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Ginkgo biloba extract for prevention of acute mountain sickness: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective Trials of ginkgo biloba extract (GBE) for the prevention of acute mountain sickness (AMS) have been published since 1996. Because of their conflicting results, the efficacy of GBE remains unclear. We performed a systematic review and meta-analysis to assess whether GBE prevents AMS.

Methods The Cochrane Library, EMBASE, Google Scholar and PubMed databases were searched for articles published up to 20 May 2017. Only randomised controlled trials were included. AMS was defined as an Environmental Symptom Questionnaire Acute Mountain Sickness-Cerebral score ≥0.7 or Lake Louise Score ≥3 with headache. The main outcome measure was the relative risk (RR) of AMS in participants receiving GBE for prophylaxis. Meta-analyses were conducted using random-effects models. Sensitivity analyses, subgroup analyses and tests for publication bias were conducted.

Results Seven study groups in six published articles met all eligibility criteria, including the article published by Leadbetter *et al*, where two randomised controlled trials were conducted. Overall, 451 participants were enrolled. In the primary meta-analysis of all seven study groups, GBE showed trend of AMS prophylaxis, but it is not statistically significant (RR=0.68; 95% CI 0.45 to 1.04; p=0.08). The I^2 statistic was 58.7% (p=0.02), indicating substantial heterogeneity. The pooled risk difference (RD) revealed a significant risk reduction in participants who use GBE (RD=−25%; 95% CI, from a reduction of 45% to 6%; p=0.011) The results of subgroup analyses of studies with low risk of bias, low starting altitude (<2500 m), number of treatment days before ascending and dosage of GBE are not statistically significant.

Conclusion The currently available data suggest that although GBE may tend towards AMS prophylaxis, there are not enough data to show the statistically significant effect of GBE on preventing AMS. Further large randomised controlled studies are warranted.

Strengths and limitations of this study

- ► This meta-analysis is the first systematic review and meta-analysis evaluating ginkgo biloba extract as an acute mountain sickness prophylactic.
- ► This meta-analysis was strengthened by a thorough quality assessment of each enrolled study and comprehensive subgroup analyses.
- ► There is notable heterogeneity and the small number of studies limits the analyses, but heterogeneity decreased after excluding studies with high risk of bias.
- ► Insufficient power may be an issue in this meta-analysis.
- ► Further large randomised controlled studies are warranted.

INTRODUCTION

Background

Rapid ascent from low to high altitude (>2500 m above sea level) is often followed by headache, fatigue, shortness of breath, sleeplessness and anorexia, a symptom complex called acute mountain sickness (AMS).[1] The Lake Louise Score (LLS) questionnaire[2] and the Environmental Symptom Questionnaire III[3] are two tools to diagnose and evaluate the severity of AMS. AMS is more likely to happen at altitudes higher than 2500 m,[4] and worldwide studies reported an incidence of AMS of 25%–37% at 1900–3400 m.[1 5] Children are more prone to develop AMS, with an incidence of 59%.[6]

The pathophysiology of AMS is associated with cerebral oedema, with the most compelling evidence coming from the brain MRI study of Hackett *et al*,[7] which showed intense T2 signals in the white matter, particularly in the splenium and corpus callosum. Vasogenic leakage increases the permeability of the endothelium, causing an elevation in intravascular pressures and inducing hypoxaemia. In addition, hypoxic ventilatory response and activation of the renin–angiotensin–aldosterone system are also reported to be associated with AMS.[8] The most effective method to prevent AMS is gradual ascent. The most common pharmacological agent used to prevent AMS is acetazolamide.[9] However,

acetazolamide can cause paresthesia, dysgeusia, and sometimes nausea or drowsiness.[10] Its use is also contraindicated in patients with a history of anaphylaxis to sulfa antibiotics or acetazolamide.

Importance

Ginkgo biloba extract (GBE) is an option for those seeking a natural alternative treatment. GBE is found to decrease tissue hypoxia, induce vasodilation, and reduce free-radical production and lung leak, which may in turn prevent AMS.[11–14] Roncin *et al*[15] in 1996 published the first study to suggest that GBE can prevent AMS. However, not all subsequent studies have shown benefit.[13 16–20] To date, there is no best evidence to support the effectiveness of GBE.

Goal of this investigation

The aim of our study was to assess the effectiveness of GBE as prophylaxis for AMS by conducting a meta-analysis and systematic review of the relevant literature.

METHODS

Databases and search strategy

We searched the Cochrane Library, EMBASE, Google Scholar and PubMed databases for articles published up to 20 May 2017. No limits were applied to our Boolean search strategy, which included keywords ('Ginkgo', 'Altitude Sickness', 'Mountain'), medical subject headings ('Ginkgo biloba', 'Altitude Sickness') and Emtree terms ('Ginkgo biloba', 'altitude disease'). The full search strategy for database is provided in the online supplementary file. References from retrieved articles were also examined to identify other relevant articles.

Studies were included in the systematic review if they (1) were randomised controlled trials (RCTs) of healthy non-acclimatised adult between the ages of 18 and 60 years; (2) compared GBE with placebo; (3) were conducted in humans; and (4) were studies that diagnosed AMS using the Lake Louise Score or the Environmental Symptom Questionnaire Acute Mountain Sickness-Cerebral score (AMS-C). We excluded studies with subjects who were pregnant and had symptoms consistent with AMS at baseline. Studies were also excluded if they were irrelevant to the aim of the study, were animal studies, lacked a placebo group, or were published as review articles, case reports, editorials or letters. The systematic review and meta-analysis was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (see online online supplementary checklist).

Outcome measures

AMS was defined as an AMS-C score ≥0.7 or an LLS ≥3 with headache. The primary outcome was the relative risk (RR) of AMS in participants receiving GBE for prophylaxis. We only extracted data when they were available in dichotomous form. The secondary outcomes of the included studies are summarised in online supplementary table 1.

Data extraction and assessment of methodological quality

Two reviewers (T-YT and Y-CS) independently screened the titles and abstracts of all articles identified from the search strategy. Inter-reviewer disagreements concerning the inclusion or exclusion of a study were resolved by consensus and, if necessary, consultation with a third reviewer (S-HW).

The Cochrane Collaboration's tool was used to assess the risk of selection, performance, detection, attrition and reporting biases in the included randomised trials.[21] We defined studies as 'high risk of bias' if one or more key domains is taken as high risk in the checklist. All coauthors discussed and made the final decisions about the overall risk of bias in the included trials. If data were not readily available or clear, we contacted the first authors and the corresponding authors to get further information. If studies were found to be at high risk of bias, meta-analyses stratified by study quality were performed.

Both reviewers independently extracted data from the articles selected for inclusion. The extracted data included the name of the first author, year of publication, numbers of participants, gender, starting and final altitudes, AMS scoring definitions, prescriptions of GBE, days of treatment prior to ascent, and number of individuals with AMS in the treatment and control groups.

Data collection, data processing and primary data analysis

Pooled RRs with corresponding 95% CIs are derived for all studies and different subgroups of interest. The main outcome measure was the RR of AMS in participants receiving GBE for prophylaxis. Random-effect models with DerSimonian and Laird method were selected for these analyses. The pooled risk difference (RD) was also measured as the alternative outcome. The pooled RD is the difference between the observed risks (proportions of participants with AMS) in the two groups.

We conducted subgroup analyses based on the quality of studies, starting altitude, number of treatment days before ascending and dosage of GBE.[22–24] Between-study heterogeneity was evaluated with the I^2 statistic.[25] The Egger regression asymmetry test and Begg adjusted rank correlation test were applied for assessment of potential publication bias.[26 27] We also conducted sensitivity analysis to evaluate the influence of each study on the overall pooled estimate. In dealing with zero cells, we add 0.5 to all cells of the 2×2 table for the study. Analyses were all conducted using STATA V.11.0. All statistical tests were two-sided and were considered significant when the p value was 0.05 or less.

Patient and public involvement statement

Participants and the public sector were not directly involved in the design and conduct of this study.

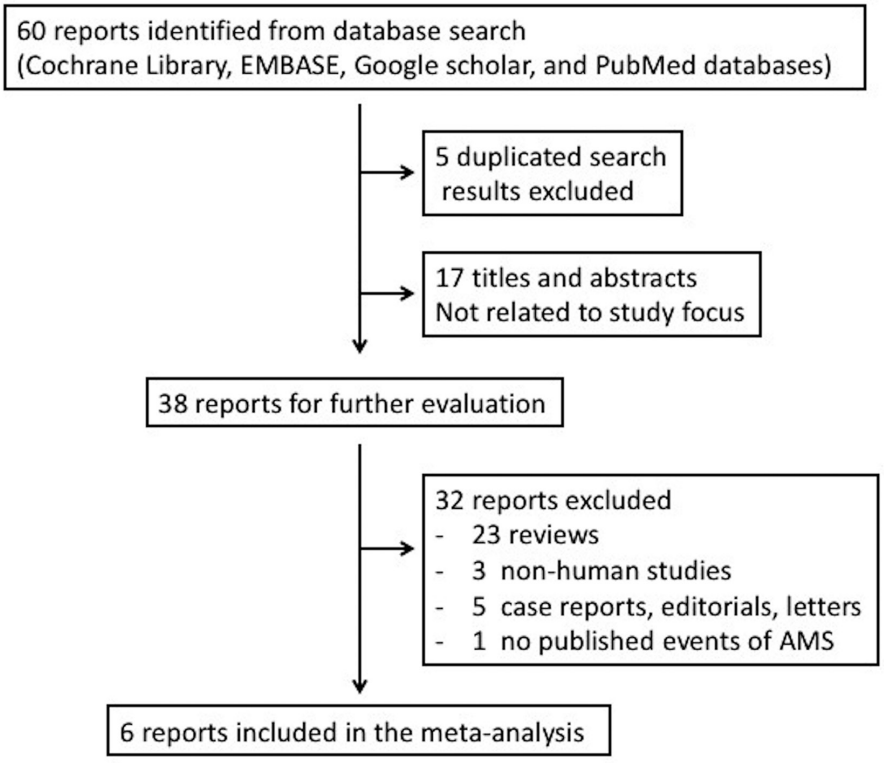

Figure 1 Trial selection algorithm. AMS, acute mountain sickness.

RESULTS

The literature search and study selection process are summarised in figure 1. After the exclusion of duplicate studies, non-relevant studies and other studies that met the exclusion criteria based on a screening of article titles and abstracts, 38 potentially relevant studies were retrieved for full review.

One publication was retrieved by hand search of references. In this study, Wang *et al*[28] compared the prophylactic effect of GBE with that of other Chinese medications on AMS. However, the study had no placebo group design[29] and had to be excluded from our meta-analysis.

In the randomised, double-blind study by Ke *et al* in 2013,[20] AMS was reported as a secondary outcome and the number of events in each group was not reported. We contacted the first and corresponding authors by email but (as of 12 June 2018) received no response. Since the published data could not be included for analysis, we excluded this study.

Six published articles met all eligibility criteria after a careful review process.[13 15–19] In the article published by Leadbetter *et al*,[19] two RCTs were conducted. As a result, a total of 7 study groups with 451 participants were enrolled. The characteristics of these studies and the participants are listed in table 1. Four study groups[13 15 16 19] demonstrated the efficacy of GBE in preventing AMS, while three[17–19] did not. All studies had small numbers of subjects except the one by Gertsch and colleagues.[17]

Table 1 Characteristics of included studies

	Participants (n)	Male (%)	Starting altitude (m)	Altitude reached (m)	Ascent rate (m/hour)	AMS definition
Roncin *et al*,[15] 1996	44	100	1800	5400	15	AMS-C>0.7
Gertsch *et al*, [16] 2002	26	46	0	4205	1402	LLS≥3 with HA
Gertsch *et al*, [17] 2004	243	70	4280–4358	4928	10–20	LLS≥3 with HA
Chow *et al*,[18] 2005	37	54	1230	3800	1285	LLS≥3 with HA
Moraga *et al*,[13] 2007	24	100	0	3696	435	LLS≥3 or one symptom score ≥3
Leadbetter *et al*,[19] 2009 study 1	40	45	2000	4300	1150	AMS-C≥0.7 + LLS≥3 with HA
Leadbetter *et al*,[19] 2009 study 2	37	44	2000	4300	1150	AMS-C≥0.7 + LLS≥3 with HA

AMS, acute mountain sickness; AMS-C, the Environmental Symptom Questionnaire III Acute Mountain Sickness-Cerebral score; HA, headache; LLS, Lake Louise Score.

Table 2 Characteristics of included studies, sources, dosage and duration of ginkgo biloba

	Ginkgo biloba extract source	Dose	Days of treatment prior to ascent
Roncin *et al*,[15] 1996	Tanakan DCI: EGb 761, Ipsen, Paris, France	60 mg twice daily	0
Gertsch *et al*,[16] 2002	GK501 Memfit, EGb 761, Pharmaton	60 mg three times a day	1
Gertsch *et al*,[17] 2004	GK501 International, Pharmaton	120 mg twice daily	1–2
Chow *et al*,[18] 2005	Ginkgo biloba 120 mg, Vegetarian NOW Foods	120 mg twice daily	5
Moraga *et al*,[13] 2007	EGb 761 Rokan, Andromaco Laboratories, Chile	80 mg twice daily	1
Leadbetter *et al*,[19] 2009, study 1	Spectrum Quality, Laboratories Products	120 mg twice daily	4
Leadbetter *et al*,[19] 2009, study 2	Technical Sourcing	120 mg twice daily	3

Of note, participants in the study conducted by Gertsch *et al*[17] published in 2004 started GBE treatment at high altitude (4280–4358 m), which was different from the other studies. Further information such as study dosage, prescription frequency, number of days prior to ascending and source of GBE is summarised in table 2. The number of AMS events and its incidence is summarised in figure 2. The quality of evidence of these studies as assessed by Cochrane Collaboration's tool is presented in table 3. Two of six articles were not double-blinded and both of them included male participants only.[13 15] The study conducted by Gertsch *et al*[16] in 2002 used 'first-come first-served basis' after receiving signed consent. Therefore, we judge it as 'unclear random-sequence generation'. In addition, we appraised it as incomplete outcome data (attrition bias) because the study presented data on only 26 subjects when the intention was to enrol 100 subjects.

In the primary meta-analysis of all seven study groups, GBE showed trend of AMS prophylaxis, but it is not statistically significant (RR=0.68; 95% CI 0.45 to 1.04; p=0.08) (figure 2). The I^2 statistic was 58.7% (p=0.02), indicating substantial heterogeneity. The pooled RD revealed a significant risk reduction in participants who use GBE (RD=−25%; 95% CI, from a reduction of 45% to 6%; p<0.001) (figure 3). After excluding three high-risk bias studies,[13 15 16] the I^2 statistic became 40.2% (p=0.17) and the result did not change (RR=0.84; 95% CI 0.59 to 1.21; p=0.36). In the same subgroup the pooled RD is also not statistically significant (RD=−9.7%; 95% CI, from a reduction of 27.4% to 7.9%; p=0.28). The Egger's test and Begg's test (p=0.22 and p=0.31, respectively) indicate the absence of statistical evidence of publication bias after excluding our presumed high-risk bias articles.

Sensitivity analysis was conducted by removing one trial at a time to determine what influence each study had on the pooled analysis. The pooled result seemed to be robust. For example, removing the study conducted by Leadbetter *et al* in 2009[19] only changed the pooled estimate from 0.68 to 0.74 (95% CI 0.48 to 1.16; p=0.19; see online supplementary figure 1).

The results of several preplanned subgroup analyses were similar. Excluding the study by Gertsch and colleagues in 2004,[17] GBE was not prophylactic when the starting altitude was below 2500 m (RR=0.56; 95% CI 0.31 to 1.01).[13 15 16 18 19] Regarding the number of treatment days before ascending, GBE was not prophylactic when given '3–5 days prior to ascent'[18 19] (RR=0.72; 95% CI 0.41 to 1.26) or '0–2 days prior to ascent'[13 15–17] (RR=0.56; 95% CI 0.25 to 1.25). Dosage of GBE was also not prophylactic for AMS when given 'less than 200 mg per day'[13 15 16] (RR=0.16; 95% CI 0.01 to 2.57) or 'more than 200 mg per day'[17–19] (RR=0.84;

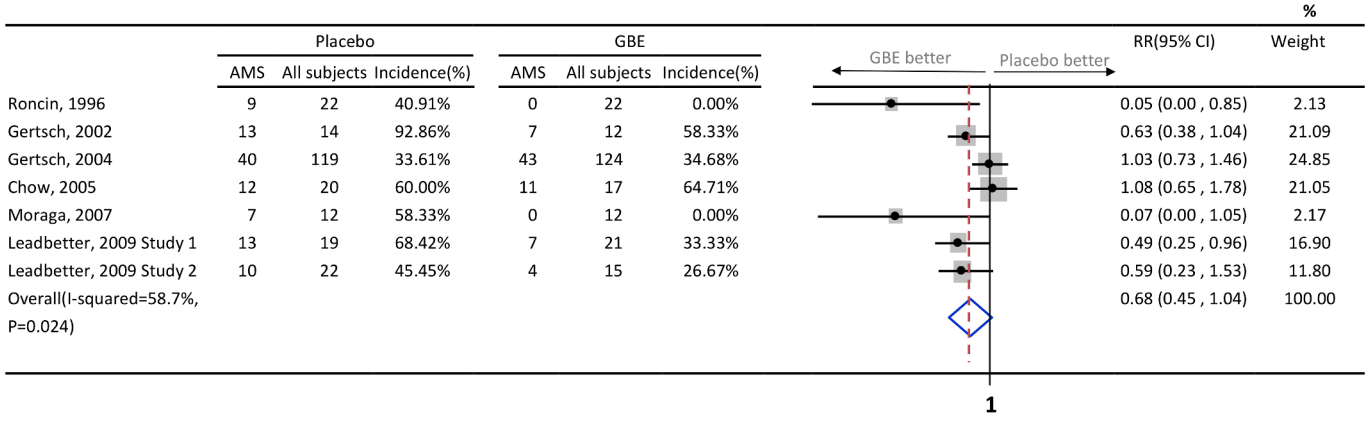

Figure 2 Events of acute mountain sickness between placebo and GBE, and forest plot of meta-analysis. AMS, acute mountain sickness; GBE, ginkgo biloba extract; RR, relative risk.

Table 3 Risk of bias in included studies

Risk of bias domain	Roncin *et al*,[15] 1996	Gertsch *et al*,[16] 2002	Gertsch *et al*,[17] 2004	Chow *et al*,[18] 2005	Moraga *et al*,[13] 2007	Leadbetter *et al*,[19] 2009
Random-sequence generation (selection bias)	Unclear	Unclear	Low	Low	Low	Low
Allocation concealment (selection bias)	Unclear	Low	Low	Low	Unclear	Low
Blinding of participants (performance bias)	High	Low	Low	Low	High	Low
Blinding of outcome assessment (detection bias)	High	Low	Low	Low	High	Low
Incomplete outcome data (attrition bias)	High	High	Low	Low	Low	Low
Selective outcome reporting (reporting bias)	Low	Low	Low	Low	Low	Low
Other source of bias	High	Low	High	Low	High	Low
Overall risk of bias	High	High	Low	Low	High	Low

95% CI 0.59 to 1.21). Data on the number of participants and enrolled studies in each subgroup are summarised in online supplementary table 2.

DISCUSSION

To our knowledge, this is the first meta-analysis of RCTs evaluating GBE as an AMS prophylactic. In pooled analyses, we found that although GBE may tend towards AMS prophylaxis, it had no statistically significant prophylactic effect (RR=0.68; 95% CI 0.45 to 1.04; p=0.08). The results of several subgroup analyses were similar. GBE also failed to show benefits in preventing AMS in low-risk bias studies, studies in which the starting altitude was low, studies differing in the initial treatment regimen prior to ascent and different dosage of GBE.

The effectiveness of GBE in AMS prophylaxis has been reported.[13 15 16 19] Zhang and colleagues[29] in 2003 reported that GBE was the most effective of six Chinese medicines tested for AMS prophylaxis. GBE has been used primarily for the treatment of dementias (eg, Alzheimer's disease), peripheral vascular diseases (eg, intermittent claudication) and neurosensory problems (eg, tinnitus).[30] Hypotheses have been proposed to explain the possible role that GBE plays in preventing AMS. Hypoxia is a common feature of AMS. Several studies have suggested that nitric oxide (NO) may play a pathogenic role in AMS by mediating hypoxia-induced cerebral vasodilation in humans.[11–13] GBE was found to be an NO scavenger. NO scavenging can result in decreased intracellular NO level.[14] Furthermore, GBE may inhibit phosphodiesterase activity, thus enhancing relaxation of parietal smooth muscle cells and so lead to vasodilation of parietal vessels. Vasodilation in turn increases tissue perfusion and decreases local hypoxia.[14] Other potential mechanisms include increasing endogenous antioxidants,[31] reducing free-radical production[32] and reducing lung leak during hypoxia.[33] GBE was also

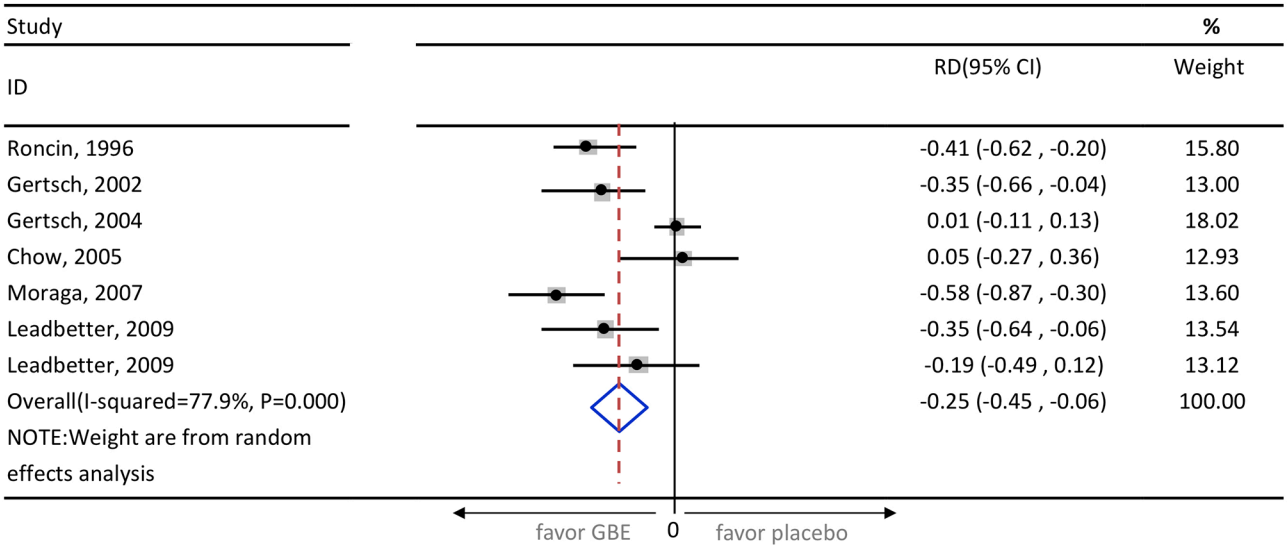

Figure 3 Pooled risk difference of enrolled studies. GBE, ginkgo biloba extract; RD, risk difference.

shown to prevent high-altitude pulmonary oedema in a rat model.[34]

On the other hand, several studies failed to demonstrate the benefit of GBE in AMS prophylaxis.[17 18 20] The duration of therapy before ascent, dosage of GBE and differences in the altitude at which GBE is initiated may account for the conflicts between trial results. To test these hypotheses, we conducted subgroup analyses and obtained similar results to those obtained with the original pooled data. Another explanation for the differences in efficacy may be variation in the GBE composition. For instance, Leadbetter and colleagues[19] in 2009 compared GBE from two different sources and found they differed in composition as well as ability to reduce the incidence and severity of AMS following rapid ascent to high altitude. The German Federal Institute for Drugs and Medicinal Devices Commission E recommends similar specifications for standardisation of GBE. All included studies used GBE that met the German E commission standard, but most of the studies use products from different companies. As an herbal supplement, more than 60% of GBE component is not mandated by law and composition may vary considerably between manufacturers. A lack of bioequivalence has been noted between brands of GBE.[35 36]

Limitations

Our systematic review has several limitations. First, to limit the influence of study biases on pooled evaluation, we decided to only include RCTs. However, there were few RCTs in this field. Moreover, only four of six RCTs were double-blinded. Second, because of the difficulty in carrying out high-altitude medicine studies, many studies involved only a small number of cases. In our primary pooled analysis, a total of 451 participants were enrolled. Insufficient power may be an issue in this meta-analysis. There are not enough data to show the statistically significant effect of GBE on preventing AMS, and further studies are warranted. Third, the participants were predominantly adult men, and whether there is gender or age difference between treatment (GBE vs placebo) groups or response (no AMS vs AMS) groups is unknown. Fourth, GBE is a complex mixture of natural components. It is difficult to standardise all components. A lack of consistency between commercially available GBE preparations may explain these differing results. Finally, differences between studies in factors such as the strength, rate of ascent and other characteristics of participants may also account for inconsistent results.

CONCLUSION

The currently available data suggest that although GBE may tend towards AMS prophylaxis, there are not enough data to show the statistically significant effect of GBE on preventing AMS. Further large randomised control studies are warranted.

Contributors T-YT analysed and interpreted the data and was a major contributor to writing the manuscript. S-HW interpreted the data. Y-KL supervised the study and interpreted the data. Y-CS interpreted the data and wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data can be accessed via the Dryad Data Repository at http://datadryad.org/ with the doi: 10.5061/dryad.35h13bg.

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