2008).

Three trials included patients with taste disorders due to trauma, cranial injuries, oral lesions, and neurological problems, etc. (Henkin 1976; Sprenger 1983; Yoshida 1991).

One trial included patients with taste disorders secondary to radiotherapy, including parotid carcinoma cases, where the patients could have experienced xerostomia (Velargo 2012).

Studies awaiting classification

See Characteristics of studies awaiting classification tables for further details.

We grouped six trials as studies awaiting classification. One clinical trial was completed but unpublished; hence the trial group refused to share the results (JPRN-C000000401). The full-text was not available for three trials, and hence we could not decide on the inclusion/exclusion of the studies (Mahajan 1979; Sanchez 1993; Sturniolo 1985). We need additional information for two trials (JapicCTI-121907; Sakai 2017).

Ongoing studies

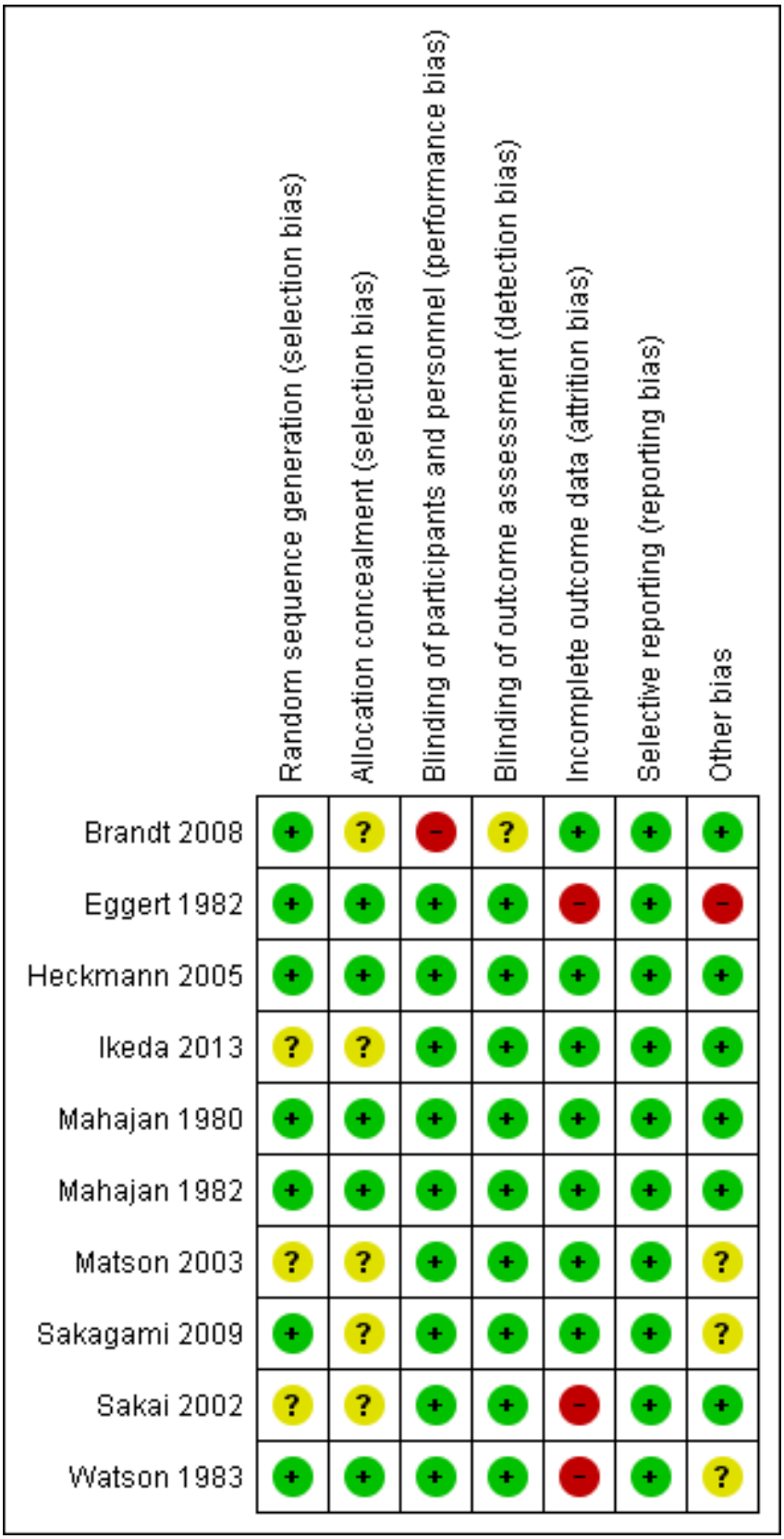
See Characteristics of ongoing studies table for further details.

We identified one ongoing clinical trial. NCT02475928 was supposed to be completed by December 2016. We will consider the results of this trial in our future update of the review if it is published or the authors agree to share the results.

Risk of bias in included studies

See the 'Risk of bias' tables within Characteristics of included studies for further details. For a graphical summary, see Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We documented the risk of bias for included studies based on the full-text articles. Wherever there was a need for clarification, we contacted the authors. Based on the available data, the 'Risk of bias' assessment was either 'low risk', 'high risk' or 'unclear risk'. If the trial report mentioned it as 'double-blind' we considered it as at low risk of bias for blinding and if the trial was 'single-blind' (Brandt 2008), we assessed it as at high risk of bias for this domain.

We assessed three trials (30%) as at low overall risk of bias (Heckmann 2005; Mahajan 1980; Mahajan 1982), four trials (40%) as at high overall risk of bias (Brandt 2008; Eggert 1982; Sakai 2002; Watson 1983), and three trials (30%) as at unclear risk of bias (Ikeda 2013; Matson 2003; Sakagami 2009).

Allocation

Seven of the included trials (Brandt 2008; Eggert 1982; Heckmann 2005; Mahajan 1980; Mahajan 1982; Sakagami 2009; Watson 1983) reported the method of sequence generation and five of the included studies (Eggert 1982; Heckmann 2005; Mahajan 1980; Mahajan 1982; Watson 1983) reported concealment of allocation (Figure 2).

Blinding

Six trials (Eggert 1982; Ikeda 2013; Matson 2003; Sakagami 2009; Sakai 2002; Watson 1983) described their studies as "double-blind", but no other details were given.

Out of 10 included trials, blinding of participants and personnel was not done in one trial (Brandt 2008).

Blinding of outcome assessors was unclear in one trial (Brandt 2008), whereas three trials described that assessors were blinded (Heckmann 2005; Mahajan 1980; Mahajan 1982).

Incomplete outcome data

Attrition bias was reported in three of the included studies (Eggert 1982; Sakai 2002; Watson 1983).

Selective reporting

None of the included trials had reporting bias.

Other potential sources of bias

We have assessed biases in this section according to the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 8.15 (Higgins 2011).

One of the trials had a high risk of other bias as this cross-over trial did not have any washout period (Eggert 1982). We could not rule out the influence of the pharmaceutical company in the Sakagami 2009 trial. Routine medications (no details of those medications described) were continued during the trial which could have caused dysgeusia in the Watson 1983 trial. Matson 2003 used the sip and spit method for taste assessment and this method cannot detect region damage of taste cells which might give wrong results.

Effects of interventions

See: **Summary of findings for the main comparison** Zinc compared to placebo for the management of taste disturbances; **Summary of findings 2** Acupuncture compared to sham control for the management of taste disturbances

Zinc supplements versus placebo

See Summary of findings table 1.

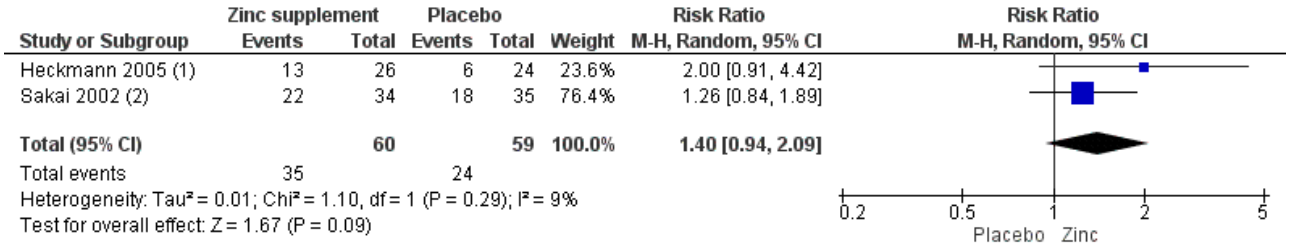
Out of 10 included trials, nine compared zinc supplements with placebo for taste disorder patients. One of these nine trials reported the results using median values (Watson 1983) and three trials reported the results in graphs (Eggert 1982; Matson 2003; Watson 1983). Two trials assessed patient-reported outcomes (Heckmann 2005; Sakai 2002), and eight trials reported objective improvement based on different taste detection tests (Eggert 1982; Heckmann 2005; Ikeda 2013; Mahajan 1980; Mahajan 1982; Matson 2003; Sakagami 2009; Sakai 2002).

Taste acuity improvement

Taste acuity improvement - Patient-reported outcome

Analysis 1.1; Figure 3.

Figure 3. Forest plot of comparison: 1 Zinc versus placebo, outcome: 1.1 Taste acuity improvement - Patient-reported outcome.



Footnotes
(1) VAS scale: 0 - no impairment and 10 - extremely impaired. Study authors have defined improvement in dysgeusia as "improvement of more...
(2) Questionnaire method (1 - no taste and 5 - normal)

We first evaluated our primary outcome, taste acuity as reported by the patient. Two trials (Heckmann 2005; Sakai 2002) assessed the patient-reported outcome for taste acuity improvement. The Heckmann 2005 trial was at low risk of bias and the Sakai 2002 trial at high risk of bias.

Heckmann 2005 used zinc gluconate in idiopathic dysgeusia patients and assessed the improvement using a visual analogue scale (VAS) (0 to 10 where 0 was no impairment and 10 was extremely impaired). However, the trial authors presented the dichotomized results using the criteria as described in the Characteristics of included studies table. Sakai 2002 used zinc picolinate in patients either with idiopathic dysgeusia or zinc-deficient dysgeusia, and assessed the improvement using a questionnaire method (1 to 5 where 1 was no taste and 5 was normal). The forest plot shows an I^2 of 9%, depicting low heterogeneity, and the confidence interval (CI) ranges from 0.94 to 2.09, indicating that the effect estimate ranges between no benefit to appreciable benefit. The overall effect favours zinc supplements over placebo for this patient-reported outcome (risk ratio (RR) 1.40, 95% CI 0.94 to 2.09; 2 trials, 119 participants; Analysis 1.1).

Taste acuity improvement - Objective outcome

Taste acuity can be tested objectively using methods like the filter paper disk method, and the three-drop technique, etc.. We included eight trials (Eggert 1982; Heckmann 2005; Ikeda 2013; Mahajan 1980; Mahajan 1982; Matson 2003; Sakagami 2009; Sakai 2002) that used different objective taste testing methods to see the improvement in taste acuity. Heckmann 2005 used the filter paper strip method whereas Ikeda 2013; Sakagami 2009; and Sakai 2002 used the filter paper disk method. Eggert 1982; Mahajan 1980; and Mahajan 1982 used the three-drop stimulus method in their trials. Matson 2003 used the sip and spit method.

Ikeda 2013 described the results in both continuous data and dichotomous data. Sakagami 2009 described the results as continuous data for taste acuity whereas Mahajan 1982 and Sakai 2002 described the results as dichotomous data. Heckmann 2005 reported continuous data (in addition to dichotomous data for this patient-reported outcome). Hence, we analysed the data from Heckmann 2005; Ikeda 2013; and Sakagami 2009 under continuous data (Analysis 1.2) and data from Ikeda 2013; Mahajan 1982; and Sakai 2002 under dichotomous data (Analysis 1.5).

Mahajan 1980 described the results as continuous data for each taste sensation and was analysed separately (Analysis 1.3).

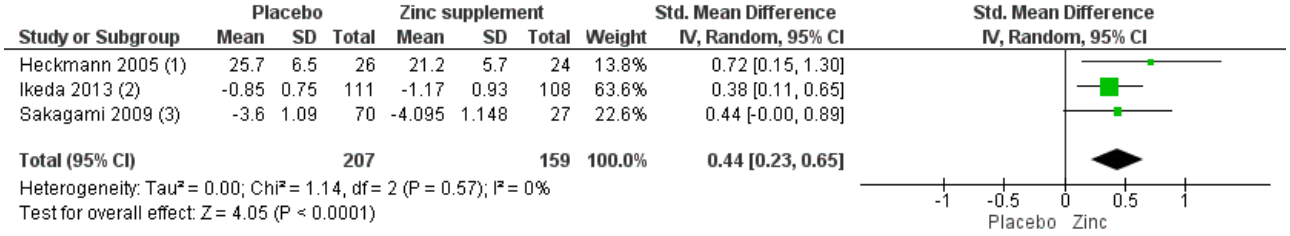
We used the data from the first half of the cross-over trial by Eggert 1982 and analysed the data for taste detection and taste recognition (Analysis 1.4).

We could not include Matson 2003 and Watson 1983 in the meta-analysis related to taste improvement due to missing data.

Taste acuity improvement - Objective outcome (continuous data)

Analysis 1.2; Figure 4.

Figure 4. Forest plot of comparison: 1 Zinc versus placebo, outcome: 1.2 Taste acuity improvement - Objective outcome - Continuous data.



Footnotes
(1) Filter paper strip method
(2) Paper filter disk method (Tomita)
(3) Paper filter disk method (Tomita). Data from 17 mg, 34 mg and 68 mg zinc group were combined using the method described in Cochrane...

Three trials were included in the meta-analysis for this outcome (Heckmann 2005; Ikeda 2013; Sakagami 2009) as they studied taste disorders in idiopathic dysgeusia. One of these trials (Heckmann 2005) was at low risk of bias and two trials (Ikeda 2013; Sakagami 2009) were at unclear risk of bias.

In the Heckmann 2005 trial, 32 filter paper strips impregnated with various tastants were used, and an average was taken for each group. An improvement by six points in the taste test was regarded as substantial. Ikeda 2013 and Sakagami 2009 used the filter paper disk method. Ikeda 2013 explained the results in mean improvement of the taste grades whereas Sakagami 2009 explained the results in mean improvement for three different dosages of zinc (17 mg, 34 mg, and 68 mg). Hence, we combined these data according to the method described in the *Cochrane Handbook for Systematic Reviews of Interventions,* Section 7.7.3.8 (Higgins 2011). The grade was expressed as negative value in the Sakagami 2009 trial because the values were regarded as improvement only when it was less than the baseline data.

In the Ikeda 2013 trial, the average zinc intake from the diet in both the intervention and control groups were the same (obtained from food frequency questionnaire method and was 7.9 mg/day). But there were no data available for the zinc intake from the diet in the Sakagami 2009 trial.

Three trials included for meta-analysis (Heckmann 2005; Ikeda 2013; Sakagami 2009) used different taste detection tests, and hence we calculated the standardised mean difference (SMD). The overall effect favoured zinc supplements (SMD 0.44, 95% CI 0.23 to 0.65; 3 trials, 366 participants; Analysis 1.2).

Taste acuity improvement for different taste sensations

Analysis 1.3.

The results of the Mahajan 1980 trial were described as an improvement for each individual taste quality. The salt, sugar and bitter taste acuity (detection and recognition) significantly improved in the interventional group compared to the control

group. Bitter taste quality improvement was similar in both groups. The data were derived from the graphs. The mean difference (MD) for the Mahajan 1980 trial was calculated for four types of taste sensations: salt (MD 285, 95% CI 238.75 to 331.25; 22 participants; Analysis 1.3); sweet (MD 190, 95% CI 142.36 to 237.64; 22 participants; Analysis 1.3); sour (MD 10, 95% CI -16.43 to 36.43; 22 participants; Analysis 1.3); and bitter (MD 2.40, 95% CI 2.14 to 2.66; 22 participants; Analysis 1.3).

In a similar way, Matson 2003 reported three taste perceptions (sweet, sour, and salt) before and after the intervention. In this trial, sour was often confused with salt, and sour solutions of different concentrations were not distinguishable. There was no difference in the taste scores after six weeks in either of the groups. We could not include this trial in the meta-analysis as the data related to the placebo group were missing.

Watson 1983 reported taste acuity for four taste sensations (sweet, sour, salt, and bitter) before and after the intervention as median values using graphs. We could not extract the data as the percentage of change between pre- and post-treatment was minimal and was not detectable in the graph.

Taste acuity improvement - Cross-over trial

Analysis 1.4.

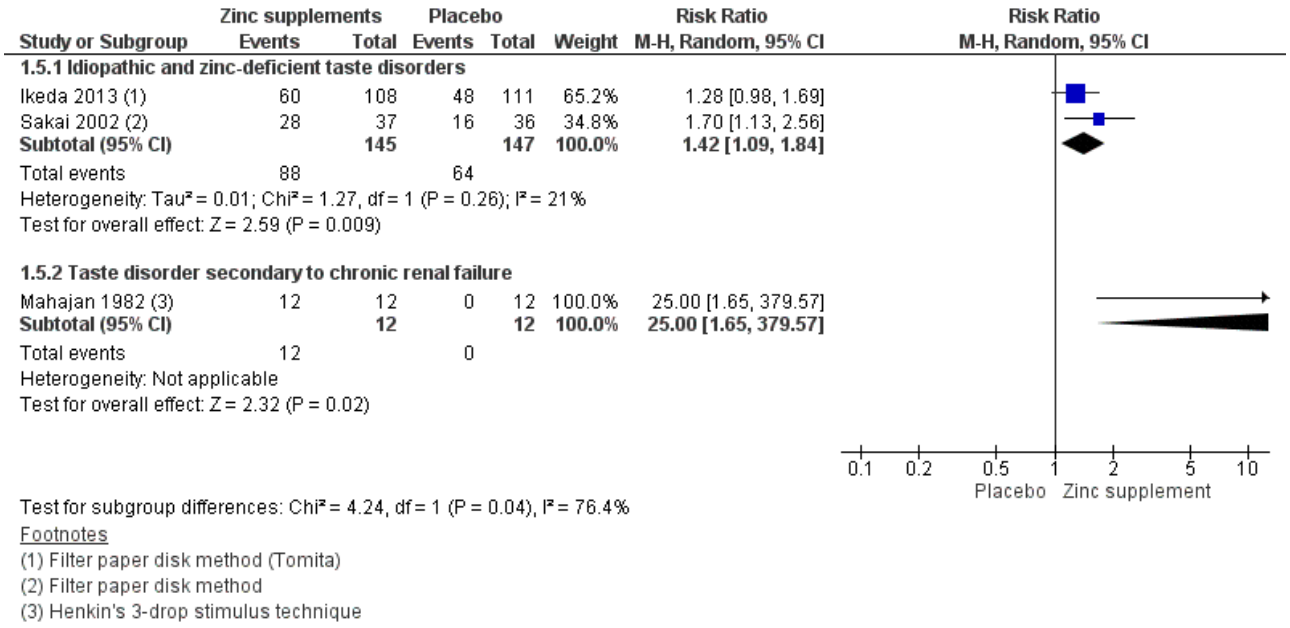
Eggert 1982 described the results as taste detection and taste recognition in children with chronic renal failure in a cross-over trial. We took the results of taste recognition before the cross-over to prevent the carry-over effect (the trial did not have any washout period). The data were derived from the graphs.

Eggert 1982 showed improvement in taste detection (MD 2.50, 95% CI 0.93 to 4.07; 14 participants; Analysis 1.4) and taste recognition for the zinc group (MD 3, 95% CI 0.66 to 5.34; 14 participants; Analysis 1.4).

Taste acuity improvement - Objective outcome (dichotomous data)

Analysis 1.5; Figure 5.

Figure 5. Forest plot of comparison: 1 Zinc versus placebo, outcome: 1.5 Taste acuity improvement - Objective outcome - Dichotomous.



Only three trials (Ikeda 2013; Mahajan 1982; Sakai 2002) described the objective outcome as dichotomous data. Meta-analysis of these three studies showed high heterogeneity because of the different populations (idiopathic and zinc-deficient taste disorder in the Ikeda 2013 and Sakai 2002 trials and taste disorder secondary to chronic renal failure in the Mahajan 1982 trial). Hence, we did subgroup analyses.

Meta-analysis of idiopathic and zinc-deficient taste disorder showed improvement in the taste acuity for the zinc supplement group (RR 1.42, 95% CI 1.09 to 1.84; 292 participants; Analysis 1.5).

A lack of events in the placebo group in the Mahajan 1982 trial resulted in a high upper limit in the CI (RR 25, 95% CI 1.65 to 379.57; 24 participants; Analysis 1.5). Effect estimates of both the subgroups favoured zinc supplements.

Taste discrimination improvement

Matson 2003 used zinc sulphate for testing taste discrimination and was at unclear risk of bias. Taste discrimination was tested using the sip and spit method. However, the trial did not report the details of the placebo group and thus we could not meta-analyse the results.

Adverse events

See Additional Table 9; Additional Table 10; Analysis 1.6; and Summary of findings table 1 for adverse events in trials comparing zinc with placebo for the management of taste disturbances.

Out of nine trials using zinc supplementation, four reported adverse events (Ikeda 2013; Sakagami 2009; Sakai 2002; Watson 1983). Ikeda 2013 reported one case of eczema. Sakai 2002 reported adverse events like nausea, abdominal pain and diarrhoea in 16% of patients (Additional Table 9). Watson 1983 reported nausea and vomiting in one patient after the zinc intervention only. Sakagami 2009 reported adverse events like stomach discomfort, abdominal distension, constipation, decrease in blood iron, increase in blood alkaline phosphatase and minor increase in blood triglycerides in all four groups of the trial (Additional Table 10). We did not include this trial in the analysis since it did not report any further details on the number of events. Zinc intervention groups reported adverse events compared to placebo (RR 5.20, 95% CI 0.90 to 30.19; 3 trials, 335 participants; Analysis 1.6).

The other five trials (Eggert 1982; Heckmann 2005; Mahajan 1980; Mahajan 1982; Matson 2003) did not give any data on adverse events.

Health-related quality of life

None of the studies reported data on health-related quality of life. Heckmann 2005 reported that the signs of depression in the zinc group were less severe (Beck Depression Inventory, $P < 0.05$; mood scale, $P < 0.05$) and these findings were independent of the actual levels of zinc in serum/saliva (Additional Table 6).

Acupuncture versus sham control

See Summary of findings 2.

Taste acuity improvement

There were no data on taste acuity improvement in the included acupuncture trial (Brandt 2008).

Taste discrimination improvement

See Analysis 2.1 and Summary of findings table 2 for the main comparison of acupuncture to sham for the management of taste disturbances.

Brandt 2008 tested taste discrimination using acupuncture and was at high risk of bias. Taste discrimination was tested using the filter paper strip method and results were described in means of filter paper strips. The acupuncture group showed improvement in taste discrimination compared to the sham group (MD 2.80, 95% CI -1.18 to 6.78; 1 trial, 37 participants; Analysis 2.1). As we had only one trial using acupuncture, we considered that the evidence is insufficient to conclude if there is any difference between acupuncture and sham acupuncture with laser to improve taste discrimination.

Adverse events

The acupuncture trial (Brandt 2008) did not give any data on adverse events in either group.

Health-related quality of life

Brandt 2008 assessed health-related quality of life in dysgeusia patients. The trial reported significant improvement in psychological symptoms in the interventional group (acupuncture) and increased quality of life in both groups (no statistically significant difference between the two groups) (Additional Table 8). We could not meta-analyse the health-related quality of life outcome due to missing data.

DISCUSSION

Summary of main results

The main objective of this review was to evaluate the efficacy of various interventions to improve taste acuity and taste discrimination. We included 10 randomised controlled trials (RCTs) in our review. We assessed three trials (30%) as at low risk of bias, four trials (40%) as at high risk of bias, and three trials (30%) as at unclear risk of bias.

Nine trials compared the efficacy of different zinc supplements for improvement of taste acuity, and one trial compared the efficacy of acupuncture for improvement of taste discrimination in dysgeusia patients. However, the Mahajan 1980 and Matson 2003 trials were not included in the 'Summary of findings' tables because each taste sensation was analysed, rather than overall taste acuity and Matson 2003 did not report data for the placebo group. We did not pool the first half of the cross-over trial by Eggert 1982 because of the different trial designs and we did not include Mahajan 1982 in the 'Summary of findings' tables due to the large confidence interval (CI). Based on the available data, we conducted a meta-analysis for taste acuity and taste discrimination separately.

Out of seven trials that reported taste acuity as their outcome, two trials (Heckmann 2005; Sakai 2002) documented this as a patient-reported outcome. We assessed the body of evidence for this comparison using GRADE which incorporates risk of bias, the directness of the evidence, inconsistency of the results, the precision of the estimates, and the risk of publication bias (Summary of findings for the main comparison). We assessed the evidence from these two trials, which included 119 participants, with a mean trial period of three months. The quality of the evidence assessed was very low and was insufficient to conclude if there is any benefit of zinc supplementation for improvement in taste acuity.

Three trials (Heckmann 2005; Ikeda 2013; Sakagami 2009) described taste improvement (Summary of findings for the main comparison). We used GRADE to assess the evidence from these three trials, which included 366 participants with a mean trial period of three months. The quality of the evidence assessed was very low. We assessed one trial (Eggert 1982) as having very low-quality evidence for taste detection and taste recognition improvement.

We assessed two trials (Ikeda 2013; Sakai 2002) in zinc-deficient/idiopathic taste disorder patients which described taste acuity improvement. The evidence assessed from these trials included 292 participants with a trial period of three months. We assessed the quality of the evidence as very low and further research may change the estimate.

Two trials reported taste discrimination as the outcome (Brandt 2008; Matson 2003). We assessed the evidence from Brandt 2008, which included 37 participants with a trial period of eight weeks, using acupuncture, as very low (Summary of findings 2).

Overall completeness and applicability of evidence

We systematically searched for trials according to the methodology written in our protocol. We included all RCTs that fit the inclusion criteria in our review. All the included trials had patients with

dysgeusia or hypogeusia. None of them reported phantogeusia, ageusia, parageusia or cacogeusia in their participants.

For taste acuity improvement, we included nine trials using zinc supplements in different forms. We included two trials for taste discrimination improvement using acupuncture and zinc sulphate. Zinc supplement is the most commonly used intervention for taste disorders and our review highlights the usage of zinc in the majority of the included trials. Taste acuity and taste discrimination were our two primary outcomes. Health-related quality of life due to taste impairment is an important issue to be addressed. We only found two trials addressing health-related quality of life due to taste disorders. We included in the analysis all trials that reported adverse events appropriately.

Trials which were not included in the meta-analysis were explained in the results. We did not exclude any trial due to missing data. In a cross-over trial (Eggert 1982) without a sufficient washout period and suspected carry-over effect, we included data before the cross-over.

This review has limited evidence on the primary outcomes of taste acuity and taste discrimination, and is not conclusive in demonstrating improvement in taste perception with zinc supplements or acupuncture. However, the review encourages further high quality RCTs with primary outcomes of taste acuity and taste discrimination using zinc supplements or acupuncture for taste disorder patients to derive definitive conclusions and recommendations.

Quality of the evidence

We included seven parallel and two cross-over RCTs with 566 participants in the meta-analyses. The quality of the evidence is discussed for each outcome. One parallel-group RCT with 15 participants is discussed in the review but not included in the meta-analyses.

Zinc supplements versus placebo

Taste acuity - patient-reported outcome

Of the two trials comparing zinc supplements and placebo that were suitable for pooling in this meta-analysis for the outcome of patient-reported taste acuity, we considered one to be at low risk of bias (Heckmann 2005) and one to be at high risk of bias (Sakai 2002). We downgraded the quality of the evidence by one due to high attrition bias, imprecision, and publication bias (Summary of findings for the main comparison). The results, therefore, do not allow us to draw a robust conclusion regarding the patient-reported outcome in taste acuity. We assessed the results of this outcome to be of very low quality.

Both trials excluded dysgeusia/hypogeusia subjects secondary to systemic illnesses. However, Sakai 2002 included idiopathic dysgeusia and dysgeusia due to zinc deficiency. Neither of the trials mentioned dietary zinc which could have been a major confounder here. Future studies on zinc interventions in dysgeusia cases should standardise dietary zinc to clearly ascertain the role of zinc in the improvement of dysgeusia. Gender differences between these two trials (Heckmann 2005; Sakai 2002) could have been another confounder that should be considered.

Taste acuity - objective outcome

We included seven trials in the meta-analysis for this outcome. Three trials (Heckmann 2005; Ikeda 2013; Sakagami 2009) reported taste acuity improvement as objective, continuous data, and we found the quality of the evidence to be very low. One trial (Mahajan 1980) presented the data in the form of a graph for each taste sensation (salt, sweet, bitter, sour) and could not be grouped with the other three trials. One cross-over trial (Eggert 1982) showed better taste detection and taste recognition improvement in the zinc group among chronic renal failure patients and presented the data in the form of a graph. Due to clinical heterogeneity, we did not include this trial in the meta-analysis. We assessed the evidence for the outcomes of these two comparisons from Mahajan 1980 and Eggert 1982 studies separately to be of very low quality.

Three trials (Ikeda 2013; Mahajan 1982; Sakai 2002) reported the objective outcome for taste acuity in the form of dichotomous data. We did subgroup analyses based on the diagnosis and graded results of idiopathic/zinc-deficient taste disorders subgroup separately. The results showed very low-quality evidence for taste acuity improvement (Summary of findings for the main comparison). As there were no events in the placebo group and all participants in the intervention group showed improvement, we could not grade the results of the other subgroup, taste disorders secondary to chronic renal failure.

Watson 1983 reported taste recognition as median values in the form of a graph for each taste sensation and did not mention interquartile range for post-treatment changes. Matson 2003 did not report data for the placebo group. Hence we could not include these two trials in the meta-analysis.

Adverse events

We included only three trials in the meta-analysis which reported adverse events in the zinc supplements group. The reported adverse events were either gastrointestinal or dermatological. The results were of very low quality and therefore do not allow us to draw a strong conclusion regarding the prediction of adverse events related to zinc supplementation (Summary of findings for the main comparison).

We could not assess the quality of the evidence for the health-related quality of life outcome as this outcome was not meta-analysed in this comparison.

Acupuncture versus sham control

Taste discrimination

We included only one trial (Brandt 2008) for the outcome of taste discrimination, and we assessed the quality of the evidence as very low (Summary of findings 2). The results therefore do not allow us to draw a robust conclusion regarding taste discrimination using acupuncture.

We could not assess the quality of the evidence for the outcomes taste recognition, health-related quality of life, and adverse events as these outcomes were not meta-analysed in this comparison.

Potential biases in the review process

We have taken steps to minimise bias in every stage of the review. We searched all the above mentioned databases, conference

proceedings, and trial registries to include all relevant reports. We included foreign language reports and alternative medicine reports in our review. We tried to contact trial authors for missing data through emails. If the reports were very old, we tried to get the contact details of the authors through peer contacts, Google search and university/hospital websites where they were previously affiliated. Nevertheless, there could be unpublished data which we could not trace with the above methods. Trials with missing data were included qualitatively.

Two review authors independently reviewed data extraction forms obtained from translators and cross-checked doubtful areas using Google translator. We tried our best to follow the methodology stated in the protocol. However, post hoc changes in the inclusion criteria could have introduced some bias in our review (Differences between protocol and review).

Agreements and disagreements with other studies or reviews

We found two systematic reviews on dysgeusia associated with cancer therapies (Hovan 2010; McLaughlin 2014).

The purpose of the review by Hovan 2010 was to select relevant scientific papers written since 1989, which focused on the prevalence and management of dysgeusia as an oral side effect of cancer treatment. The literature search in the review was limited to English language papers published between 1990 and 2008. A total of 30 papers were reviewed. The trial authors concluded that from the current literature, there does not appear to be a predictable way of preventing or treating dysgeusia.

In the review by McLaughlin 2014, a meta-analysis was done to assess the relationship between the impaired taste sensation and the type of treatment and tumour site in head and neck cancer treatment survivors.

In our review, we excluded prevention studies and trials including taste disorders secondary to cancer treatment. We included idiopathic dysgeusia/hypogeusia and dysgeusia/hypogeusia secondary to renal failure. The difference in opinion could be due to these reasons.

AUTHORS' CONCLUSIONS

Implications for practice

We found very low-quality evidence that is not sufficient to conclude the role of zinc supplements to improve taste acuity (patient-reported outcome and objective outcome) in zinc-deficient/idiopathic taste disorder patients.

We found very low-quality evidence for the role of zinc supplements to improve taste detection and recognition in children having taste disorders secondary to chronic renal failure.

We did not find any evidence to conclude the role of zinc supplements for improvement in taste discrimination.

We found very low-quality evidence for the risk of adverse events in the zinc intervention group.

We also found very low-quality evidence that is not sufficient to conclude the role of acupuncture to improve taste discrimination in idiopathic dysgeusia and hypogeusia patients.

We were unable to draw any conclusions regarding the superiority of zinc supplements or acupuncture as none of the trials compared these interventions.

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.

Implications for research

Further research should be undertaken in the management of taste disorders by conducting well planned randomised controlled trials (RCTs) with more clarity and uniformity in the variables. In designing such clinical trials, the following needs to be considered.

- Evidence: the present evidence was insufficient to conclude that zinc supplements and acupuncture will improve taste acuity and discrimination in patients with taste disorders. All the trials should evaluate improvement in taste acuity and taste discrimination; the patient-reported outcome and objective testing should be evaluated in these trials. Furthermore, reports on clinical trials would be improved by following CONSORT group guidelines.
- Population: inclusion criteria for clinical trials should be well defined. Idiopathic taste disorders and zinc deficiency taste disorders should be evaluated separately. The trials should include both genders in equal distribution. More clinical trials should be encouraged in low-income countries where zinc deficiency can be prevalent. If trials include children less than five years of age, the outcome measures should be clearly defined. In zinc supplement interventions, dietary zinc intake should be taken into consideration. All patients with taste disorders should be assessed for alterations in smell acuity and discrimination. Comparisons should be done for taste disorders, smell disorders, and taste and smell disorders separately. Future trials should test all five taste sensations.
- Intervention: more interventional studies should be conducted for zinc supplements and acupuncture to provide sufficient evidence. Future trials using gingko biloba, transmagnetic stimulation, and miracle fruit should be conducted.
- Comparison: well-designed placebo-controlled trials should be conducted in order to see if any interventions actually improve taste disturbance. Whenever a cross-over trial design is used, appropriate washout periods should be considered.
- Outcome: other than taste improvement, outcomes like health-related quality of life and improvement in nourishment should be considered in future trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brandt 2008

Methods	Title: efficacy of acupuncture in the treatment of idiopathic taste disorders - a randomised placebo-controlled trial Year of publication: 2008 Language: German Trial design (including number of arms): randomised placebo-controlled trial (single-blind), 2 treatment arms Location: university clinic, Dresden, Germany Number of centres: 1 Recruitment period: December 2003 - December 2005 Funding source: German Doctor's Association for Acupuncture
Participants	Inclusion criteria: 1. idiopathic dysgeusia combined with hypogeusia Exclusion criteria: 1. dysosmia 2. dysgeusia due to radiation, chemotherapy, pharmaceuticals, operations, trauma, Morbus Parkinson, Morbus Alzheimer, Diabetes mellitus, psychological/neurological disease

Brandt 2008 *(Continued)*

	Baseline taste acuity: not given Baseline taste discrimination: Group A: 11.7; Group B: 11.9 Standard deviation not given, scale used: 32 taste strips, hypogeusia threshold: < 16 for ages 60 and younger/ < 14 for ages 60 and older Type of test: taste strips Age (standard deviation) at baseline: only given for the 2 groups combined: mean 63 years, range 25-83 (standard deviation not given) Gender: only given for the 2 groups combined: 25 female; 12 male Any other details of important prognostic factors: disease duration across both groups: mean 19 months (range 1 month to 12 years) Number randomised: 37 Method of randomisation: assigned by lot Number evaluated: 37
Interventions	Comparison: Group A (n = 17): acupuncture with needles Group B (n = 20): sham acupuncture with deactivated acupuncture laser Duration of treatment: 15 acupuncture treatments (2 patients in the interventions group did not require further acupuncture treatment after 10 treatments), over a course of 8 weeks
Outcomes	Taste discrimination: taste strips (scale used 32 taste strips, hypogeusia threshold: < 16 for ages 60 and younger/ < 14 for ages 60 and older) assessed before and after treatment Quality of life: 5 questions to be answered via visual analogue scale Depressive symptoms: Beck Depression Inventory Subjective well-being: Zerssen Mood Scale
Notes	Sample size calculation: reported Adverse events: not reported Health-related quality of life: reported Correspondence required: email sent on 27 November 2013 for missing data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Assigned by lot"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind trial

Brandt 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not possible (needle versus sham laser acupuncture)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All the outcomes mentioned in the methodology section are reported
Other bias	Low risk	The characteristics of the 2 groups before treatment did not differ significantly

Eggert 1982

Methods	Title: zinc supplementation in chronic renal failure Year of publication: 1982 Language: English Trial design (including number of arms): double-blind cross-over design Location: Division of Nephrology, Department of Pediatrics, University of Utah School of Medicine, Provo and Salt Lake City, USA Number of centres: 1 Recruitment period: 1 year Funding source: Thrasher Research Fund
Participants	Total number: 17 Inclusion criteria: paediatric patients, varying degrees of chronic renal failure, not yet on dialysis or in need of a transplant, taste impairment Exclusion criteria: none if they were in paediatric renal clinic (from personal communication) Baseline taste acuity/ discrimination: impaired in all patients (taste detection and recognition) • Method of Henkin: sodium chloride (3.0 g/L, 5.3 g/L, 10 g/L; sucrose 1000 mg/dL, 1750 mg/dL, 2650 mg/dL; hydrogen chloride .07, .16, .33 normality; and urea 460 mg/dL, 860 mg/dL, 1460 mg/dL - from personal communication • Serum creatinine concentration • Plasma zinc level • Zinc red blood cell (RBC) test Type of test: quote from personal communication: "see above, initially we bought the kit with the 12 dropper bottles from Henkin, then our laboratory could make refills. For the 6-month old child, as I recall we were limited to a smile with the sucrose bottle and making a grimace or turning away from the other solutions as being 'data'" Age at baseline: mean age of 14 patients who completed the trial was 10 years with a range of 0.5 years to 19 years Gender: not mentioned Any other details of important prognostic factors: nil

Eggert 1982 *(Continued)*

	Number randomised: 14 from personal communication Method of randomisation: quote from personal communication: "pharmacy prepared capsules and numbered bottles randomly and kept 'the code' until the end of the trial. We just gave each enrollee the next set of bottles" Number evaluated: 14
Interventions	Total number of intervention groups: 2 Comparison: zinc sulphate (0.50 mg/Zn/kg/day to 0.75 mg/Zn/kg/day) and placebo Group 1 (n = 7*): first they received placebo and then zinc Group 2 (n = 7*): first they received zinc and then placebo Duration of treatment: each sequence lasted for 6 months *(*n = 7 based on personal communication)*
Outcomes	Taste acuity: taste detection and recognition improved (P < 0.05) in both groups following zinc supplementation Data were taken before the cross-over period in the meta-analysis
Notes	Sample size calculation: not done as this was a limited population. We started with 17 patients (7 male; 10 female). 2 patients left the area. 1 patient died leaving 14 patients, unknown what the gender mix was of the 14 Adverse events: none reported Health-related quality of life: none Key conclusions of the trial authors: zinc supplementation increased RBC zinc concentration and taste acuity. In those with less advanced renal failure (serum creatinine < 5.0 mg/dL) it also improved caloric intake Correspondence required: contacted and reply received on 22 December 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is assumed that the pharmacy did use an acceptable random sequence generation
Allocation concealment (selection bias)	Low risk	Pharmacy-prepared random numbered capsules – from personal communication
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 17, only 14 participants completed the trial

Eggert 1982 *(Continued)*

Selective reporting (reporting bias)	Low risk	Reasons for dropouts: quote from personal communication: "2 patients left the area. 1 patient died leaving 14 patients"
Other bias	High risk	1. As it is a cross-over trial, possible carry-over effect could be there because of "no washout period" 2. Inclusion of 6-month child (1), 3-year old patient (1), 5-year old patients (2) for assessment of taste acuity is questionable 3. Data on taste acuity was only assessed by smile or grimace in these participants

Heckmann 2005

Methods	Title: zinc gluconate in the treatment of dysgeusia - a randomised clinical trial Year of publication: 2005 Language: English Trial design: randomised controlled trial (double-blind), fixed block randomisation Location: Smell and Taste Clinic, Department of Otorhinolaryngology, University of Dresden, Germany Number of centres: 1 Recruitment period (duration): 1999 to 2001 Funding source: Sander-Stiftung (No 2001.019.1); taste strips given by Christian Müller, University of Vienna
Participants	Total number: 50 Inclusion criteria: • idiopathic dysgeusia • diagnosis of dysgeusia based on patient's reports as described by Deems 1991 Exclusion criteria: • allergy to a dental material • dysgeusia in combination with burning mouth syndrome, systemic disease, neurological or psychiatric or metabolic disease • drug-induced dysgeusia Baseline taste acuity (+ standard deviation + scale used) Scales used (before and after treatment): 1. filter paper strip for gustatory sensitivity (means of number of correctly identified out of 32) 2. visual analogue scale (10 cm equivalent to 100%: 0 - no impairment and 10 - extremely impaired) 3. Beck Depression Inventory 4. Zerssen Mood Scale 5. Zinc (mg/dL), sodium (mmol/L), calcium (mmol/L), potassium (mmol/L), and chloride (mmol/L) in both the serum and saliva 1. Filter paper strip at baseline 2. visual analogue scale 3. Beck Depression Inventory 4. Mood Scale 5. Zinc in serum: placebo

Heckmann 2005 *(Continued)*

	6. Zinc in saliva: placebo Age: placebo = 61.0 ± 8.9; zinc gluconate = 61.1 ± 10.6 Gender: placebo = 2 male, 22 female; zinc gluconate = 5 male, 21 female Any other details of important prognostic factors: • zinc gluconate (140 mg/day, equivalent to 20 mg/day of elemental zinc) • participants were advised to swallow the drug whole on an empty stomach with ample water Number randomised: 50 Method of randomisation: special computer software program RANDOM Number evaluated: 50
Interventions	Total number of intervention groups: 2 Comparison: placebo (n = 26) versus zinc gluconate (n = 24) Duration of treatment: 3 months
Outcomes	Taste acuity: taste strips (an improvement by 6 points in the taste test could be regarded as substantial) Visual analogue scale (VAS scale): 0 - no impairment and 10 - extremely impaired. Study authors have defined improvement in dysgeusia as "improvement of more than 5% patient ratings in VAS scale"
Notes	Sample size calculation: unclear Adverse events: not reported Health-related quality of life: reported Key conclusions: in conclusion, zinc appears to improve general gustatory function and, consequently, general mood scores in dysgeusia patients Correspondence required: nil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Blinding and randomisation were performed by an independent individual using a special computer software program (RANDOM by Joern Loetsch, Institute of Clinical Pharmacology, University of Frankfurt, Germany)"
Allocation concealment (selection bias)	Low risk	Quotes: "The bottles were sealed and labelled with the study code and the enrolment number. After the initial investigation for the baseline data, each patient was given an enrolment number and the corresponding screw-top bottle"; "The zinc and placebo showed no significant difference in taste"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Screw-top bottles were prepared containing either 100 zinc gluconate tablets (140 mg, "Zink Verla"®) or 100 placebo tablets (lactose, "Placebo Lichtenstein 10 mm"). The bottles were sealed and labelled with the study code and the enrolment number"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither patient nor investigator had any knowledge during the study as to whether the patient was being treated with zinc or placebo. When the study was complete, this information was then revealed by the independent individual

Heckmann 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methodology section are reported
Other bias	Low risk	The characteristics of the 2 groups before treatment did not differ significantly

Ikeda 2013

Methods	Title: the effect of zinc agent in 219 patients with zinc deficiency-inductive/idiopathic taste disorder: a placebo controlled randomized study Year of publication: 2013 Language: Japanese Trial design: randomised controlled trial with 2 arms (zinc tablets versus placebo) Location: university hospitals, mostly departments of otolaryngology, Japan Number of centres: 32 Recruitment period: from November 2008 to January 2010 Funding source: Zeria Pharmaceutical Co Ltd, Japan
Participants	Inclusion criteria: zinc deficiency-inducive and idiopathic taste disorder Exclusion criteria: who had unbalanced eating habits identified with meal diary during the screening period Baseline taste acuity: average taste scores of 4 types of taste less than 4.5 by filter disc method were included in both Group A and B. Exact baseline scores and variations were not described in the text Baseline taste discrimination: only average taste scores of 4 types by filter disc method were described in the text Type of test: filter paper disk method by Tomita Average age at baseline: Group A: 43.3 years; Group B: 47.1 years (no standard deviation values were indicated in the text) Gender: Group A: male 48/female 60; Group B: male 39/female 72 Other details of important prognostic factors: • average serum zinc concentration: Group A: 71.8 µg/dL, Group B: 73.5 µg/dL • average zinc intake from food: Group A: 7.9 mg/day, Group B: 7.9 mg/day (assumed by food frequency questionnaire) Number randomised: 219 Method of randomisation: randomisation method was not described Number evaluated: 219
Interventions	Comparison: zinc agents versus placebo

Ikeda 2013 *(Continued)*

	Group A (n = 108): prescribed 17 mg of zinc containing tablets (Polaprezinc, Promac, Zeria Pharmaceutical Co Ltd, Japan), twice a day for 12 weeks Group B (n = 111): prescribed placebo tablets without zinc, twice/day for 12 weeks Duration of treatment: 12 weeks
Outcomes	Main outcome measure was the change of the average 4 basic taste sensitivity scores by filter paper disk method at 4, 8, 12 weeks from baseline and 4 weeks after the end of zinc tablets administration Another outcome measure they used was binary measure: improved/not improved Patients showing taste acuity equal or less than 3.0 of average 4 taste sensitivity by filter disc method were regarded as improved, or patients showing more than 1.0 of improvement Taste discrimination was not described in the text
Notes	Sample size calculation: not calculated prior to the trial Adverse events: 1 case of eczema was reported with zinc containing tablets. No severe adverse event was reported Correspondence required: yes, details about random sequence generation and allocation concealment needed. Email sent on 25 November 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided by the translator (foreign language article)
Allocation concealment (selection bias)	Unclear risk	No information provided by the translator (foreign language article)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% of participants were included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the method section are reported adequately
Other bias	Low risk	The characteristics of the 2 groups before treatment did not differ significantly

Mahajan 1980

Methods	Title: improvement of uraemic hypogeusia by zinc: a double-blind study Year of publication: 1980

Mahajan 1980 *(Continued)*

	Language: English Trial design: 3 arms (placebo group: 25 mg sucrose; study group: 25 mg zinc acetate; control group 20 healthy age and gender matched controls were also studied for taste and plasma zinc determination for comparison) Location: Department of Medicine, Veterans Administration Medical Center, Allen Park, Harper Hospital and Wayne State University School of Medicine, Detroit, Michigan Number of centres: 1 Recruitment: 6 to 12 weeks Funding source: supported in part by grant AM19338 from NIAMDD and BMA Management Research Fund of Boston, Massachusetts
Participants	Total number: 42 (placebo = 11; zinc acetate = 11; control = 20) Inclusion criteria: • stable patients undergoing thrice weekly maintenance haemodialysis for a period of more than 6 months • informed consent Exclusion criteria: none Baseline taste acuity and taste discrimination: • baseline detection thresholds for sodium chloride correlated well with detection thresholds for sucrose, urea and hydrochloric acid • baseline recognition thresholds for sodium chloride also correlated well with those for sucrose, urea and hydrogen chloride Type of test: 3-drop stimulus technique. Thresholds for taste detection and recognition were determined for 1 taste quality before proceeding to the next taste quality. Lowest concentration of solute that the patient could consistently distinguish as different from water for each taste quality was called the detection threshold. The lowest concentration of solute that the patient could consistently recognise correctly as salty, sweet, sour or bitter was called the recognition threshold Nerve conduction velocity: placebo: 50.4 ± 1.8; zinc acetate: 47.9 ± 2.6 (normal range is 43 to 56 m/s) Age (± standard deviation) at baseline: placebo: 55.1 ± 2.8; zinc acetate: 51.3 ± 3.2 Gender: not mentioned Any other details of important prognostic factors: smokers were asked not to smoke at least 1 to 2 hours prior to taste testing. Water was allowed up to the time of testing Number randomised: placebo: 11, zinc acetate: 11 Method of randomisation: the patients were assigned to the treatment or placebo group by the pharmacist by opening the consecutively numbered sealed envelopes which indicated zinc acetate or placebo in equal numbers. As each patient entered the trial, the next sequential envelope was opened and the patient was assigned to the appropriate treatment group. Identical capsules containing either 25 mg zinc acetate or 25 mg sucrose were used. Neither patients nor physicians were aware of the medication being given Number evaluated: 22
Interventions	Total number of intervention groups: 2 (zinc acetate and placebo) and control Comparison:

Mahajan 1980 *(Continued)*

- Group A (n = 11): the treatment group received 25 mg of elemental zinc as zinc acetate and then each patient was tested for taste and blood samples were drawn for plasma zinc before and at various intervals exceeding 6 weeks after starting the treatment. Test for taste that was used was taste detection and recognition thresholds measured for sodium chloride, sucrose, hydrogen chloride and urea, to monitor the 4 tastes salt, sweet, sour and bitter
- Group B (n = 11): the placebo group received 25 mg of sucrose and then each patient was tested for taste and blood samples were drawn for plasma zinc before and at various intervals exceeding 6 weeks after starting the treatment. Test for taste that was used was taste detection and recognition thresholds measured for sodium chloride, sucrose, hydrogen chloride and urea, to monitor the 4 tastes salt, sweet, sour and bitter

Duration of treatment: 6 to 12 weeks

Outcomes

Taste detection and recognition:

- sodium chloride: placebo (baseline) and zinc acetate (baseline): not statistically significant
- baseline (placebo) and end point (placebo): P < 0.01 (for both detection and recognition)
- placebo and zinc acetate: P < 0.05 for detection and P < 0.005 for recognition
- sucrose: placebo (baseline) and zinc acetate (baseline): not statistically significant
- baseline (placebo) and end point (placebo): P < 0.025
- placebo and zinc acetate: P < 0.05

Comparison between placebo and zinc acetate group for detection threshold and recognition threshold:

- the mean detection and recognition thresholds of taste for sodium chloride, sucrose and urea decreased significantly in the treatment group and were not different from those in the normal controls
- in contrast, the patients receiving placebo did not show significant improvement in any of the taste modalities tested
- no significant change occurred in taste detection and recognition thresholds for hydrogen chloride in the treatment group
- no significant correlation was found between plasma zinc concentration and detection or recognition thresholds for all 4 tastes

Notes

Sample size calculation: not mentioned

Adverse events: not reported

Health-related quality of life: not reported

Key conclusions of the trial authors:

- dialysis patients have diminished taste acuity and hypozincemia, both of which can be reversed by oral zinc therapy in most of these patients
- the decreased ability to detect taste of sodium chloride in uremic patients is of potential importance in as much as some of these patients may increase the ingestion of salt unintentionally
- further studies are needed to establish the causal relationship between hypogeusia and zinc deficiency in uremic patients

Correspondence required: yes, for the missing data; co-author Anand Prasad contacted and received reply on 7 November 2013 and on 17 December 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is assumed that the pharmacy did use an acceptable random sequence generation

Mahajan 1980 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The patients were assigned to the treatment or placebo group by the pharmacist by consecutively numbered sealed envelopes.... Pharmacy controlled randomisation, sealed envelopes, identical capsules of zinc acetate and sucrose (placebo)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "neither patients nor physicians were aware of the medication being given"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "neither patients nor physicians were aware of the medication being given"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts in the trial
Selective reporting (reporting bias)	Low risk	All the stated outcomes in the methodology are adequately reported
Other bias	Low risk	The timing of end point analysis is not clear. The trial says that the post-treatment evaluation was done after 6 weeks to 12 weeks. This will not affect the outcome of the study clinically

Mahajan 1982

Methods	Title: zinc deficiency: a reversible complication of uremia Year of publication: 1982 Language: English Trial design (including number of arms): double-blind study Location: Department of Medicine, Veterans Administration Medical Center, Allen Part, Michigan, and Harper Hospital, and Wayne State University School of Medicine, Detroit, MI, USA Number of centres: 2 Recruitment period (duration): 6 months Funding source: supported in part by a sickle cell centre grant from the National Heart, Lung and Blood Institute and a grant from the United States Department of Agriculture
Participants	Total number: 24 Inclusion criteria: • stable patients with end stage renal disease undergoing maintenance haemodialysis for more than 6 months • written informed consent Exclusion criteria: not mentioned Baseline taste acuity (± standard deviation + scale used): 17 patients had lack of appetite, or taste, or both, for various foods and metallic sensation in the mouth and remaining 7 had no symptoms regarding their taste. At baseline testing, all had decreased taste acuity. (Mean and standard deviation not given, no scale given)

Mahajan 1982 *(Continued)*

	Baseline taste discrimination: not mentioned Type of test: Henkin's 3-drop stimulus technique Age (± standard deviation) at baseline: Group A (zinc acetate): 46 ± 8; Group B (placebo): 49 ± 12 Gender: all males Any other details of important prognostic factors: none of the patients had an intercurrent illness of gastrointestinal tract disorder. All patients were consuming weight-maintaining diets consisting of 60 g to 80 g of protein with variable sodium restriction. The aetiology of the end stage renal disease was hypertensive nephrosclerosis in 15 patients, chronic glomerulonephritis in 8 patients and diabetic glomerulosclerosis in 1 patient. All patients were receiving phosphate-binding gels, multivitamins, folic acid and iron Number randomised: 24 (12: zinc, 12: placebo) Method of randomisation: not mentioned Number evaluated: 24
Interventions	Total number of intervention groups: 2 (zinc acetate and placebo) Comparison: Group A (zinc acetate, n = 12): no other details given; Group B (placebo, n =12) Duration of treatment: 6 months
Outcomes	Taste acuity: • zinc acetate group: significant improvement in their ability to taste various foods occurred in 8 of the 9 symptomatic patients. Taste detection and recognition thresholds for sodium chloride, sucrose, urea normalised in all patients after 6 months; but not hydrochloric acid. Improvement in taste acuity was demonstrated as early as 12 weeks in some patients • placebo group: symptoms of abnormal taste persisted in all the 8 symptomatic patients and there was no significant improvement in any of the taste modality tested
Notes	Sample size calculation: not mentioned Adverse events: none reported Health-related quality of life: none reported Key conclusions of the trial authors: zinc supplementation is able to improve taste in uremic males and uremia is a zinc deficient state Correspondence required: yes, comparative data were needed; co-author, Anand Prasad contacted and received reply on 7 November 2013 and on 17 December 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is assumed that the pharmacy did use an acceptable random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "The patients were assigned to the treatment or placebo groups by opening consecutively numbered, sealed envelopes that indicated zinc acetate or placebo in equal numbers. As each patient entered the trial, the next sequential envelope was opened and the patient was assigned to the appropriate treatment. Identical capsules containing 25 mg of elemental zinc as zinc acetate or 25 mg of sucrose were used"

Mahajan 1982 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the patients nor physicians were aware of the content of the capsules being given"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the patients nor physicians were aware of the content of the capsules being given"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts in the trial
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the method section are reported adequately
Other bias	Low risk	The characteristics of the 2 groups before treatment did not differ significantly

Matson 2003

Methods	Title: zinc supplementation at conventional doses does not improve the disturbance of taste perception in haemodialysis patients Year of publication: 2003 Language: English Trial design (including number of arms): double-blind randomised placebo-controlled trial Location: Renal Unit, Leeds General Infirmary, Leeds, UK Number of centres: 1 Recruitment period (duration): 6 weeks Funding source: no details given
Participants	Total number: 15 (placebo = 8; zinc sulphate = 7) Inclusion criteria: • stable patients undergoing thrice weekly maintenance haemodialysis for a period of at least 3 months • informed consent Exclusion criteria: none Baseline taste acuity and taste discrimination: taste tests to assess perception of 3 principal taste modalities (sweet, sour and salt) were tested using 4 different concentrations per taste perception using sucrose, citric acid and salt respectively at baseline Type of test: sip and spit. The patients drank a mouthful of chilled water. They were then asked to take a sip from the first test cup, rinse the solution around their mouth, and spit it out. A further mouthful of cold water was then given to rinse their mouths Age at baseline: placebo = 67 (30 to 72); zinc sulphate = 60 (31 to 76) Gender: placebo = 6 men, 2 women; zinc sulphate = 5 men, 2 women Any other details of important prognostic factors: none

Matson 2003 *(Continued)*

	Number randomised: placebo = 8, zinc acetate = 7 Method of randomisation: not mentioned Number evaluated: 15
Interventions	Total number of intervention groups: 2 (zinc sulphate and placebo) Comparison: zinc sulphate (220 mg (45 mg elemental zinc once daily), n = 7) versus placebo (n = 8) Duration of treatment: 6 weeks
Outcomes	Taste acuity: taste recognition was tested using 0-100 VAS scale (10 cm horizontal line) where 0 was marked as "not at all" and 100 was marked as "extremely". After each solution was tested, it was rated on a series of 4 VAS. Each solution was rated by the following questions: a. How salty was the solution?; b. How sour was the solution?; c. How sweet was the solution?; and d. How palatable was the solution? Taste discrimination: after each solution was tested, the patiens were asked to place a vertical mark on each line at the point they considered most appropriate Results: • taste acuity: taste recognition was correct for sweet and salt at all concentrations in both groups. There was little distinction between concentrations of the sour solution • taste discrimination: sour solution was often confused with the salty solution and salt solutions though correctly identified, attracted relatively high sourness ratings Taste scores were not different after 6 weeks for either group
Notes	Sample size calculation: not mentioned Adverse events: none reported Health-related quality of life: none reported Key conclusions of the trial authors: taste perception in haemodialysis patients, particularly sour taste perception was not corrected by zinc supplementation Correspondence required: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details available
Allocation concealment (selection bias)	Unclear risk	No details available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Zinc supplements were encased in an opaque cellulose capsule, as were the placebos"; "The pharmacy clinical trials unit prepared the tablets and performed the randomisation, thus ensuring that the study was double-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The pharmacy clinical trials unit prepared the tablets and performed the randomisation, thus ensuring that the study was double-blinded" Comment: no other details given
Incomplete outcome data (attrition bias)	Low risk	Outcomes of all the randomised participants are reported

Matson 2003 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the method section are reported adequately
Other bias	Unclear risk	The trial used sip and spit method for taste assessment. Disadvantage of this method is the regional damage (e.g. on the front or tip of the tongue) would be masked by stimulation of the remaining taste cells elsewhere in the mouth. We are not sure if the included patients had any regional damage of taste cells in tongue or not

Sakagami 2009

Methods	Title: a zinc-containing compound, Polaprezinc, is effective for patients with taste disorders: randomized, double-blind, placebo-controlled, multi-center study Year of publication: 2009 Language: English Trial design: 4 arms: placebo group and 3 study groups with different dosage of Polaprezinc (75 mg (17 mg zinc), 150 mg (34 mg zinc) and 300 mg (68 mg zinc)) Location: university hospitals, across various places in Japan Number of centres: 22 Recruitment period: 12 weeks Funding source: Polaprezinc and placebo were provided by Zeria Pharmaceutical Co Ltd (from personal communication)
Participants	Total number: 109 Inclusion criteria: idiopathic taste disorder, age 20 - 80 years, disease duration of less than 6 months, no underlying illness, not being administered any drugs affecting the disease condition Baseline taste acuity: 2 scales were used: 1. filter paper disk method 2. subjective symptoms using questionnaire Baseline taste discrimination: not available Age (standard deviation) at baseline: placebo group: 44.9 ± 15.4; 17 mg zinc group: 47.1 ± 16.5; 34 mg zinc group: 43.7 ± 18.1; 68 mg zinc group: 44.7 ± 15.6 Gender: placebo group: male 12, female 15; 17 mg zinc group: male 18, female 9; 34 mg zinc group: male 12, female 13; 68 mg zinc group: male 9, female 19 Number randomised: placebo group: 28, 17 mg zinc group: 27, 34 mg zinc group: 26, 68 mg zinc group: 28 Method of randomisation: permuted block method with a number independent from the drugs and administered to subjects in an ascending order of informed consent (from personal communication) Number evaluated: 107
Interventions	Total number of intervention groups: 3 (Polaprezinc and placebo) Filter paper disk method: mean values of all 4 regions taken

Sakagami 2009 *(Continued)*

	Filter paper disk scale: normal < 3.5; mild ≥ 3.5 to < 4.5; moderate ≥ 4.5 to < 5.5; severe ≥ 5.5 Subjective symptoms using questionnaire method: scale used: 1 to 5 scale, 1 - no taste and 5 - normal taste Placebo group (n = 27): baseline - not available 17 mg zinc group (n = 27): baseline - not available 34 mg zinc group (n = 25): baseline - not available 68 mg zinc group (n = 28): baseline - not available There was no significant imbalance amongst the 4 groups in the data of subjective symptoms prior to administration (from personal communication)
Outcomes	Filter paper disk method: cured, overall mean values were < 3.5; improved, improvement of 1.0 either in the area of chorda tympani or glossopharyngeal nerves; unchanged, neither cured nor improved nor worsened; aggravated, aggravation of ≥1.0 in both chorda tympani and glossopharyngeal nerve areas Overall mean value was calculated by dividing the sum of the score of the disc containing each taste quality that was obtained at 4 different locations by 16. The number of 'efficient' cases was presented as a sum of the 'cured' and 'improved' cases Subjective symptoms questionnaire: the change in subjective symptoms was defined as the difference of the value obtained before and after the treatment Mean subjective symptoms score in 34 mg and 68 mg zinc groups were improved compared with placebo group (descriptive)
Notes	Sample size calculation: not mentioned Adverse events: seen in all 4 groups: • minor increase in blood triglycerides • increase in blood alkaline phosphatase • decrease in blood iron • constipation • stomach discomfort • abdominal distension Key conclusion: Polaprezinc is effective in improving the gustatory sensitivity of patients with idiopathic taste disorder with a daily dose of over 150 mg and 300 mg without any serious side effects Correspondence required: yes, email sent on 12 November 2013, received reply on 20 November 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block method (from personal communication)
Allocation concealment (selection bias)	Unclear risk	Quote from personal communication: "Drugs were labelled with a number independent from the drugs and administered to subjects in an ascending order of informed consent" Comment: this does not clearly say that the concealment of allocation was done

Sakagami 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Double-blind". No details of the blinding given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". No details of the blinding given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 dropouts out of 109 (less than 10%). 1 patient was disqualified due to noncompliance with participation criteria and another 1 patient discontinued the trial voluntarily
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methodology are reported
Other bias	Unclear risk	• Pharmaceutical company's (Zeria Pharma) involvement in the trial could have influenced the trial outcome • The characteristics of both groups before treatment were not compared

Sakai 2002

Methods	Title: double-blind, placebo-controlled trial of zinc picolinate for taste disorders Year of publication: 2002 Language: English Trial design: 2 arms - placebo and zinc picolinate Location: special outpatient clinic for taste disorders of Nihon University, Itabashi Hospital, Tokyo, Japan Number of centres: 1 Recruitment period: 3 months, between July 1991 to May 1994 Funding source: none
Participants	Total number: 89 (only 73 completed the trial) Inclusion criteria: main complaint of taste disorder, who were found by the filter paper disk taste test to be suffering from a taste disorder, no underlying illness. Such patients were tested for serum zinc levels. If their serum zinc levels were ≤ 68 µg/dL, zinc-deficient taste disorder was diagnosed and if their serum zinc levels were ≥ 70 µg/dL, idiopathic taste disorder was diagnosed Exclusion criteria: none Baseline taste acuity (standard deviation + scale used): 48 suffered from idiopathic taste disorders and 25 had zinc deficiency taste disorders Placebo group: severe: 17, moderate: 12 and mild: 7 Zinc picolinate group: severe: 16, moderate: 18 and mild: 3 Type of test (before and after treatment): • subjective symptoms questionnaire: scale of 1 to 5, with 1 - no taste and 5 - normal taste • filter paper disk method: 5 - not recognise any taste and 6 - recognise a taste incorrectly. Severity of taste disorder was rated as: none: < 3.5 and all disk values ≤ 4; mild: overall mean value ≥ 3.5 and <

Sakai 2002 *(Continued)*

4.5 or mean value < 3.5 but a disk value of ≥ 5 for or more regions, or overall mean value < 3.5 but mean values of ≥ 3.5 for the 4 basic tastes in either the distribution of the chorda tympani nerve or the distribution of the glossopharyngeal nerve; moderate: overall mean value of ≥ 4.5 and < 5.5; severe: overall mean value ≥ 5

- measurement of serum zinc levels

Age (standard deviation) at baseline: 23 to 79 years; mean age 55.2 years for zinc picolinate group and 50.4 years for the placebo group, standard deviation not given

Gender: placebo group: 13 male and 23 female; zinc picolinate group: 13 male and 24 female

Any other details of important prognostic factors: nil

Number randomised: 89

Method of randomisation: not mentioned

Number evaluated: 73

Interventions	Total number of intervention groups: 2 Comparison: zinc picolinate versus placebo 1. Subjective symptoms questionnaire: placebo (n = 35); zinc picolinate (n = 34) 2. Filter paper disk method: placebo (n = 36); zinc picolinate (n = 37) 3. Serum zinc levels: placebo (n = not available); zinc picolinate (n = not available) Duration of treatment: 3 months
Outcomes	Taste acuity: questionnaire scale of 1 - 5 Filter paper disk method: • cured: final overall filter paper disk value of ≤ 3.5 at the end of the treatment period • improved: improvement of ≥ 1 between the initial and final mean filter paper disk values recorded from the distribution area of either the chorda tympani nerve or glossopharyngeal nerve; and • unchanged: neither cured nor improved Serum zinc levels: before and after trial, in µg/dL
Notes	Sample size calculation: not reported Adverse events: 6 patients (16%) reported side effects: • gastrointestinal effects like nausea, abdominal pain and diarrhoea • 1 patient had persistent side effects and discontinued because of these side effects • 5 patients had temporary side effects Health-related quality of life: not reported Key conclusions of the trial authors: administration of zinc picolinate was significantly (P < 0.01) more effective than placebo in improving taste function in patients with zinc deficiency or idiopathic taste disorders. In addition, serum zinc level was found to increase significantly with 3 months of zinc picolinate therapy Correspondence required: yes, for clarifications on allocation concealment and blinding of participants and assessors, reasons for dropout. No current contact details for any of the 3 authors were available (checked in Nihon University's website on 17 November 2013)

Risk of bias

Bias	Authors' judgement	Support for judgement

Sakai 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "89 patients were randomly assigned to receive placebo (lactose) capsules or capsules containing 28.9 mg of zinc picolinate plus lactose" Comment: no details of random sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". No details of the blinding given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". No details of the blinding given
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 89, only 73 (> 10%) patients completed the trial for flame photometric detection method and 69 (> 10%) completed the subjective questionnaire. Reasons for dropout not mentioned in the report
Selective reporting (reporting bias)	Low risk	All outcomes stated in methodology section are reported adequately
Other bias	Low risk	The characteristics of the 2 groups before treatment did not differ significantly

Watson 1983

Methods	Title: zinc supplementation and its effect on taste acuity in children with chronic renal failure Year of publication: 1983 Language: English Trial design (including number of arms): double-blind cross-over trial, 2 arms (zinc sulphate and placebo) Location: Department of Paediatrics, Royal Manchester Children's Hospital, Manchester, and Booth Hall Children's Hospital, Blackley, Manchester, UK Number of centres: 2 Recruitment period (duration): 18 weeks (2 6-week periods for intervention and 6-week washout period) Funding source: none declared
Participants	Total number: 25 Inclusion criteria: children with chronic renal failure with hypogeusia Exclusion criteria: none mentioned Baseline taste acuity (+ standard deviation + scale used): median detection thresholds were salt: 30 mmol/L (range 6-500); sucrose: (range 12-800); urea 300 mmol/L (range 120-1000); and hydrogen chloride: 6 mmol/L (range 0.8-30) Scale used: • salt and sucrose: 6, 12, 30, 60, 90, 150, 300, 500, 800, 1000

Watson 1983 *(Continued)*

	• urea: 60, 90, 120, 150, 300, 500, 800, 1000, 2000, 5000 • hydrogen chloride: 0.5, 0.8, 3, 6, 15, 30, 60, 90, 150, 300, 500, 800, 1000 Baseline taste discrimination: not done (just mentioned that the study population were unable to distinguish clearly between acid and bitter solutions) Type of test: 3-drop stir technique Age (standard deviation) at baseline: mean age 11.2 (range 7-17 years) Gender: 7 girls and 13 boys Any other details of important prognostic factors: mean baseline glomerular filtration rate was 28 mL/min/1.73 m^2 (range 8-60 mL/min/1.73 m^2). None of the patients had a serum albumin of less than 30 g/L Number randomised: 25 Method of randomisation: not mentioned Number evaluated: 20
Interventions	Total number of intervention groups: 2 Comparison: zinc sulphate versus placebo 1. Group A (zinc sulphate group, n = 9): 15 mg elemental zinc (0.23 mmol) for children under 10 years of age and 50 mg (0.77 mmol) for adolescents / Group B (placebo group, n = 11): identical lactose placebo capsules 2. Group A (placebo group): n =9 / Group B (zinc sulphate group): n = 11 Duration of treatment: 18 weeks
Outcomes	Taste acuity: no significant improvement at the 5% level in the detection or recognition thresholds for each taste modality during the zinc supplementation period compared to placebo Taste discrimination: not mentioned
Notes	Sample size calculation: not mentioned Adverse events: nausea and vomiting in a patient on 50 mg zinc sulphate Health-related quality of life: no significant difference in energy, protein and dietary zinc intakes during the zinc supplementation period compared to placebo Key conclusions of the trial authors: children with varying degrees of chronic renal failure have variable taste thresholds. Oral zinc therapy did not improve taste acuity in such patients and the trial provides no support for the belief that routine zinc supplements are necessary in such children Correspondence required: yes, to get the raw data (mean, standard deviation). Current contact details for trialists could not be found

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It is assumed that the pharmacy did use an acceptable random sequence generation
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation

Watson 1983 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". No other details available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". No other details available
Incomplete outcome data (attrition bias) All outcomes	High risk	5 out of 25 randomised patients failed to complete the trial (20% attrition); dropout details from which group are not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methodology are reported
Other bias	Unclear risk	Quote: "Routine medications were continued throughout the trial" Comment: these medications could have a role in the causation of dysgeusia

VAS = visual analogue scale; Zn = zinc.

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

Study	Reason for exclusion
Atkin-Thor 1978	Included 1 participant with normal taste acuity
Brisbois 2011	Subjects undergoing chemotherapy and radiotherapy were included in the study
Dahl 1984	Patients without gustatory disorder were also included in the trial
Deniz 2016	Hypothyroidism and normal subjects were randomised into 2 groups
Green 2013	Subjects were under maintenance-opiate treatment or intravenous naloxone
Halyard 2007	Participants were given zinc sulphate to prevent therapy-induced taste alterations
Hartman-Petrycka 2016	Healthy subjects were included in the control group
Henkin 1976	Subjects included in the study had dysgeusia secondary to head trauma (14 cases), postoperative (6 cases), encephalitis (2 cases), cerebral vascular accident (1 case), xerostomia (1 case), lingual anaesthesia (1 case) and tic douloureux (1 case). All these were excluded in our study. 44 patients were taking various drugs before and during the study period for other disorders
Jham 2009	Subjects included in the study were given bethanechol to prevent taste loss
Kamphuis 2003	The study included healthy subjects to study the effect of linoleic acid
Lyckholm 2012	Patients receiving chemotherapy were also included in the study Patients with mucositis and oral infections secondary to chemotherapy were included in the study
Mahajan 1992	Subjects included in the study were only normal healthy male volunteers

Study	Reason for exclusion
Najafizade 2013	Study aimed at prevention of taste alterations in patients undergoing radiation therapy using zinc sulphate
NCT01143285	Trial aimed at prevention of dysgeusia in patients undergoing chemotherapy giving active nutritional support
Ohno 2003	Subjects with taste disorders were excluded from the study
Ripamonti 1998	Study aims at prevention of taste disorders by administering zinc sulphate
Sprenger 1983	Subjects included in the study were diagnosed to have uraemic neuropathy and had decreased nerve conduction velocity (neurological problems) i.e. < 43 to 56 m/s
Stewart-Knox 2008	Subjects included were healthy older European adults
Strasser 2008	Subjects included in the study were given glutamine to prevent the docetaxel or paclitaxel associated taste alterations
Treldal 2016	Only 6 participants out of 18 had taste alterations before the trial started
Tupe 2009	Subjects included in the study were healthy adolescent girls
UMIN000027177	Drug-induced dysgeusia patients were included in the trial
Velargo 2012	Included parotid cancer patients having undergone radiation therapy for a minimum of 54 Gy. Xerostomia could have lead to change in taste perception in such patients
Yoshida 1991	Taste disorders due to local organic damage were included in the study

Gy = gray.

Characteristics of studies awaiting assessment *[ordered by study ID]*

JapicCTI-121907

Methods	Phase III randomised, multicentre, double-blind, placebo-controlled, parallel-group study
Participants	Patients diagnosed with the following 3 types: 1. zinc-deficient taste disorder 2. idiopathic taste disorder 3. drug-induced taste disorder (with some exceptions) 20 to 74 years old, both genders Exclusion criteria: • central nervous system disorder • peripheral neuropathy • intraoral defect and salivary gland disorder • psychiatric disorder • systemic disorders that cause taste disorder n = 260
Interventions	Z103: oral administration of 1 tablet twice a day after meal

JapicCTI-121907 *(Continued)*

	Placebo: oral administration of 1 tablet twice a day after meal
Outcomes	Primary outcome: final overall efficacy evaluation Secondary outcome: efficacy evaluation at each evaluation period Test: filter-paper disk method
Notes	

JPRN-C000000401

Methods	Randomised, parallel, double-blind, placebo-controlled study
Participants	20 to 80 years old, both genders Inclusion criteria: • patients who do not fall in any of the 'exclusion criteria concerning diagnosis' and are diagnosed to be suffering from zinc-deficient and idiopathic taste disorders • patients whose results of filter paper disk method examination during the observation period satisfy all the following criteria. Here, in a case in which only the criterion (3) is not satisfied in the second observation period, the observation period may be extended only once: (1) the total mean value is 3.5 or higher (2) compared with the first observation period, an improvement of 1 or higher in terms of the total mean value is not observed (3) the absolute value of difference between the total mean values and the mean value of the 2 occasions immediately before the trial drug administration period is less than 0.75 • patients who have been suffering from taste disorder 1 year or less from the time of their recognition of the onset of taste disorder, at the time of obtaining consents from them • patients of 20 years or older and younger than 80 at the time of obtaining their consents • outpatients • patients who understand the substances of this trial and can consent in writing Exclusion criteria: • exclusion criteria concerning diagnosis: 1) drug-induced taste disorder; 2) systemic disorder-induced taste disorder; 3) psychogenic taste disorder; 4) taste disorder due to disorders of the oral cavity and salivary gland; 5) taste disorder due to disorders of the peripheral nerves; 6) taste disorder due to central nerve disorders; 7) taste disorder due to genetic disorders; 8) disorders of the olfactory sense and flavour sensing; and 9) other taste disorder for which medically clear causes are recognised • exclusion criteria concerning the characteristics of subjects: 1) patients taking drugs prohibited for concomitant use or drugs whose concomitant use is restricted within 7 days immediately before the first examination date of the observation period 2) patients taking Polaprezinc within 28 days immediately before the first examination of the observation period 3) patients taking other zinc-containing drugs within 28 days immediately before the first examination of the observation period or patients who have taken a zinc-containing supplement under the guidance of a physician during the same period 4) patients who take meals only once a day or so, or who clearly limit food intake with a purpose of reducing body weight

JPRN-C000000401 *(Continued)*

	5) patients having serious cardiac diseases or blood diseases 6) patients having anaemia 7) patients being treated for mental or nervous disorders 8) patients being treated for malignant tumours 9) patients whose stomach, duodenum or small intestines have been excised 10) patients having a history of serious drug allergies 11) female subjects who are pregnant, lactating or wish to become pregnant 12) patients who had participated in a study for taste disorder by Z-103 in the past 13) patients who are participating in other studies or have participated in other studies within 3 months before obtaining a consent 14) patients who are otherwise judged unfit as a subject for this trial by a principal investigator or investigators participating in this trial Target sample: 150
Interventions	3 arms: 1. placebo group: placebo administration group: 2 packs of 75 mg of granular Z-103 (as a zinc content, 0 mg/day) 2. intervention group 1: 150 mg administration group: 1 pack of 75 mg granular Z-103 and 1 pack of 75 mg of placebo granules (as a zinc content, 33.87 mg/day) 3. intervention group 2: 300 mg administration group: 2 packs of 75 mg granular Z-103 (as a zinc content, 67.74 mg/day)
Outcomes	Primary outcome: final judgement of the effects by filter paper disk method examination Secondary outcome: judgement of effects of each evaluation period by filter paper disk method examination Judgement of effects by filter paper disk method examination according to the evaluation criteria of phase II clinical study
Notes	Unpublished trial Contact author: Akinori Kida and Zeria Pharmaceutical Pvt Ltd. Company person contacted via email on 27 October 2013 and email bounced. We have contacted another person from same company, Tadahiro Ooshiro on 21 November 2013 - received reply on 26 November 2013: refused to share any details of the study

Mahajan 1979

Methods	Not known
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	No details available. Co-author Ananda Prasad contacted for the full text on 7 November 2013. Reply received on 17 December 2013 and he was unable to find the same

Sakai 2017

Methods	Randomised, double-blind, placebo-controlled cross-over study
Participants	30 patients with type 2 diabetes (22 males and 8 females)
Interventions	Fucoidan as intervention and placebo as control. 60 mL of test drink containing 1620 mg of fucoidan or placebo for 12 weeks each for both groups
Outcomes	Taste sensitivity was measured using filter paper disk method for 5 basic tastes
Notes	We are not sure if the included patients had any taste disorder

Sanchez 1993

Methods	Not known
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	No details available from British Medical Library

Sturniolo 1985

Methods	Not known
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	No details available from British Medical Library

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

NCT02475928

Trial name or title	Zinc supplementation in cirrhotic patients (ZnDCP)
Methods	Randomised parallel-group placebo-controlled study
Participants	Ages eligible for study: 18 to 70 years Gender: all Estimated enrolment: 70

NCT02475928 *(Continued)*	Inclusion criteria: cirrhotic patients by any aetiology, with any dysgeusia (presence of any taste disorder at 6 months) Exclusion criteria: • patients with hepatic encephalopathy at the time of dysgeusia evaluation • patients with any neurological disease • patients with respiratory diseases at the time of dysgeusia evaluation • patients with active alcohol consumption
Interventions	Experimental arm: 100 mg zinc (zinc gluconate) supplement and nutritional education Placebo comparator arm: 100 mg placebo and nutritional education
Outcomes	Evaluation of any taste disorder, according to questionnaires and evaluation of perception and recognition thresholds with ascending molar concentrations of basic tastes
Starting date	April 2015
Contact information	Norberto C Chavez-Tapia: nchavezt@medicasur.org.mx Eva Juarez-Hernandez: evajuarezh@hotmail.com
Notes	Mail sent on 20 September 2017 for details on methods/results

DATA AND ANALYSES

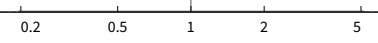
Comparison 1. Zinc versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Taste acuity improvement - Patient-reported outcome	2	119	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.94, 2.09]
2 Taste acuity improvement - Objective outcome - Continuous data	3	366	Std. Mean Difference (IV, Random, 95% CI)	0.44 [0.23, 0.65]
3 Taste acuity improvement for different taste sensations	1	88	Mean Difference (IV, Random, 95% CI)	119.43 [14.48, 224.39]
3.1 Salt	1	22	Mean Difference (IV, Random, 95% CI)	285.0 [238.75, 331.25]
3.2 Sweet	1	22	Mean Difference (IV, Random, 95% CI)	190.0 [142.36, 237.64]
3.3 Sour	1	22	Mean Difference (IV, Random, 95% CI)	10.0 [-16.43, 36.43]
3.4 Bitter	1	22	Mean Difference (IV, Random, 95% CI)	2.4 [2.14, 2.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Taste acuity improvement - Cross-over study	1	28	Mean Difference (IV, Random, 95% CI)	2.66 [1.35, 3.96]
4.1 Taste detection	1	14	Mean Difference (IV, Random, 95% CI)	2.5 [0.93, 4.07]
4.2 Taste recognition	1	14	Mean Difference (IV, Random, 95% CI)	3.00 [0.66, 5.34]
5 Taste acuity improvement - Objective outcome - Dichotomous	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Idiopathic and zinc-deficient taste disorders	2	292	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.09, 1.84]
5.2 Taste disorder secondary to chronic renal failure	1	24	Risk Ratio (M-H, Random, 95% CI)	25.00 [1.65, 379.57]
6 Adverse events	3	335	Risk Ratio (M-H, Random, 95% CI)	5.20 [0.90, 30.19]

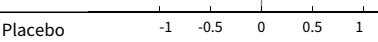
Analysis 1.1. Comparison 1 Zinc versus placebo, Outcome 1 Taste acuity improvement - Patient-reported outcome.

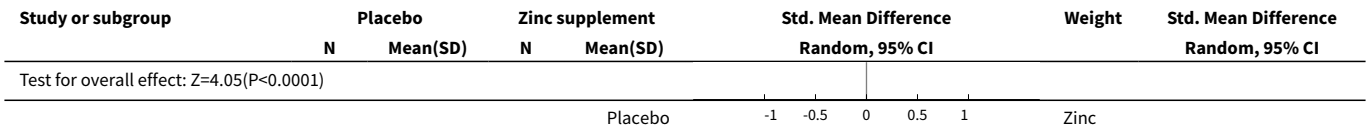
Study or subgroup	Zinc supplement n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heckmann 2005	13/26	6/24		23.56%	2[0.91,4.42]
Sakai 2002	22/34	18/35		76.44%	1.26[0.84,1.89]
Total (95% CI)	**60**	**59**		**100%**	**1.4[0.94,2.09]**
Total events: 35 (Zinc supplement), 24 (Placebo)					
Heterogeneity: Tau^2=0.01; Chi^2=1.1, df=1(P=0.29); I^2=9.33%					
Test for overall effect: Z=1.67(P=0.09)					



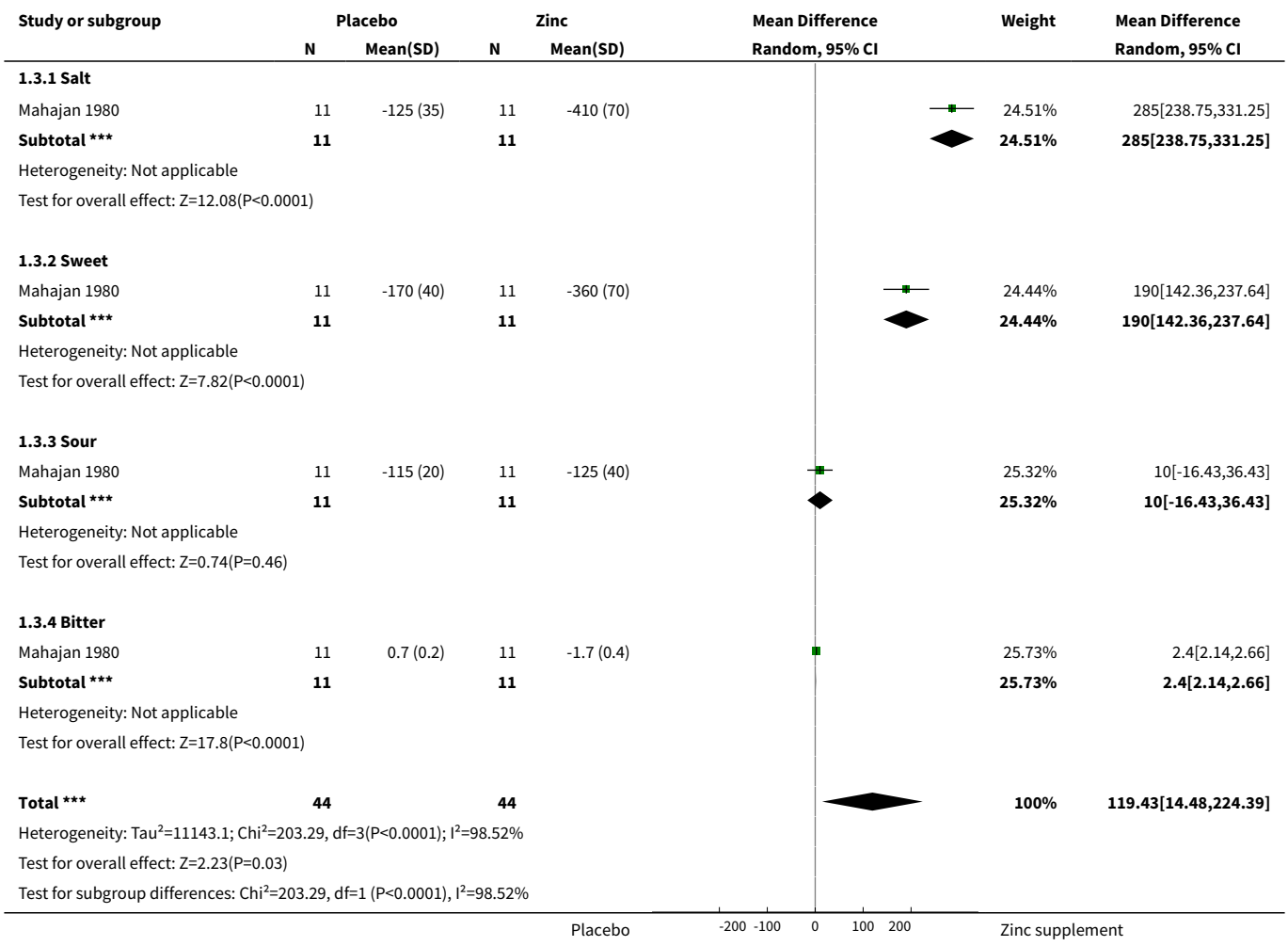
Analysis 1.2. Comparison 1 Zinc versus placebo, Outcome 2 Taste acuity improvement - Objective outcome - Continuous data.

Study or subgroup	Placebo N	Placebo Mean(SD)	Zinc supplement N	Zinc supplement Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Heckmann 2005	26	25.7 (6.5)	24	21.2 (5.7)		13.79%	0.72[0.15,1.3]
Ikeda 2013	111	-0.8 (0.8)	108	-1.2 (0.9)		63.62%	0.38[0.11,0.65]
Sakagami 2009	70	-3.6 (1.1)	27	-4.1 (1.1)		22.59%	0.44[-0,0.89]
Total ***	**207**		**159**			**100%**	**0.44[0.23,0.65]**
Heterogeneity: Tau^2=0; Chi^2=1.14, df=2(P=0.57); I^2=0%							

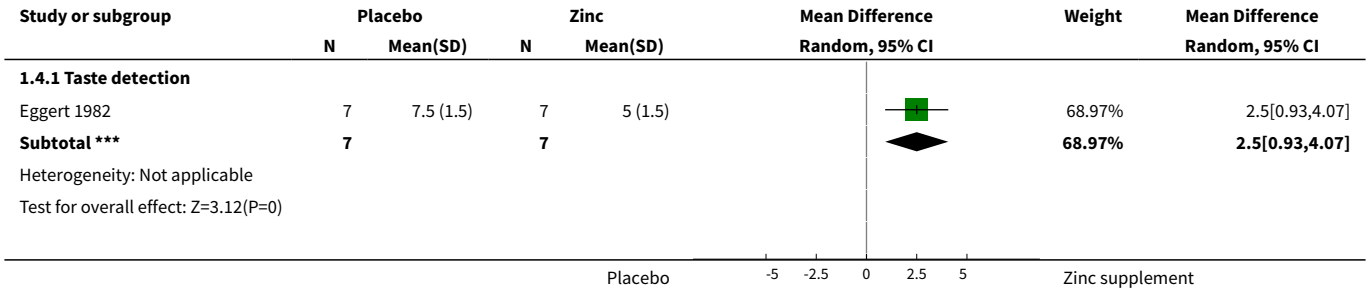


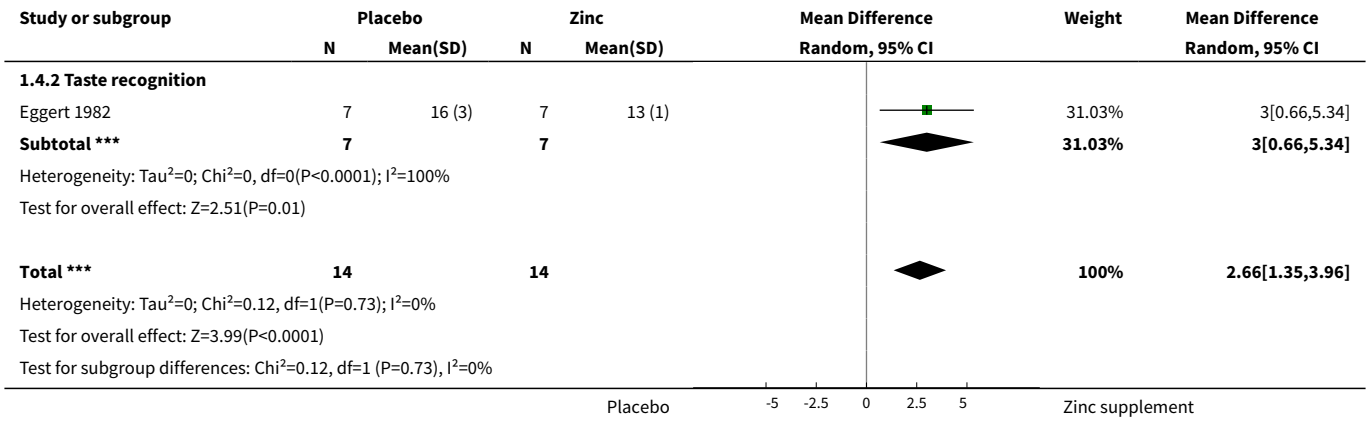


Analysis 1.3. Comparison 1 Zinc versus placebo, Outcome 3 Taste acuity improvement for different taste sensations.

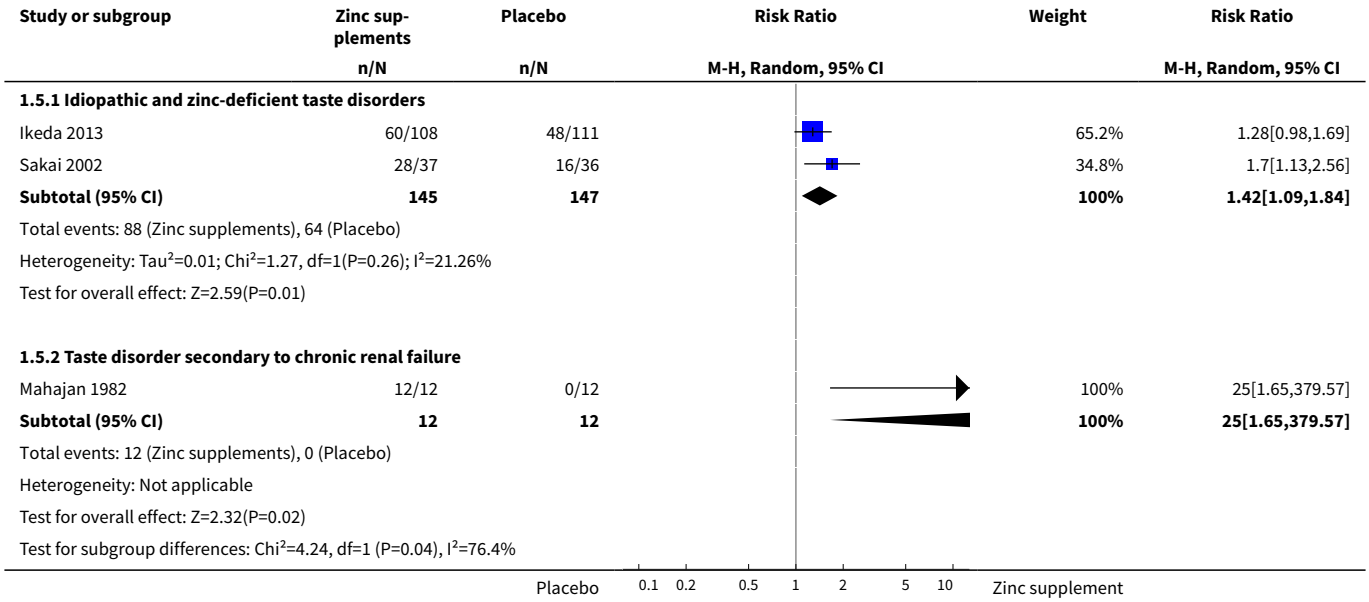


Analysis 1.4. Comparison 1 Zinc versus placebo, Outcome 4 Taste acuity improvement - Cross-over study.

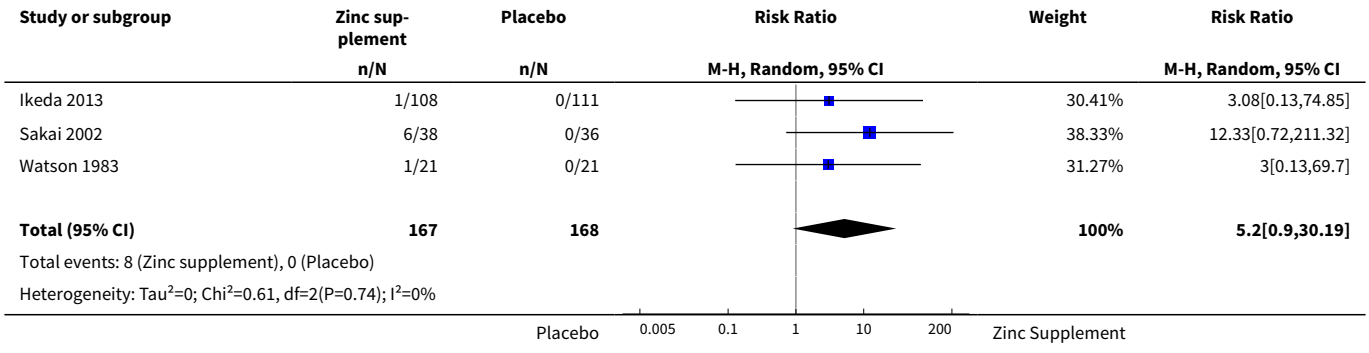


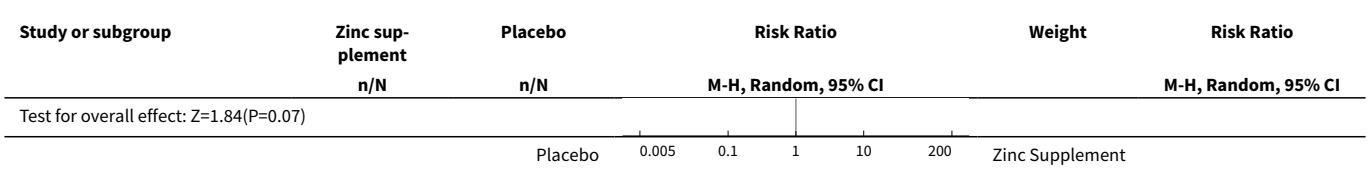


Analysis 1.5. Comparison 1 Zinc versus placebo, Outcome 5 Taste acuity improvement - Objective outcome - Dichotomous.



Analysis 1.6. Comparison 1 Zinc versus placebo, Outcome 6 Adverse events.

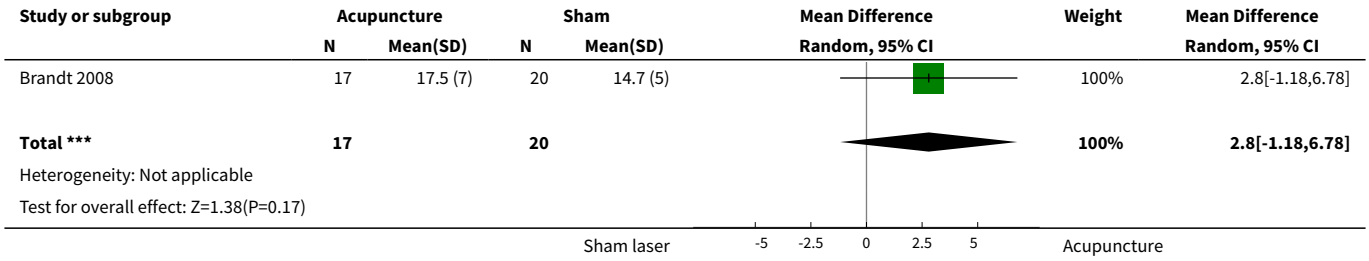




Comparison 2. Acupuncture versus sham control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Taste discrimination	1	37	Mean Difference (IV, Random, 95% CI)	2.80 [-1.18, 6.78]

Analysis 2.1. Comparison 2 Acupuncture versus sham control, Outcome 1 Taste discrimination.



ADDITIONAL TABLES

Table 1. Ikeda 2013 - Continuous data

Outcome	Group A			Group B			Time when measured
	Mean*	SD	n	Mean*	SD	n	
Change of the mean 4 basic taste sensitivity scores from baseline	-0.52	0.68	108	-0.47	0.61	111	4 weeks
	-0.90	0.85	108	-0.67	0.73	111	8 weeks
	-1.17	0.93	108	-0.85	0.75	111	12 weeks
	-1.28	0.94	108	-0.97	0.76	111	4 weeks after treatment

*Minus change score means better by filter paper disc method by Tomita.
SD = standard deviation.

Table 2. Ikeda 2013 - Dichotomous data

Outcome	Group A events (Improved)	Group A total	Group B events	Group B total	Time when measured
Improved/not improved	60	108	48	111	12 weeks

Table 3. Sakagami 2009 - Continuous data

Outcome	Group A (Placebo) n = 27		Group B (17 mg zinc) n = 27		Group C (34 mg zinc) n = 25		Group D (68 mg zinc) n = 28		Time when measured
Secondary outcome	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**12 weeks**
Mean filter paper disk test scores (filter paper disk)	4.095	1.148	4.350	1.030	3.448	0.928	3.454	1.138	—
Mean serum zinc level	1.8	12.7	5.7	13.5	11.4	16.6	20.6	21.3	—
-	**Group A**		**Group B**		**Group C**		**Group D**		—
Increase in the average score of subjective symptoms	0.6		0.9		1.2		1.0		—

SD = standard deviation.

Table 4. Sakagami 2009 - Dichotomous data

Primary outcome: quantitative analysis of taste perception using filter paper disk method	**Event (success)** Cured + improved	**No event (fail)** Unchanged, neither cured nor improved nor worsened; aggravated	**Total**
Experimental intervention (17 mg zinc)	$S_E = 14$	$F_E = 13$	$N_E = 27$
Control intervention (placebo)	$S_C = 17$	$F_C = 10$	$N_C = 27$
RR = 0.824; OR = 0.634; RD = 0.447			
Experimental intervention (34 mg zinc)	$S_E = 20$	$F_E = 5$	$N_E = 25$
Control intervention (placebo)	$S_C = 17$	$F_C = 10$	$N_C = 27$
RR = 0.318; OR = 2.353; RD = 0.17			
Experimental intervention (68 mg zinc)	$S_E = 25$	$F_E = 3$	$N_E = 28$
Control intervention (placebo)	$S_C = 17$	$F_C = 10$	$N_C = 27$
RR = 1.418; OR = 4.902; RD = 0.263			

OR = odds ratio: odds of event in experimental group/odds of event in control group; RD = risk difference: risk of event in experimental group/risk of event in control group; RR = risk ratio: risk of event in experimental group/risk of event in control group.

Table 5. Sakai 2002

Filter paper disk method	**Event (success)** Improved (+ cured)	**No event (fail)** Unchanged	**Total (n = 73)**
Experimental intervention (zinc picolinate)	$S_E = 28$	$F_E = 9$	$N_E = 37$
Control intervention (placebo)	$S_C = 16$	$F_C = 20$	$N_C = 36$
RR = 1.703; OR = 3.889; RD = 0.312			
Experimental intervention (zinc picolinate)	$S_E = 22$	$F_E = 12$	$N_E = 34$
Control intervention (placebo)	$S_C = 18$	$F_C = 17$	$N_C = 35$
RR = 1.258 ; OR = 1.732; RD = 0.133			

OR = odds ratio: odds of event in experimental group/odds of event in control group; RD = risk difference: risk of event in experimental group/risk of event in control group; RR = risk ratio: risk of event in experimental group/risk of event in control group.

Table 6. Heckman 2005 - Continuous data

Outcome	Group A (zinc treatment)			Group B (placebo)			Time when measured
	Mean	SD	n	Mean	SD	n	At the end of 3 months
Primary outcome	—						
Taste test (32-filter paper strip method by Mueller 2003)	25.7	6.5	26	21.2	5.7	24	—
Self-rated impairment in % (VAS scale of 10 cm length equivalent to 100%; 0 to 10; 0 = no impairment; 10 = extremely impaired)	45.0	4.4	26	43.8	3.6	24	—
Secondary outcome	—						
Beck Depression Inventory (BDI)	7.5	7.0	26	11.3	10.9	24	—
Zerssen Mood Scale (ZMS)	10.7	7.5	26	18.8	14.6	24	—
Zinc in serum (µg/dL)	81.53	19.61	26	72.01	10.22	24	—

SD = standard deviation; VAS = visual analogue scale.

Table 7. Heckman 2005 - Dichotomous data

Type of intervention	Event (success) Improved	No event (fail)	Total
Experimental intervention (zinc)	$S_E = 13$	$F_E = 13$	$N_E = 26$
Control intervention	$S_C = 6$	$F_C = 18$	$N_C = 24$
RR = 2; OR = 3; RD = 0.25			

OR = odds ratio: odds of event in experimental group/odds of event in control group; RD = risk difference: risk of event in experimental group/risk of event in control group; RR = risk ratio: risk of event in experimental group/risk of event in control group.

Table 8. Brandt 2008

Outcome	Group A			Group B			Time when measured
	Mean	SD*	n = 17	Mean	SD*	n = 20	
Taste discrimination	11.7 (before)/ 17.5 (after)	4 (before)/ 7 (after)	—	11.9 (before)/ 14.7(after)	5 (before)/ 5 (after)	—	Before and after treatment
Quality of life	Not estimable (changes per group only given for each of the 5 individual questions of the questionnaire, but no combined score/analysis stated). Only information given: "both treatments resulted in an increased quality of life, however, no statistically significant difference could be found"						Before and after treatment
Depressive symptoms	11 (before)/ 6 (after)*	5 (before) / 4 (after)*	—	10.5 (before)/ 10 (after)*	7 (before)/ 7 (after)*	—	Before and after treatment
	Quote: "The psychological well-being of the intervention groups increased for 94.1% of all patients in the intervention group, but only for 60% of patients in the control group. This difference was statistically significant"						
Subjective well-being	16 (before)/ 12 (after)*	10 (before)/ 7 (after)*	—	20 (before)/ 18 (after)*	9 (before)/ 14 (after)*	—	Before and after treatment
	Quote: "58.8% of all patients in the intervention group felt better, whereas only 45% of all patients in the control group felt better. This difference was not statistically significant"						

*Only given in graph -> estimated from graph.
SD = standard deviation.

Table 9. Sakai 2002 - Adverse events

Outcome	Group A - Zinc picolinate events	Group A total	Group B - Placebo events	Group B total	Time when measured
Adverse events	6	37	0	36	3 months

Table 10. Sakagami 2009 - Adverse events

Outcome	Group A - 17 mg zinc events	Group A total	Group B - 34 mg zinc events	Group B total	Group C - 68 mg zinc events	Group C total	Group D - Placebo events	Group D total	Time when measured
Adverse events	5	27	6	25	7	28	3	27	12 weeks

APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

#1 ((ageusi* or hypogeusi* or dysgeusi* or parageusi*):ti,ab) AND (INREGISTER)
#2 ((taste and (distort* or dysfunction* or disorder* or alter* or change* or abnormal* or blind*)):ti,ab) AND (INREGISTER)
#3 ((gustatory and (perception* or sensitiv* or distort*)):ti,ab) AND (INREGISTER)
#4 (#1 or #2 or #3) AND (INREGISTER)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh "Taste disorders"]
#2 [mh ^"Taste perception"]
#3 (ageusi* or hypogeusi* or dysgeusi* or parageusi*)
#4 (taste near/3 (distort* or dysfunction* or disorder* or alter* or change* or abnormal* or blind*))
#5 (gustatory near/3 (perception* or sensitiv* or distort*))
#6 #1 or #2 or #3 or #4 or #5

Appendix 3. MEDLINE Ovid search strategy

1. exp Taste disorders/
2. Taste perception/
3. (ageusia$ or hypogeusia$ or dysgeusia$ or parageusia$).mp.
4. (taste adj3 (distort$ or dysfunction$ or disorder$ or alter$ or change$ or abnormal$ or blind$)).mp.
5. (gustatory adj3 (perception$ or sensitive$ or distort$)).mp.
6. or/1-5

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the*Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Lefebvre 2011).

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. Taste disorder/
2. (ageusi$ or hypogeusi$ or dysgeusi$ or parageusi$).mp.
3. (taste adj3 (distort$ or dysfunction$ or disorder$ or alter$ or change$ or abnormal$ or blind$)).mp.
4. (gustatory adj3 (perception$ or sensitiv$ or distort$)).mp.
5. or/1-4

This subject search was linked to an adapted version of the Cochrane Embase Project filter for identifying RCTs in Embase Ovid (see http://www.cochranelibrary.com/help/central-creation-details.html for information).

1. Randomized controlled trial/
2. Controlled clinical study/
3. Random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.

10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. trial.ti.
19. or/1-18
20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
21. 19 not 20

Appendix 5. CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) search strategy

S1 (MH "Taste disorders+")
S2 TI ((ageusi* or hypogeusi* or dysgeusi* or parageusi*)) OR AB ((ageusi* or hypogeusi* or dysgeusi* or parageusi*))
S3 TI ((taste N3 (distort* or dysfunction* or disorder* or alter* or change* or abnormal* or blind*))) OR AB ((taste N3 (distort* or dysfunction* or disorder* or alter* or change* or abnormal* or blind*)))
S4 TI ((gustatory N3 (perception* or sensitiv* or distort*))) OR AB ((gustatory N3 (perception* or sensitiv* or distort*)))
S5 S1 or S2 or S3 or S4

This subject search was linked to Cochrane Oral Health's filter for CINAHL EBSCO.

S1 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH crossover design or MH Factorial Design
S2 TI ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or AB ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or SU ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study")
S3 TI random* or AB random*
S4 AB "latin square" or TI "latin square"
S5 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)
S6 MH Placebos
S7 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)
S8 TI blind* or AB mask* or AB blind* or TI mask*
S9 S7 and S8
S10 TI Placebo* or AB Placebo* or SU Placebo*
S11 MH Clinical Trials
S12 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)
S13 S1 or S2 or S3 or S4 or S5 or S6 or S9 or S10 or S11 or S12

Appendix 6. AMED Ovid (Allied and Complementary Medicine) search strategy

1. Taste disorders/
2. (ageusi$ or hypogeusi$ or dysgeusi$ or parageusi$).mp.
3. (taste adj3 (distort$ or dysfunction$ or disorder$ or alter$ or change$ or abnormal$ or blind$)).mp.
4. (gustatory adj3 (perception$ or sensitiv$ or distort$)).mp.
5. or/1-4

Appendix 7. US National Institutes of Health Trials Registry (ClinicalTrials.gov) search strategy

Condition = Taste disorder
Condition = Taste disturbance

Appendix 8. WHO International Clinical Trials Registry search strategy

taste disorder
taste disturbance

Appendix 9. International Association for Dental Research (IADR) Conference Abstracts search strategy

taste disorder
dysgeusia

Appendix 10. Association for Research in Otolaryngology Conference Proceedings search strategy

taste disorder
dysgeusia

Appendix 11. Search strategies used in 2014 review

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Clinical Trials Portal search strategy

taste disorder
taste disturbance

metaRegister of Controlled Trials search strategy

taste AND disorder
taste AND disturbance

WHAT'S NEW

Date	Event	Description
4 July 2017	New search has been performed	New search performed 4 July 2017. One new study found for inclusion.
4 July 2017	New citation required and conclusions have changed	One additional trial is included qualitatively. Quality of the evidence was changed to 'very low' for all outcomes under zinc versus placebo comparison. The review authors were of the opinion that the reason given for publication bias in the 'Summary of findings' table is applicable for all outcomes under zinc versus placebo comparison. Other reasons were based on the unclear selection bias in two of the included trials and wide confidence intervals in all three included trials. Prevalence of the disease is updated in the background section.

HISTORY

Protocol first published: Issue 4, 2013
Review first published: Issue 11, 2014

Date	Event	Description
24 November 2014	Amended	Minor edits.

CONTRIBUTIONS OF AUTHORS

- Sumanth Kumbargere Nagraj: protocol, data extraction, entering data, analyses, final review, and updating the review.
- Renjith P George: searching for trials, data extraction, drafting the final review, and updating the review.
- Naresh Shetty: obtaining copies of trials and selecting trials.
- David Levenson: protocol, selecting trials, drafting the final review, and updating the review.
- Debra M Ferraiolo: protocol, selecting trials, drafting the final review, and updating the review.
- Ashish Shreshta: carrying out and interpreting the analyses.

DECLARATIONS OF INTEREST

Sumanth Kumbargere Nagraj: none known.

Renjith P George: none known.
Naresh Shetty: none known.
David Levenson: none known.
Debra M Ferraiolo: none known.
Ashish Shrestha: none known.

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- Cochrane Oral Health Global Alliance, Other.

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- Professor BV Moses Centre for Research & Training in Evidence-Informed Healthcare, ICMR Advanced Centre for Evidence-Based Medicine, Cochrane South Asia, Christian Medical College, Vellore, India.

  For training in review completion

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not mention any method for data described in ordinal scales in our protocol in the section 'Measures of treatment effect'. In our review, we converted the ordinal scale (degree of improvement in 3 Likert scale) as dichotomous data and analysed this for the Sakai 2002 trial.

We included two cross-over trials in our review. We could not use the data for meta-analysis of the primary outcome, as stated in our protocol ('Unit of analysis issues' and 'Data synthesis' sections) because the Watson 1983 trial reported the results in median values. In the Eggert 1982 trial, we derived the data from graphs and used only the data before cross-over due to the insufficient washout period. We did not use the generic variance method to incorporate the data in our meta-analysis, as stated in our protocol.

We did not convert continuous data to dichotomous data, as stated in our protocol, and we analysed them separately.

In our protocol we did not mention any methodology for extracting data from graphs; in our review, we obtained data from graphs in two trials (Eggert 1982; Mahajan 1980).

We had not mentioned any method for combining data for analysis in our protocol; in our review, we combined data for one trial (Sakagami 2009) as this trial had tested different dosages of polaprezinc.

We could not contact authors for three trials (Matson 2003; Sakai 2002; Watson 1983) as stated in our protocol due to non-availability of contact details.

According to our protocol we intended to do a test of asymmetry to assess reporting bias, but we did not do this test as we only included nine trials in our meta-analysis and one trial could not be included in the meta-analysis.

In our protocol, we did not exclude taste disorders secondary to xerostomia. Xerostomia can hamper taste perception and due to this, we excluded the Velargo 2012 trial in the review. We have modified this exclusion criteria as 'taste disorders secondary to hyposalivation'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Acupuncture Therapy; Quality of Life; Randomized Controlled Trials as Topic; Taste Disorders [diagnosis] [etiology] [*therapy]; Taste Perception; Zinc [deficiency]; Zinc Compounds [adverse effects] [*therapeutic use]

MeSH check words

Adolescent; Adult; Child; Humans