Acetazolamide for OSA and central sleep apnea : a comprehensive systematic review and meta-analysis

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ABSTRACT

Background: Therapy options for obstructive (OSA) and central (CSA) sleep apnea are limited, thus many patients remain untreated. Clinically acetazolamide is sometimes used for central sleep apnea (CSA), but given overlapping pathophysiology of OSA and CSA, we hypothesized that acetazolamide is equally effective for both types. Prior reviews focused on specific subtypes of sleep apnea, study designs and languages, thus including few studies (typically ≤3) limiting insights.

Research Question: How efficacious is acetazolamide for sleep apnea, and is its effect modified by sleep apnea type or acetazolamide dose?

Study Design and Methods: We queried MEDLINE, EMBASE and ClinicalTrials.gov from inception until 3/11/2019. Any study in which adults with OSA/CSA received oral acetazolamide vs no acetazolamide (control) reporting sleep apnea-related outcomes was eligible, independent of study design or language. Two reviewers independently assessed eligibility and abstracted data. Primary outcomes were apnea-hypopnea index (AHI) and SpO_2 nadir. Quality of evidence (QoE) was rated using GRADE-methodology.

Results: We included 28 studies (13 OSA/15 CSA; $N_{Subjects,Acetazolamide}$=542, $N_{Subjects,Control}$=553) enabling meta-analyses for 24 outcomes. Acetazolamide doses ranged from 36-1000mg/day and treatment duration from 1-90 days (median 6days). Overall, acetazolamide vs control lowered the AHI by -0.7 effect sizes (95%-CI -0.83 to -0.58; I^2=0%; moderate QoE) corresponding to a reduction of 37.7% (95%-CI -44.7 to -31.3) or 13.8/h (95%-CI -16.3 to -11.4; $AHI_{Control}$=36.5/h). The AHI reduction was similar in OSA vs CSA, but significantly greater with higher doses (at least up to 500mg/day). Furthermore, acetazolamide improved SpO_2 nadir by +4.4% (95%-CI

2.3 to 6.5; I^2=63%; no evidence of effect modification; very low QoE) and several secondary outcomes including sleep quality measures and blood pressure (mostly low QoE).

Interpretation: Short-term acetazolamide improved both OSA and CSA. Rigorous studies with long-term follow-up are warranted to assess acetazolamide's value for the chronic management of sleep apnea patients.

Registration: PROSPERO (CRD42019147504)

KEY WORDS

Acetazolamide, Sleep apnea, Lung, Control of breathing

ABBREVIATIONS

AHI apnea-hypopnea index, BMI body mass index, CI confidence interval, CHF congestive heart failure, CPAP continuous positive airway pressure, CSA central sleep apnea, HA high altitude, IQR interquartile range, NNT number needed to treat, OSA obstructive sleep apnea, RCT randomized controlled trial, SD standard deviation, SMD, standardized mean difference, TST total sleep time

INTRODUCTION

Obstructive (OSA) and central (CSA) sleep apnea are highly prevalent and have been associated with many important neurocognitive and cardiovascular sequelae.[1-4] Therapy for both conditions is currently imperfect; thus, pharmacotherapy has been a major goal, albeit largely elusive to date.[5-11] Ventilatory instability or "high loop gain" is the cause of most types of CSA (including CSA due to high altitude or heart failure, idiopathic CSA, and many cases of opioid-induced CSA),[3,11-13] but it is also increasingly recognized as an important contributory mechanism in OSA.[3,12-16] Loop gain has two major components: "controller" gain (chemoresponsiveness – the desired change in ventilation for a given change in arterial carbon dioxide [paCO2]) and "plant" gain (change in paCO2 for a given change in ventilation).[13,16] Importantly, plant gain and thus overall loop gain can be lowered with acetazolamide,[14] a carbonic anhydrase inhibitor, which induces bicarbonaturia thereby causing a metabolic acidosis which increases ventilation within 1-2 days of administration.[17] We recently completed a review of acetazolamide's side effect profile, which showed that serious events are rare, and that some common side effects such as paresthesias are dose-dependent raising questions about the optimal dose for sleep apnea.[18]

The objective of the present study was to test our hypothesis that acetazolamide improves sleep apnea related outcomes, and to test if the effect on sleep apnea severity is modified by sleep apnea type or acetazolamide dose.

In the absence of large randomized controlled trials (RCTs), observational studies may be an important source of information for causal inferences[19], thus non-randomized studies were included *a priori* while considering study design as a potential source of heterogeneity. We

further emphasized comprehensiveness by considering a broad range of outcomes and by including articles irrespective of language. This approach contrasts with prior reviews[8-10,20-23] which focused on certain subtypes of sleep apnea (e.g. high altitude CSA), study designs (RCTs), few outcomes (usually <3) and/or English articles only (Table E1, online supplement). Consequently, prior reviews on this topic have included very few studies (0 to 8 studies) and subjects thus allowing only limited insights in the potential value of acetazolamide for sleep apnea. Some of the results of this study have been previously reported in the form of an abstract.[24]

METHODS

This systematic review was registered at PROSPERO (CRD42019147504) and was performed according to a pre-specified protocol (Appendix E1, online supplement) following PRISMA and MOOSE guidelines (Table E2 & E3, online supplement).

Identification of Eligible Studies

We considered any study in which adults with obstructive or central sleep apnea received oral acetazolamide and were compared against a control condition (i.e. no acetazolamide or placebo) with regards to sleep apnea-related outcomes. Primary outcomes were apnea-hypopnea index (AHI) and oxygen saturation (SpO_2) nadir. Secondary outcomes were other sleep apnea characteristics (percent of total sleep time [TST] with periodic breathing, SpO_2 mean, percent of TST with SpO_2 <90%, obstructive/central apnea-hypopnea indices, oxygen desaturation index), sleep parameters (TST, sleep efficiency, percent of TST in each sleep stage, arousal index), blood pressure, Epworth sleepiness score and any other patient-centered outcomes. We included

both randomized and non-randomized studies, but case reports were excluded. Further, we excluded studies in which subjects were non-human, <18y of age, intubated or on hemodialysis. Lastly, we excluded studies in which acetazolamide was administered parenterally, or co-administered with other interventions that precluded isolation of acetazolamide's effect on sleep apnea.

We (investigators) searched MEDLINE, EMBASE and ClinicalTrials.gov from inception until 3/11/2019, hand-searched reference lists from eligible articles and prior systematic reviews, and contacted several authors for additional information. The final search strategies were:

- MEDLINE: *("Acetazolamide"[Mesh] OR "Acetazolamide"[tiab]) AND ("Sleep Apnea Syndromes"[Mesh] OR "Sleep Apnea"[tiab] OR "AHI"[tiab] OR "apnea hypopnea index"[tiab])*
- EMBASE: *('acetazolamide':ti,ab,kw OR 'acetazolamide'/exp) AND ('sleep disordered breathing'/exp OR 'sleep apnea':ti,ab,kw OR 'apnea hypopnea index':ti,ab,kw) NOT 'review'/it*

Study Selection, Data Collection and Risk of Bias Assessment

Two authors independently screened retrieved records (CS, AM), assessed final eligibility based on full-text articles for every record which had not been unanimously excluded during the screening process (CS, SL), collected data from eligible studies using piloted Excel sheets (CS, SL), and assessed risk of bias for each included study as described below (CS, SL). All disagreements could be resolved by discussion and/or by seeking clarifications from authors.

Abstracted data included information about study participants (age, sex, body mass index [BMI], co-morbid congestive heart failure [CHF]), intervention (acetazolamide total daily dose, days of administration), pertinent labs (pH, pCO_2, pO_2, plasma bicarbonate, potassium, chloride, and creatinine concentration), and the outcomes listed above. For each outcome, we collected the mean, standard deviation and number of subjects in the acetazolamide vs control condition. If necessary, we estimated the mean from the reported median, and the standard deviation (SD) from reported standard errors, interquartile ranges or 95%-confidence intervals (CI) using standard techniques (Cochrane Handbook, Chapter 7.7.3).[25]

Risk of bias was assessed on the study-level using four domains of the Cochrane risk-of-bias tool for RCTs (selection, performance, detection and attrition bias) and three domains of a modified Newcastle-Ottawa scale (selection, comparability, outcome assessment) for observational studies (Appendix E1, online supplement). Each domain was rated as "high", "unclear", or "low" risk of bias; the overall risk of bias for a given study was defined as the highest risk in any of the domains.

Synthesis of Results

Summary Measures: For outcomes reported by at least two studies a pooled effect estimate was attempted using "weighted" mean differences. However, the AHI data were based on widely varying definitions and measurement techniques used across studies (e.g. some studies scored hypopneas based on arousals, others only based on oxygen desaturations of varying degrees and some did not include hypopneas at all; some used nasal pressure transducers, others only oronasal thermistors). Thus, the overall effect on the AHI was estimated using standardized

mean differences (SMD), but for better interpretability back-transformed[26] using the following equations:

$$Absolute\ AHI\ change\ =\ SMD\ \times\ SD_{pooled[acetazolamide,control]}$$

$$Percent\ AHI\ change\ =\ \frac{Absolute\ AHI\ change}{AHI_{pooled[control]}}\ \times\ 100$$

Meta-Analyses & Heterogeneity: Based on the I^2 statistic, we arbitrarily categorized heterogeneity as low (<30%), moderate (30-50%), or high (>50%);[25,27] If I^2 was <30%, then results were pooled based on a fixed effects model. In case of I^2 ≥30% attempts were made to identify the source of heterogeneity based on qualitative assessments and/or using meta-regression (if $n_{studies}$ ≥8, considering the candidate effect modifiers listed below); in select cases we also explored "baseline risk" as a potential source of heterogeneity by calculating *relative* rather than *absolute* effect estimates via the ratio of means method[28]. If heterogeneity could not be resolved, then we estimated the overall effect based on a random effects model, unless the direction of individual study effects was in opposing directions in which case a pooled estimate would be misleading and thus was deferred. For primary outcomes (AHI, SpO_2 nadir), several sensitivity analyses were performed to assess the robustness of results. Quality of evidence was rated using GRADE.

Subgroup Analyses & Bias Assessment: According to our study objective, we assessed primary outcomes (AHI, SpO_2 nadir) for effect modification by sleep apnea type and dose using meta-regression (primary subgroup analyses). As pre-specified, for primary outcomes we further tested if duration of acetazolamide administration, population characteristics (e.g. mean age, but also study location as a proxy for race), laboratory values, or quality indicators (i.e. risk of bias,

study design, industry funding) modified the effect. The risk of publication bias was evaluated via funnel plots and Egger's test.

Post hoc Responder-Analyses: We were able to obtain individual patient-level data for the AHI from 8 cross-over studies through a combination of individual data reported in published tables and figures (using averaged values abstracted by two independent reviewers [CS, JEO]) and author communications. Thus, we explored variability of acetazolamide's effect across individuals and estimated the number needed to treat (NNT) for one sleep apnea patient to have an AHI reduction of at least 50% (+/- $AHI_{Acetazolamide}$<10/h), as well as the NNT for one sleep apnea patient to experience an increase in AHI by at least 50%.

Software: All meta-analyses were performed using Stata 12.1 (StataCorp, TX) with P<0.05 judged as significant.

RESULTS

We identified 28 eligible studies (subjects: $N_{Acetazolamide}$=542; $N_{Control}$=553)[14,29-55] including two Japanese-language articles[43,49] (Figure 1). We received clarifications and/or additional information from authors of nine studies.[29,30,32,38,42,46-48,53,56]

Table 1 provides an overview of the study characteristics (for details of individual studies see Table 4, online supplement): studies included mostly men, with a wide range of mean ages (31 to 69years) and mean BMIs (21.9 to 38.3kg/m^2); race was rarely reported, but about one third of studies were performed in Asia. Approximately half the studies focused on OSA, while the

others included subjects with CSA due to variety of causes. Studies administered between 36 to 1000mg/day (mean 528mg/day) of acetazolamide for 1 to 90days (median 6days). In one study acetazolamide was co-administered with CPAP (both in the acetazolamide and placebo arm, allowing isolation of the acetazolamide effect),[30] whereas in all other studies acetazolamide was given to sleep apnea patients off CPAP (i.e. untreated patients). Acetazolamide administration was randomized in about half the studies. Overall risk of bias was rated as low/unclear vs high in 46% vs 54%, respectively.

Effects on Primary Outcomes

Based on moderate quality evidence from 26 studies[14,29-34,36-49,51-55], acetazolamide reduced the AHI overall by -0.70 effect sizes (95%-CI: -0.83 to -0.58; I^2=0%; Table 2), which corresponds to a reduction in AHI of 37.7% (95%-CI -44.7 to -31.3) or 13.8/h (95%-CI -16.3 to 11.4; $AHI_{Control}$ = 36.5/h) for those with severe sleep apnea. In meta-regression including OSA and CSA studies, higher doses of acetazolamide were significantly associated with greater reductions in AHI (P=0.005; results were similar when stratified by sleep apnea type, Appendix E2, online supplement), but a *post hoc* analysis suggested that the dose-dependent effect of acetazolamide on the AHI plateaus at 500mg/day (Figure 2). Acetazolamide's effect on the AHI was similar in OSA vs CSA studies (Figure 3): the effect was numerically larger in studies of CSA due to high altitude or heart failure, but the differences across sleep apnea subtypes did not reach statistical significance (P=0.22; Figure 3 and Appendix E2, online supplement). Overall, the reduction in AHI was significantly greater in high (4 CSA, 1 OSA) vs low altitude studies, in randomized vs non-randomized studies, in studies rated as low/unclear vs high risk of bias, and in studies performed outside of Asia (Figure 3). There was no effect modification by any other candidate

variable including acetazolamide duration (Appendix E2, online supplement). The results were similar across several sensitivity analyses, and there was no evidence of publication bias (P=0.11). A *post hoc* analysis of patient-level data from 8 studies[14,32,34,39,41,43,44,52] ($N_{Subjects}$=122) suggested that responses varied between individuals independent of OSA type or acetazolamide dose (Figure 4): in 48% of patients the AHI improved by 50% or more ($NNT_{>50\%\ AHI\text{-}Reduction}$=2.1 [95%-CI 1.7 to 2.5]), but in 9% of subjects the AHI worsened by 50% or more ($NNT_{>50\%\ AHI\text{-}Increase}$ = 11.1 [95%-CI 7.1 to 25.4]). Of note, 24% of the 122 subjects were "responders" according to standard definitions (AHI-reduction >50% and $AHI_{Acetazolamide}$<10/h; $NNT_{Responder}$=4.1 [95%-CI 3.1 to 5.9]).

SpO_2 nadir improved overall by 4.4% (95%-CI 2.3 to 6.5; N=13[14,31,32,34,36,38-40,43,44,50-52]), but heterogeneity was high (I^2=63%) with no clear source of heterogeneity or effect modifier identified (Appendix E2, online supplement), thus the level of evidence was rated as very low. The results were similar in sensitivity analyses and there was no evidence of publication bias (P=0.41).

Effects on Secondary Outcomes

Other Metrics of Sleep Apnea Severity: Acetazolamide improved SpO_2 mean, oxygen desaturation index, and central AHI, but heterogeneity was high and quality of evidence for these outcomes was judged as low to very low (Table 2).

Sleep Parameters: Based on low to very low level of evidence, acetazolamide improved several markers of sleep quality: Sleep duration increased, the arousal index decreased and there was a shift towards deeper sleep stages.

Cardiovascular Outcomes: Based on low level of evidence from five studies[31,32,38,48,51], there was a statistically significant and clinically large reduction in blood pressure. Based on *post hoc* analyses, the blood pressure reduction was most pronounced in two studies[31,38] which included a large fraction of untreated hypertensive subjects. Furthermore, one study[51,57] reported relative improvements in myocardial oxygen supply/demand ratio in high altitude CSA, and one study[32] measuring ventricular ejection fractions reported no difference after 6 days of acetazolamide vs placebo in 12 patients with CSA due to heart failure.

Neurocognitive & Other Outcomes: Overall based on a meta-analysis of three studies, there was no change in Epworth Sleepiness score (range 0-24), but in two of these studies[29,38] the control score was within the normal range (<10); in the third study[53] there was a statistically non-significant but clinically important[58,59] reduction by -2.7 points (N=10, P=0.08). Two studies further assessed psychomotor vigilance: in one[29] reaction time worsened (+17.3ms; P=0.004), but the other study[30] reported a non-significant improvement of similar magnitude (-15ms; P>0.05), thus results were not pooled (I^2=80%). In addition, six studies[32,34,41,42,44,45] provided data about subjective symptoms (e.g. sleepiness, insomnia, sleep quality, snoring; Table E6, online supplement): 5 studies[32,41,42,44,45] reported an improvement with acetazolamide vs 1 study[34] which reported no change in symptoms. These subjective data should be interpreted with caution as methods were variable and most studies lacked blinding. Based on meta-analyses of

laboratory tests (Table E7, online supplement), acetazolamide lowered pH, pCO_2, bicarbonate, and potassium concentrations (P<.04; high heterogeneity) and increased pO_2 (P<.001, I^2=0). Serum creatinine was reported by only one study which found a slight increase with acetazolamide 1000mg/day (+0.17mg/dl; P<0.05).[14]

DISCUSSION

Increasing evidence suggests that obstructive and central sleep apnea share an overlapping pathogenesis, with CSA being characterized by elevated ventilatory instability or high loop gain.[12-16] By including studies independent of sleep apnea type, study design and article language, we identified more than 3 times the number of studies, subjects and outcomes compared with prior reviews on this topic.[8-10,20-23] This led to several important and novel insights. Specifically, from this large meta-analysis including over 500 subjects we note several findings:

First, based on moderate quality evidence acetazolamide reduced the AHI on average by more than one third. Second, the reduction in AHI was overall similar in OSA and CSA studies, which is consistent with data from a mechanistic study[14] in which the AHI reduction among OSA patients was independent of patients' baseline loop gain. Third, acetazolamide's effect on the AHI is dose-dependent, but seems to plateau at approximately 500mg/day; this suggests that doses greater than 500mg/day may not be beneficial for sleep apnea patients while increasing the risk of side effects, which may adversely affect tolerance and adherence.[60] Of note, at 500mg/day the number needed to treat for common side effects are 2.1 for paresthesias, 22.3 for dysgeusia (abnormal taste), 17.0 for polyuria, and 11.1 for fatigue.[18] Importantly, these estimates include

many mild cases (especially paresthesias) which may not affect adherence/tolerance, and side effects typically cluster (i.e. patients tend to have either no side effects or several ones). Thus, many patients are expected to tolerate up to 500mg/day quite well.[18] Fourth, acetazolamide appears to be beneficial across several patient-centered outcomes including sleep quality measures and subjective symptoms. Importantly the observed reduction in blood pressure (SBP -8.2mmHg [-11.5 to -4.9], DBP -4.3mmHg [-6.8 to -1.8]) was substantially greater than what is commonly achieved with CPAP therapy (SBP -2 to -4mmHg, DBP -1 to -3mmHg)[61,62]. Interestingly, OSA has been associated with increased carbonic anhydrase activity,[63] and carbonic anhydrase inhibitors such as acetazolamide may lower vascular tone through several pathways.[64,65] Thus, the comparatively greater effectiveness may be due to mechanistic reasons, but the observed effect on blood pressure may (in part) be independent of acetazolamide's effects on sleep apnea. Further, we note that the number of subjects in our meta-analysis for this outcome was relatively small (N~100) and the level of evidence was low, precluding firm conclusions. Fifth, based on a *post hoc* analysis, individual responses to acetazolamide appear to be quite variable (potentially due to varying effects on chemosensitivity vs plant gain, two of the determinants of overall loop gain[66]): Approximately one in 11 patients treated with acetazolamide experienced substantial worsening of the AHI, thus monitoring of sleep apnea severity during initiation or at close follow up is clearly warranted. On the other hand, about one in 4 patients experienced full resolution of sleep apnea based on standard criteria (independent of sleep apnea severity at baseline). Furthermore, combination of acetazolamide with therapies targeting pathophysiological traits other than loop gain may result in additive effects and thus augment partial responses.[40] More research is needed to confirm that acetazolamide's effect is maintained long-term and to help identify responders *a priori*, but for many patients who do not

tolerate standard therapies such as CPAP, acetazolamide alone or in combination with other modalities may be an efficacious treatment option.

Previous reviews of acetazolamide for sleep apnea reported AHI reductions of similar magnitude as in our study, but for various reasons the number of included studies was generally ≤3 (Table E1, online supplement). Thus, in the official practice guidelines from the American Academy of Sleep Medicine (AASM) concerning treatment of sleep apnea, acetazolamide plays almost no role at all: the practice parameters for CSA[20] list acetazolamide as an "option" for idiopathic CSA (based on 2 studies[42,45]) and for CSA due to congestive heart failure (based on 1 study[32]), but concludes that there is insufficient evidence for acetazolamide's use in high altitude CSA (based on 1 study[33]). Neither the clinical guideline for the management of OSA[67], nor the practice parameters for the medical therapy of OSA[10,68] mention acetazolamide. We believe that the cumulative evidence of acetazolamide's efficacy for sleep apnea and its side effect profile (see [18]) warrants greater discussion in future revisions of these documents. But when "going from evidence to recommendations", patients' values, preferences and treatment costs will need to be taken into account.[69,70]

A major strength of the current review is its comprehensiveness with regards to studies and outcomes. Moreover, robustness of results in sensitivity analyses, the dose-dependent effect on the AHI, and beneficial effects across a variety of outcomes (without any clear harmful effects on any outcome) increase our confidence in the validity of findings. To achieve this comprehensiveness and enable complex analyses, we deliberately combined data from somewhat different study populations. We believe this approach to be valid, because i.) loop gain is an

important pathophysiological component of all subtypes of sleep apnea included in this study providing an *a priori* rationale for this approach; ii.) for primary outcomes formal testing did not reveal significant differences across OSA/CSA-subtypes *a posteriori*; iii.) effect estimates are provided separately for significant subgroups (e.g. high vs low altitude). But we acknowledge that we had limited power to detect differences across sleep apnea subtypes, thus one may question the generalizability of our overall results for the different sleep apnea subtypes and view our findings as hypothesis-generating rather than definitive insights. Similarly, meta-analyses of obstructive AHI were based on only 3 studies limiting insights about acetazolamide's effects on purely obstructive events. Another key limitations is that most studies assess acetazolamide's effect on sleep apnea for a maximum of two weeks, thus results may not generalize to long-term therapy. Similarly, most study participants were male and lack of effect modification by sex only provides limited reassurance (low power; risk of ecological bias when testing for patient characteristics). Further, we found insufficient data to test for effect modification by race, but the lower efficacy of acetazolamide in Asian studies may reflect true biological variation considering that OSA in Chinese vs Caucasian patients is caused more by anatomical predisposition and less by ventilatory instability.[71] Another limitation is that the level of evidence for most outcomes was judged as low, most studies were rated as high or unclear risk of bias, and many lacked placebo-control. In RCTs high/unclear risk of bias was often due to a lack of details about the randomization methods used, which may reflect reporting issues rather than true methodological flaws. Importantly, the effect on the AHI was actually greater in low/unclear vs high risk of bias studies (and in placebo vs non-placebo controlled studies), suggesting that the net effects of potential biases was towards the null (i.e. not driving the positive results). Another issue is that sleep position can affect OSA severity, but was not controlled in most studies, which may

explain some of the inter-individual variability noted. Potential imbalances in sleep position across study conditions are expected to be more pronounced in non-randomized studies, thus it is further reassuring that acetazolamide's effect on the AHI was actually greater in RCTs than in observational studies (i.e. unmeasured confounders such as sleep position or first-night effects likely did not drive the positive results).

INTERPRETATION

Short-term administration of acetazolamide appears beneficial for both central and obstructive sleep apnea. More research is needed to identify responders *a priori*, assess interaction effects with other therapies targeting pathophysiological mechanisms other than loop gain, and to evaluate rigorously long-term efficacy with regards to patient-centered outcomes in mixed-sex cohorts of well-defined sleep apnea subgroups. A reasonable regimen for future studies would be 125-500mg/day (1-2doses/day; evening dose 2h before bedtime) with close follow-up to rule out worsening of sleep apnea. The maximal effect for a given dose is likely achieved within a few days[17,42,72] (for high altitude CSA initiation one day prior to ascend could be considered[51], same as what is recommend for the prevention of acute mountain sickness[73]). Common side effects (e.g. paresthesias) are dose-dependent.[18] Thus it may be prudent to start with 125-250mg/day and titrate up every 3-5days as needed and tolerated. Co-administration with thiazide diuretics or angiotensin-receptor blockers increases the risk of hypokalemia and thus requires close monitoring and/or should be avoided.[18]

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Table 1. Characteristics of Included Studies (N=28).

	Mean (SD) or Median [IQR] or % ($N_{Studies}$)	Range	$N_{Studies}$
Population Characteristics			
Mean-Age, years	55.4 (9.4)	31 to 69[a]	25
Percent Female	8 [0 to 18]	0 to 75	22
Mean-BMI, kg/m^2	29 (4)	21.9 to 38.3	17
Mean-Weight, kg	81 (10.8)	65.4 to 96.1	7
Sleep Apnea Type			28
Primarily Obstructive Sleep Apnea[b]	46% (13)	na	
Comorbid Congestive Heart Failure	11% (3)	na	
Performed at High Altitude	4% (1)	na	
Primarily Central Sleep Apnea	54% (15)	na	
CSA-High Altitude	21% (6)	na	
CSA-Congestive Heart Failure	11% (3)	na	
CSA-Opioids	4% (1)	na	
CSA-Idiopathic	11% (3)	na	
CSA-Other[c]	7% (2)	na	
Study Location			28
North America	32% (9)	na	
Europe	39% (11)	na	
Asia	29% (8)	na	
Japan	18% (5)	na	
Intervention Characteristics			
Acetazolamide			
Total Daily Dose, mg/day[d]	528 (308)	36 to 1000	28
Total Daily Dose (categorical)			28
<500 mg/day	54% (15)	na	
≥500 mg/day	46% (13)	na	
Days of Administration (continuous)	6 [3 to 9]	1 to 90	28
Days of Administration (categorical)			28
<3 days	21% (6)	na	
3 to 7 days	50% (14)	na	
>7 days	29% (8)	na	
No. Subjects, Acetazolamide Arm	12 [9 to 21]	4 to 75	28
No. Subjects, Control Arm	12 [9 to 22]	4 to 75	28
Quality Indicators			
Overall Bias			28
Low	7% (2)	na	
Unclear	39% (11)	na	
High	54% (15)	na	
Study Design			28
RCT	57% (16)	na	
Parallel Group	46% (13)	na	
Cross-Over	14% (4)	na	
Observational	43% (12)	na	
Industry Funding			28
Yes/Unclear	39% (11)	na	
No	61% (17)	na	

[a] Range of mean-ages reported for the different studies; the youngest and oldest *subject* enrolled in the included studies were reported as 22 and 80, respectively.

[b] Five studies[31,36,47,49,54] included patients judged to have primarily OSA but potentially including also some patients with CSA (subgroup analyses were similar when classifying these studies as CSA instead, Appendix E2, online supplement)

[c] One study included subjects with CSA in the setting of pre-capillary pulmonary hypertension[29], the other study included subjects with CSA in the setting of spinal cord injury[46]

[d] One study[32] administered 3.5 to 4mg/kg/day - assuming an average weight of 75kg we estimated the mean daily dose as 75kg x 3.75mg/kg/day = 281mg/day. One study[48] administered 250mg/week, thus we estimated the daily dose as 250mg/7days = 36mg/day.

Table 2. Effect of Acetazolamide on Sleep Apnea Severity, Sleep Parameters, Cardiovascular and Other Outcomes. For details of meta-analyses including forest plots see Appendix E2, online supplement.

							Acetazolamide			Control		
	Δ (95%-CI)	**I^2**	**$N_{Studies}$**	**$P_{\Delta=0}$**	**Δ Type**	**GRADE**	**$Mean_{wt}$**	**(SD_{wt})**	**N_{Subj}**	**$Mean_{wt}$**	**(SD_{wt})**	**N_{Subj}**
Primary Outcomes												
AHI, effect sizes	-0.70 (-0.83 to -0.58)	0%	26	<.001*	S_F	⊕⊕⊕○	22.9	(19.2)	529	36.5	(23.2)	540
- AHI, per hour[m]	-13.8 (-16.3 to -11.4)											
- AHI, % of control[m]	-37.7 (-44.7 to 31.3)											
SpO_2 Nadir (%)[a]	+4.4 (2.3 to 6.5)	63%	13	<.001*	W_R	⊕○○○	81.1	(6.6)	245	76.8	(8.2)	247
Secondary Outcomes												
Sleep Apnea Severity												
SpO_2 Mean (%)[b]	+3.5 (2.3 to 4.8)	82%	12	<.001*	W_R	⊕⊕○○	88.9	(2.5)	218	85.3	(3.4)	215
Time with SpO_2 <90% (%TST)[c,d]	-15.1 (-31.9 to 1.6)	84%	5	.08	W_R	⊕○○○	9.7	(18.2)	101	24.8	(27.8)	101
Oxygen Desaturation Index (h^{-1})[e]	-12.2 (-19.2 to 5.2)	65%	5	.02*	W_R	⊕⊕○○	9.0	(11.1)	107	21.3	(16.9)	107
Obstructive AHI (h^{-1})[f]	-7.5 (-16.9 to 1.8)	49%	3	.11	W_R	⊕○○○	28.6	(21.9)	77	36.2	(21.0)	77
Central AHI (h^{-1})[c,g]	-9.5 (-14.0 to -4.9)	56%	8	<.001*	W_R	⊕○○○	5.8	(10.5)	214	15.3	(19.2)	214
Hypopnea Index (h^{-1})[n]	-2.3 (-6.6 to 1.9)	45%	6	.29	W_R	⊕○○○	11.7	(10.9)	96	14.0	(12.0)	96
Periodic Breathing (%TST)[c,h]	-24.2 (-53.1 to 4.7)	88%	3	.10	W_R	⊕○○○	17.6	(16.9)	36	41.8	(19.2)	36
Apnea-Hypopnea Duration (sec)[i]	+0.8 (-1.5 to 3.1)	53%	6	.50	W_R	⊕○○○	24.3	(5.9)	106	23.5	(5.5)	107
Sleep Parameters												
Arousal Index, total (h^{-1})[j]	-6.6 (-11.3 to -2.0)	32%	6	.005*	W_R	⊕⊕○○	23.9	(14.5)	140	30.5	(16.2)	140
Total Sleep Time, TST (min)[j]	+20.0 (7.1 to 32.9)	28%	10	.002*	W_F	⊕⊕○○	377.2	(72.4)	292	357.2	(86.3)	292
Sleep Efficiency (%)[j]	+5.5 (3.2 to 7.8)	0%	12	<.001*	W_F	⊕⊕○○	80.8	(12.9)	305	75.3	(15.8)	305
Stage N1 (%TST)[j]	-4.7 (-7.6 to -1.9)	14%	5	.001*	W_F	⊕⊕○○	18.0	(10.1)	118	22.7	(12.2)	118
Stage N2 (%TST)	+4.0 (0.9 to 7.1)	0%	5	.01*	W_F	⊕○○○	51.4	(12.1)	118	47.4	(12.2)	118
Stage N3 (%TST)	+1.4 (0.1 to 2.6)	6%	7	.02*	W_F	⊕⊕○○	7.8	(6.8)	237	6.5	(6.4)	237
Stage REM (%TST)[j]	0.0 (-1.4 to 1.4)	38%	11	.99	W_R	⊕⊕⊕○	12.0	(6.1)	300	12.0	(6.9)	300
Cardiovascular Outcomes												
Systolic Blood Pressure (mmHg)[h]	-8.2 (-11.5 to -4.9)	0%	5	<.001*	W_F	⊕⊕○○	128.0	(12.1)	99	136.2	(12.2)	114
Diastolic Blood Pressure (mmHg)	-4.3 (-6.8 to -1.8)	0%	5	.001*	W_F	⊕⊕○○	79.0	(8.7)	99	83.3	(9.8)	114
Mean Blood Pressure (mmHg)	-5.2 (-7.5 to -2.8)	0%	4	<.001*	W_F	⊕⊕○○	98.0	(9.4)	128	103.1	(9.7)	129
Heart Rate (min^{-1})	-1.7 (-4.2 to 0.7)	26%	7	.16	W_F	⊕⊕○○	66.7	(11.7)	164	68.5	(10.6)	165
Other Outcomes												
Weight, kg	-1.6 (-5.9 to 2.8)	0%	3	.47	W_F	⊕○○○	93.9	(17.2)	116	95.5	(16.2)	116
Epworth Sleepiness Score, ESS[k]	-0.7 (-2.2 to 0.9)	51%	3	.38	W_R	⊕○○○	9.1	(3.6)	46	9.8	(3.9)	46
6 Minute Walking Distance (m)	+3.2 (-20.5 to 26.9)	1%	3	.79	W_F	⊕○○○	503.4	(77.3)	83	500.2	(83.4)	98

Abbreviations & Explanations: Δ Type denotes whether comparison is based on "weighted" (W) or "standardized" (S) mean differences" (the subscript $_{F/R}$ denote fixed/random effects models); $Mean_{wt}$ (SD_{wt}) denote weighted mean and standard deviations; N_{Subj} number of subjects. As detailed in Table E5 in the online supplement, based on GRADE methodology quality of evidence was rated as: very low (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○) or high (⊕⊕⊕⊕).

a We could not identify a clear source of the heterogeneity, but the direction of virtually all individual study effects was in favor of acetazolamide.

b Heterogeneity likely related to ceiling effects and the sigmoid shape of the oxygen desaturation curve (see e-Appendix 2).

c *Post hoc* analyses suggested that heterogeneity may in part be due to effect modification by baseline risk: heterogeneity was less (lower I^2) when estimating the effect using a *relative* rather than an *absolute* scale (i.e. when taking into account baseline values).

d Based on a *post hoc* ratio-of-means analysis, time with SpO_2 <90% decreased by 64% (95%-CI 45 to 76%), I^2=30%, P<0.001 with acetazolamide vs control.

e Heterogeneity was primarily due to one study[33]; results were similar when excluding this study (-9.8 [95%-CI: -12.0 to -5.5], I^2=0%; P<.001)

f Heterogeneity was primarily due to one study[14], results remained non-significant when excluding this study (-2.5 [95%-CI: -11.1 to 6.0], I^2=0, P=.56)

g Based on a *post hoc* ratio-of-means analysis, central AHI decreased by 64% (95%-CI 53 to 72%; I^2=0%; P<.001) with acetazolamide vs control.

h Based on a *post hoc* ratio-of-means analysis, periodic breathing decreased by 58% (95%-CI 36 to 72%; I^2=0%; P<.001 with acetazolamide vs control.

i *Post hoc* analyses suggested potential effect modification by acetazolamide dose (P=.053); in studies administering ≥500mg/day event duration increased by 3.2 seconds (95%-CI: 0.6 to 5.9), I^2=0%, P=0.02 with acetazolamide vs control, whereas in studies administering <500mg/day event duration was unchanged (-1.1 seconds [95%-CI: -3.1 to 0.8]; P=0.21).

j Results were similar when including only randomized trials suggesting that the change in outcome was not due to confounding by first night effects (i.e. baseline/control during the first night vs acetazolamide administered during a subsequent night).

k In part heterogeneity is likely due to varying baseline severity (only one of the three studies had a baseline ESS within the abnormal range, i.e. >10)

m Calculated based on the effect size, pooled standard deviation ($SD_{Control,Acetazolamide}$ = 19.7), and the pooled $AHI_{Control}$ (36.5/h); for details see methods.

n Differences in underlying hypopnea definitions likely contributed to the heterogeneity (lower I^2 when analysis was performed using SMDs, but overall results were similar thus results from the WMD analysis are reported here; effect may also be more pronounced in OSA vs CSA studies; for details see Appendix E2, online supplement).

FIGURE-LEGENDS

Figure 1. PRISMA Flowchart.

Figure 2. Meta-Regression: Dose-Dependent Effect of Acetazolamide on AHI. Based on primary analysis higher doses of acetazolamide were associated with greater reductions in AHI ($\beta_{per100mg}$ = -0.08 [95%-CI -0.14 to -0.03], P=0.005; dashed line). However, a *post hoc* analysis suggested that the dose-dependent effect of acetazolamide on the AHI plateaus at 500mg/day ($\beta_{per100mg}$ = -0.16, P=0.008 up to 500mg, but $\beta_{per100mg}$ = -0.03, P=0.52 from 500-1000mg; solid line; for details see Appendix E2, online supplement).

Figure 3. Subgroup Analyses for the Apnea-Hypopnea Index. For complete results of subgroup analyses see Appendix E2 (online supplement). Abbreviations: OSA/CSA obstructive/central sleep apnea, HA high altitude, CHF congestive heart failure, P_{EM} p-value for effect modification, SMD standardized mean difference.

Figure 4. Individual Responses based on patient-level data from 8 cross-over studies[14,32,34,39,41,43,44,52]. Median percent-change was -49.8% (IQR -67.8 to -17.6%). Across responder strata there was no significant difference between OSA vs CSA, or low vs high dose acetazolamide. Responses were also similar in patients with mild-moderate vs severe sleep apnea, except there was a significantly greater percentage of patients with severe vs mild-moderate sleep apnea whose AHI improved by -25 to 0% (P=0.047).

Figure 1 **PRISMA Flowchart.**

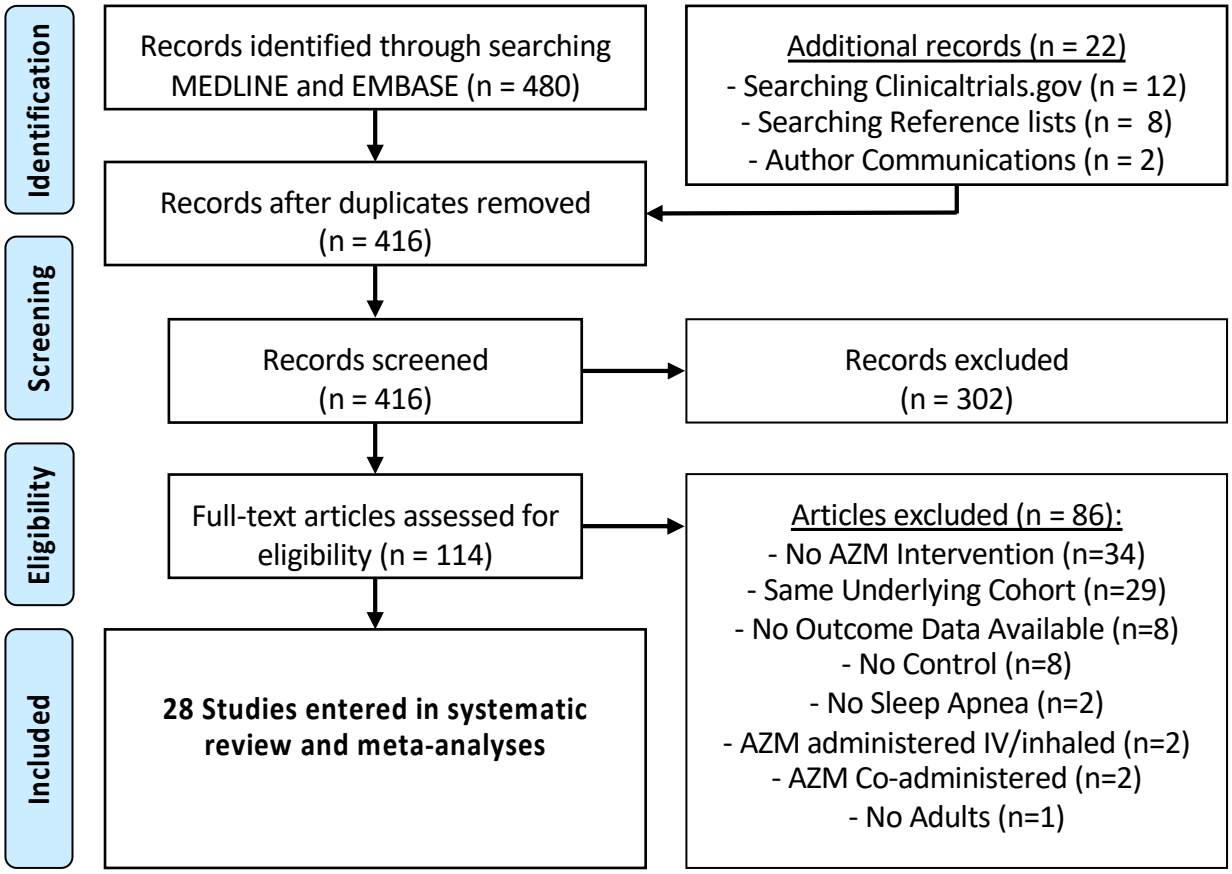


Figure 2

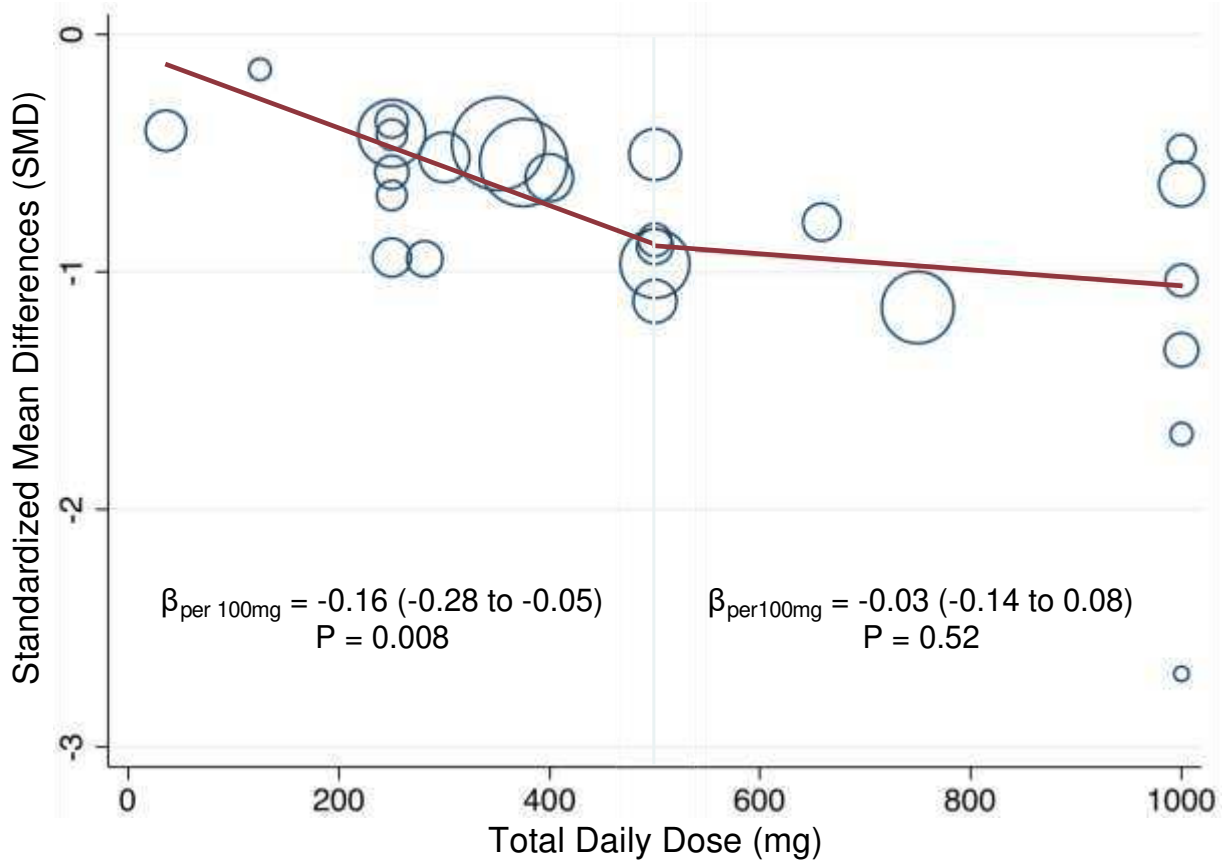


Figure 3

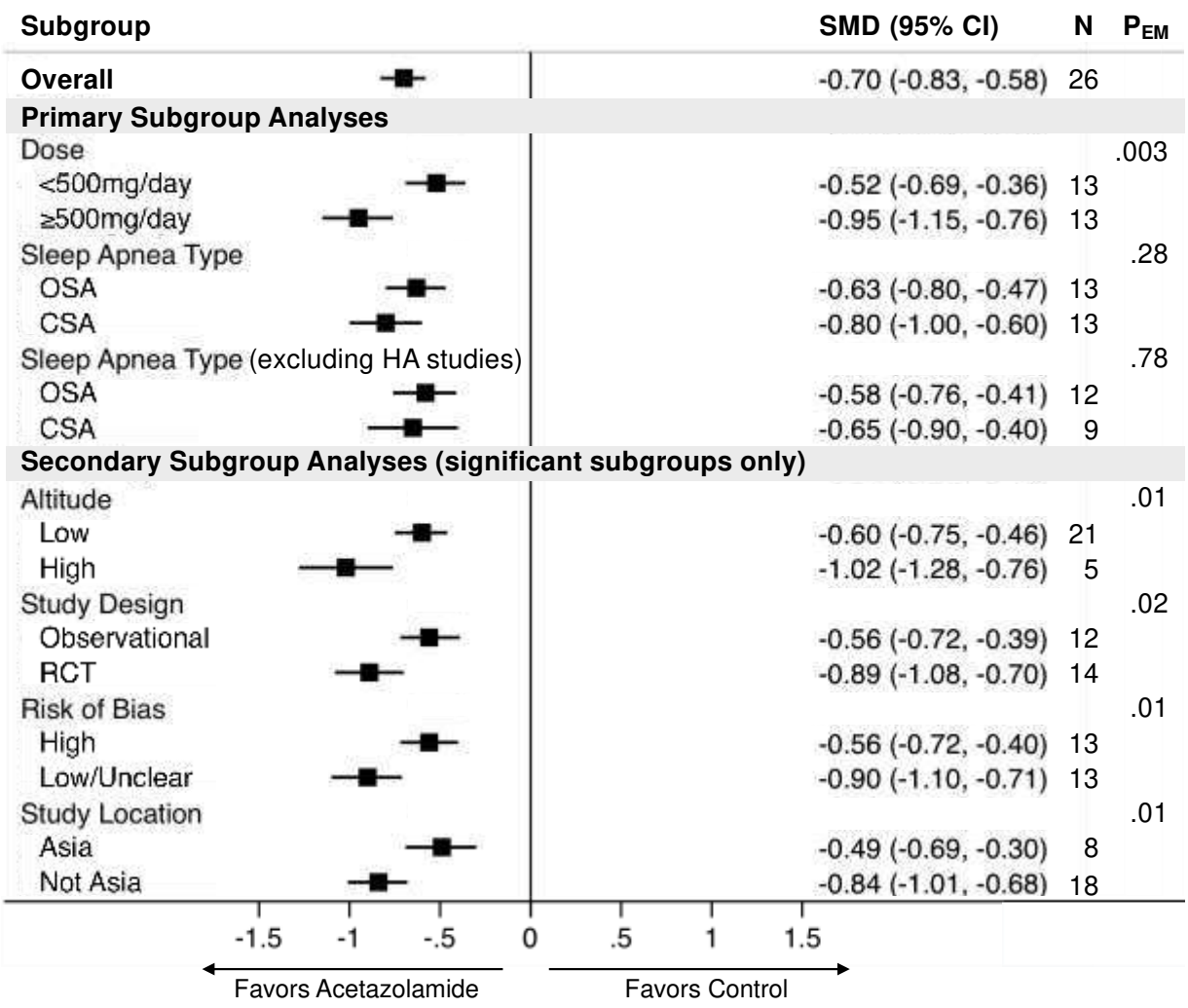
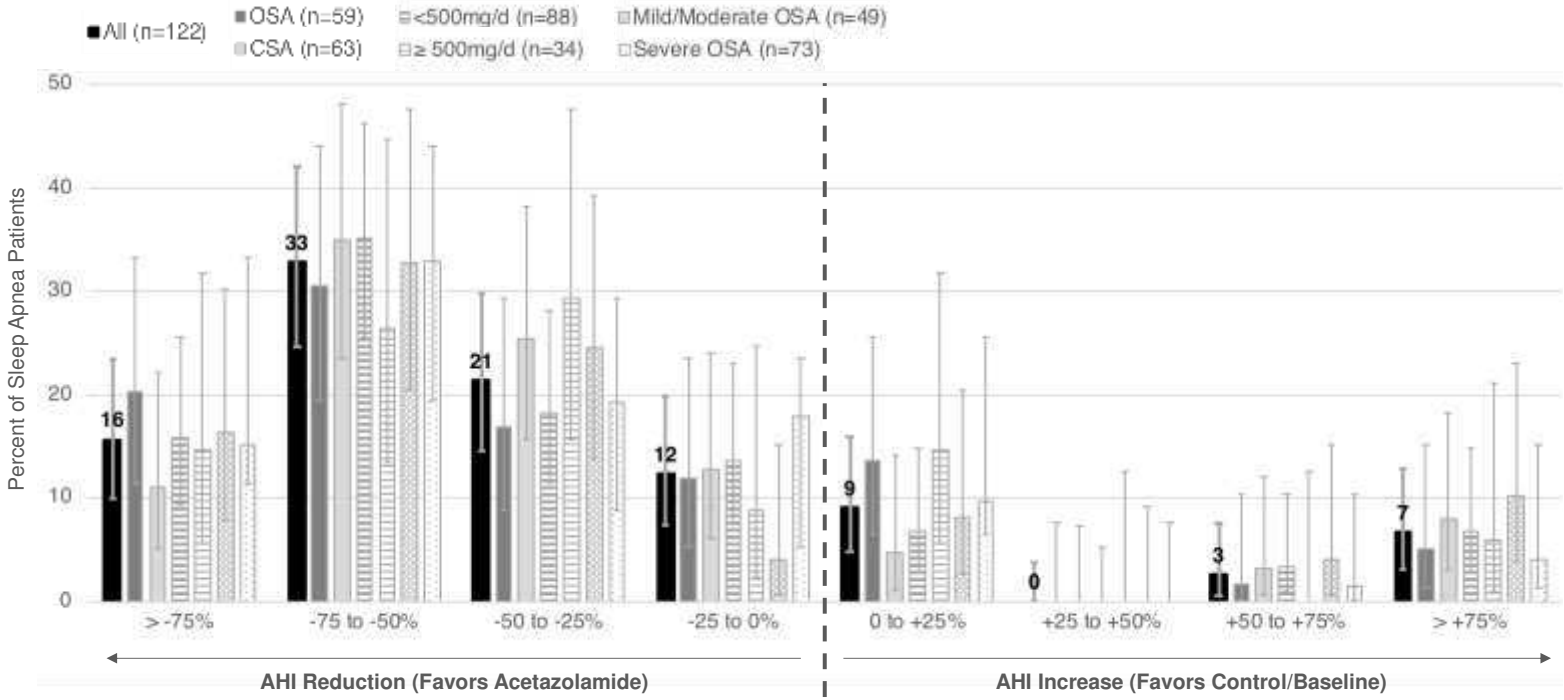

Subgroup
SMD (95% CI)
N
P_{EM}
Overall
-0.70 (-0.83, -0.58) 26
Primary Subgroup Analyses
Dose .003
<500mg/day
-0.52 (-0.69, -0.36) 13
≥500mg/day
-0.95 (-1.15, -0.76) 13
Sleep Apnea Type .28
OSA
-0.63 (-0.80, -0.47) 13
CSA
-0.80 (-1.00, -0.60) 13
Sleep Apnea Type (excluding HA studies) .78
OSA
-0.58 (-0.76, -0.41) 12
CSA
-0.65 (-0.90, -0.40) 9
Secondary Subgroup Analyses (significant subgroups only)
Altitude .01
Low
-0.60 (-0.75, -0.46) 21
High
-1.02 (-1.28, -0.76) 5
Study Design .02
Observational
-0.56 (-0.72, -0.39) 12
RCT
-0.89 (-1.08, -0.70) 14
Risk of Bias .01
High
-0.56 (-0.72, -0.40) 13
Low/Unclear
-0.90 (-1.10, -0.71) 13
Study Location .01
Asia
-0.49 (-0.69, -0.30) 8
Not Asia
-0.84 (-1.01, -0.68) 18
-1.5
-1
-.5
0
.5
1
1.5
Favors Acetazolamide
Favors Control

Figure 4


All (n=122)
OSA (n=59)
CSA (n=63)
<500mg/d (n=88)
≥ 500mg/d (n=34)
Mild/Moderate OSA (n=49)
Severe OSA (n=73)
Percent of Sleep Apnea Patients
50
40
30
20
10
0
16
33
21
12
9
0
3
7
> -75%
-75 to -50%
-50 to -25%
-25 to 0%
0 to +25%
+25 to +50%
+50 to +75%
> +75%
AHI Reduction (Favors Acetazolamide)
AHI Increase (Favors Control/Baseline)

SUPPLEMENTARY MATERIAL

The Efficacy of Acetazolamide for Obstructive and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis

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Table of Content:

eTable 1. Overview of Prior Systematic Reviews

Author Year Title	Included Studies	Type of Sleep Apnea	Key Exclusion Criteria	Reported Outcomes & Results	$N_{Studies}$	$N_{Subj\ AZM}$	$N_{Subj\ Control}$
Gaisl 2019 Efficacy of **Pharmacotherapy for OSA** in Adults: A Systematic Review and Network Meta-Analysis[1]	RCTs	OSA	OSA at high altitude; Concomitant PAP use	AHI -9.6/h (-17 to -1.4) [2,3]	2	22	22
Wongboonsin 2019 Acetazolamide Therapy in **Patients with Heart Failure**: a Meta-Analysis[4]	RCTs & Observational Studies	SDB-CHF	none	AHI [a] SMD -1.1 (-1.8 to -0.4), I^2=0% [5,6] CAI [a] SMD -1.1 (-1.8 to -0.4), I^2=0% [5,6] pH, pCO2, bicarbonate, natriuresis	2[a] 2[a]	18[a] 18[a]	18[a] 18[a]
Liu 2017 The Effect of Acetazolamide on **Sleep Apnea at High Altitude**: a Systematic Review and Meta-Analysis[7]	RCTs	CSA-HA (healthy or OSA at baseline)	none	AHI [b] -23.8/h (-35.1 to -12.6), I^2=73% [8-12] %PB -38.6 (-58.2 to 18.9), I^2=28% [13,14] SpO_2-mean 3.7 (1.6 to 5.9), I^2=0% [8-15]	6 2 8	142 13 155	143 13 156
Mason 2013 Drug Therapy for Obstructive Sleep Apnoea in Adults [Cochrane Review][16]	RCTs	OSA	Lack of placebo; Concomitant PAP use	Reports data from a single study for AHI, Arousal Index and ODI[3]	1	10	10
Aurora 2012 The Treatment of **Central Sleep Apnea** Syndromes in Adults: **Practice Parameters** with an Evidence-based Literature Review and Meta-Analyses[17]	RCTs & Observational Studies	CSA	Non-English articles	Narrative description only: - CSA-CHF: AHI, subjective sleepiness [6] - CSA-HA: AHI, mean-SpO_2 [9] - CSA idiopathic: AHI, subjective sleepiness [18,19] => AZM considered OPTION for CSA-CHF & idiopathic CSA; insufficient data to make recommendations for CSA-HA	 1 1 2	 12 10 20	 12 10 20
Veasey 2006 **Medical therapy for obstructive sleep apnea**: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force [AASM][20]	RCTs	OSA	Non-English articles	None	0	0	0
Hudgel 1998 **Pharmacologic treatment of sleep-disordered breathing**[21]	RCTs & Observational Studies	OSA & any CSA	Non-English articles	Narrative description only, providing results from original studies for AHI, %PB, subjective symptoms, sleep stages, lab tests and ventilatory response (as available) [3,13,18,19,22,23]	6[c]	53[c]	53[c]

Abbreviations: AHI apnea-hypopnea index, AZM acetazolamide, CAI central apnea index, CHF congestive heart failure, CSA central sleep apnea, HA high altitude, PAP positive airway pressure, %PB periodic breathing (percentage of total recording time), ODI oxygen desaturation index, OSA obstructive sleep apnea, RCT randomized controlled trial.

a Note, the two articles whose data were combined in this meta-analysis actually report data from the same dataset (i.e. [5] is a subset of [6])
b (*Post hoc*) subgroup analyses suggest larger effect in healthy trekkers vs subjects with OSA at baseline
c The number of studies for each outcome ranged from 1 to 5

eAppendix 1. Study Protocol

INTRODUCTION:

Rationale:

Obstructive sleep apnea (OSA) is now recognized to have multiple underlying mechanisms (endotypes).[24] Elevated loop gain (unstable ventilatory control) is the main driver of most central sleep apneas (CSA),[25] but also known to be an important endotype in a sub-set of OSA patients.[2,24] It has been shown that Acetazolamide can lower loop gain by reducing the efficiency of CO_2 excretion (i.e. reduced plant gain) thus improving sleep apnea as measured by the apnea-hypopnea index (AHI).[2] However, the dose used in the literature is highly variable and recent data suggest that common side effects are dose-dependent.[26] Thus, to facilitate clinical use of acetazolamide our goal is to identify the lowest effective dose of acetazolamide to treat sleep disordered breathing.

Objective: By conducting a systematic review of the literature we seek to determine the utility of acetazolamide in improving sleep disordered breathing (SDB; i.e. OSA or CSA) and the optimal dosage of this medication.

METHODS

Eligibility Criteria:

Inclusion Criteria (PICO):

Population: Adults with Obstructive or Central Sleep Apnea (OSA or CSA)
Intervention: Acetazolamide PO
Control: Placebo or nothing (including parallel control group or cross-over design)
Outcome:
- Primary: Apnea-Hypopnea Index, SpO_2 nadir
- Secondary: % periodic breathing, SpO_2 mean, Time with SpO_2 below 90%/88%, %subjects successfully treated, PSG parameters (e.g. stages, sleep efficiency, arousal index), Blood Pressure and any other reported patient-important outcomes

Exclusion Criteria:
- non-human subjects
- non-adult subjects (i.e. age <18)
- subjects unable to report symptoms (e.g. intubated)
- subjects on hemodialysis (heavily affects plasma levels of acetazolamide)
- administration of acetazolamide in other than PO (e.g. IV, inhaled; d/t likely different pharmacodynamics)
- co-administration of other systemic interventions that may confound effects (but co-administration with CPAP acceptable if control allows isolation of acetazolamide effect)

Study Designs: Case reports will be excluded, but case series, case-control studies, cohort studies and randomized trials will all be considered for inclusion if meeting the above criteria.[27] Thus, we will follow both PRISMA[28] and MOOSE[29] guidelines for reporting.

Information Sources:

- MEDLINE since inception
- EMBASE since inception
- Review of reference lists of retrieved articles and other relevant articles

Search Strategy:

MEDLINE:

(("Acetazolamide"[Mesh]) OR "Acetazolamide"[tiab]) AND ("Sleep Apnea Syndromes"[Mesh] OR "Sleep Apnea"[tiab] OR "AHI"[tiab] OR "apnea hypopnea index"[tiab])

EMBASE:
('acetazolamide':ti,ab,kw OR 'acetazolamide'/exp) AND ('sleep disordered breathing'/exp OR 'sleep apnea':ti,ab,kw OR 'apnea hypopnea index':ti,ab,kw) NOT 'review'/it

Data Management:

- Excel Sheet for data entry and storage
- STATA/R for analysis

Selection Process

Eligibility assessment by two independent reviewers. Abstracted data/bias assessment will be at least cross-checked by a second reviewer. Disagreements will be resolved primarily through discussion aiming to achieve a consensus agreement; if the two reviewers are unable to resolve the disagreement then arbitration will be done by a 3rd reviewer.

Data Collection process

- Entry into Excel Sheet using validation criteria (e.g. drop-down lists whenever possible)
- Clarification of data with authors if needed and possible

Data items

General Infos:

- First Author name
- Publication Year
- Type of SDB (OSA, CSA-CSB, CSA-high altitude, CSA d/t medications, CSA idiopathic)
- SDB vs healthy at baseline
- Co-administration with PAP (yes, no)
- Study Design (RCT, cohort study, case-control study, case series)
- Cross-over vs parallel group trial
- Wash-out days (for cross over trials)

Intervention Details:

- Total Daily Dose of Acetazolamide
- Number of Acetazolamide doses/day
- Days of Acetazolamide administration

Comparator Details:

- Placebo vs “no intervention”

Potential Effect modifiers:

- Percent Females
- Mean Age
- Mean BMI
- Mean Weight
- Race (Percent white, black, other)
- Adjustment of Dose by renal function (yes, no)
- Lab values (at the end of control or acetazolamide period):
    - pH
    - pO_2
    - pCO_2
    - Bicarbonate
    - Chloride
    - Creatinine
- Physiological Traits (e.g. Loop gain)
- Industry funded (yes, no, unclear)

Primary Outcomes:

- Apnea-Hypopnea Index (AHI; preferably "AHI4%")
  - AHI Definition
  - Study type (home vs inlab sleep test)
- SpO_2 nadir

Secondary Outcomes:

- % periodic breathing (percentage of sleep time)
- Mean SpO2
- Apnea Duration
- Sleep Time with SpO_2<90%
- Sleep Time with SpO_2<88%
- Oxygen Desaturation Index (ODI, preferably 4%)
- % subjects successfully treated/"responders" (i.e. AHI drop by >50% to <10/h, or as defined by the study)
- % Sleep Stages (N1, N2, N3, REM)
- Total Sleep Time (TST), Sleep Efficiency
- Arousal Index (spontaneous and respiratory related)
- Periodic Leg Movements
- Blood Pressure (systolic, diastolic, mean)
- Side Effects
- Other patient-important outcomes reported (e.g. Epworth Score)

Outcomes (primary) and prioritization:

- Apnea-Hypopnea Index:
  - Preferably number of apneas (drop in peak signal excursion by at least 90% for 10 seconds) and hypopneas with at least 4% oxygen desaturations (drop in peak signal excursion by at least 30% compared with pre-event baseline for at least 10 seconds) per hour of sleep; else (if unavailable) as defined by the study
- SpO_2 Nadir: lowest SpO_2 measured during sleep

Risk of bias in individual studies:

For RANDOMIZED studies:

- Assessment of 5 bias domains as per Cochrane Handbook, Chapter 8 (http://handbook-5-1.cochrane.org/ , modified based on Table 8.5):

1. Selection Bias	**Risk of Bias**
a.) Method of randomization was clearly described? -> Yes, No, Unclear b.) Allocation sequence was concealed so that the intervention allocation was not foreseeable? -> Yes, No, Unclear	If "Yes" & "Yes": Low If "No" to a or b: High Else: Unclear
2. Performance Bias	
a.) Participants and study personnel were (effectively) blinded to the allocated intervention? -> Yes, No, Unclear	"Yes": Low "No": High "Unclear": Unclear
3. Detection Bias	
a.) Outcome assessors were (effectively) blinded to the allocated intervention? -> Yes, No, Unclear	"Yes": Low "No": High "Unclear": Unclear
4.) Attrition Bias	
a.) Outcome assessment was performed in the majority (85%) of randomized participants or at least well accounted for (e.g. reasons for loss to follow up provided showing that attrition occurred non-differential, i.e. at random)? -> Yes, No, Unclear	"Yes": Low "No": High "Unclear": Unclear

5.) Reporting Bias	
a.) All pre-planned outcomes were reported? -> Yes, No, Unclear	"Yes": Low "No": High "Unclear": Unclear

The primary outcomes represent standard sleep study parameters and inter-rater reliability for reporting bias is low.[30] Thus, for this review we will consider selection, performance, detection and attrition bias as the 4 key domains to judge overall risk of bias.

The overall bias on the study level will be rated as Low vs Unclear vs High based on highest risk in any of the 4 key domains (sensitivity analysis: based on highest risk in any of the 5 domains).

For NON-RANDOMIZED studies:
- Assessment of bias will be assessed based on a modified Newcastle-Ottawa Scale[31]:

1. Selection	**Risk of Bias**
a.) Selection of the cohort: Has the condition of interest (e.g. OSA) been verified using standard testing (e.g. inlab sleep study)? -> Yes, No, Unclear b.) Has the exposure been ascertained: E.g. Acetazolamide taken under supervision or verified by pill count? -> Yes, No, Unclear	If "Yes" & "Yes": Low If "No" to a or b: High Else: Unclear
2. Comparability	
a.) Study controls for key any confounders (e.g. position, alcohol)? -> Yes, No, Unclear	"Yes": Low "No": High "Unclear": Unclear
3. Outcome	
a.) Outcome assessments blinded to acetazolamide administration?	"Yes": Low "No": High "Unclear": Unclear

The overall bias on the study level will be rated as Low vs Unclear vs High (based on highest risk in any of the 3 domains)

For both randomized and non-randomized trials, the effect of "overall bias" on results will be tested by doing a sensitivity analysis checking for "effect modification" by bias strata.

Data Synthesis:

Pooled Effect Estimates:

For outcomes reported by at least 2 studies a pooled effect estimate will be attempted. Most outcomes are anticipated to be continuous – if all studies considered for inclusion use the same scale then weighted mean differences will be used, else standardized mean differences will be used. For any potentially dichotomous outcomes a fixed effects model (based on odds ratios) will be used for the initial analysis.

Heterogeneity will be quantified by the I^2 statistic and arbitrarily categorized as low (<30%), moderate (30-50%), or high (>50%);[32,33]

If there is more than low amount of heterogeneity (i.e. $I^2 > 30\%$), then attempts will be made to identify/account for the source of heterogeneity through stratified meta-analysis/meta-regression.
If heterogeneity remains high ($I^2>50\%$), then the focus will be on a narrative summary rather than a pooled effect estimate.

If heterogeneity remains moderate ($I^2 = 30\text{-}50\%$), then a random effects model will be used for any potentially dichotomous outcomes.

Effect Modification/Subgroup Analyses:
For primary outcomes with a meta-analysis based on at least 8 studies, we will assess for effect modification by:

- Total daily dose
- Duration of Acetazolamide
- Type of sleep apnea

Additionally, we will test for effect modification by the following factors (for primary outcomes with a meta-analysis based on at least 8 studies):

- Mean age
- Mean BMI
- Percent Females
- Race
- Labs
- Traits
- Concomitant PAP use
- Healthy vs SDB at baseline

Interpretation of associations involving patient-level characteristics will take into account the potential risk for ecological fallacies.

Potential effects of intra-study bias will be assessed by testing for effect modification by:

- Overall bias (low vs unclear vs high)
- Industry funding (yes vs no)

Sensitivity Analysis:

Assessment of impact of eligibility and data abstraction decisions as needed
Restriction of meta-analyses for primary outcomes to studies judged low risk of bias

Meta-Bias
"Publication" bias will be assessed via:

- Funnel Plot Assessment
- Eger's test (using $P<0.05$ to indicate publication bias or other source of heterogeneity)

Confidence in cumulative evidence
Strength of evidence will be assessed using GRADE methodology.[34]

eTable 2. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6; 8-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11-12

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11-12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig1, p13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	eTable4, eAppendix2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eTable4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	eAppendix2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table2, eAppendix2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eAppendix2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	eAppendix2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	4

eTable 3. MOOSE Checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3, 5-6, 8-9
2	Hypothesis statement	3
3	Description of study outcome(s)	9-11
4	Type of exposure or intervention used	9-11
5	Type of study designs used	9
6	Study population	9
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	10
8	Search strategy, including time period included in the synthesis and key words	10
9	Effort to include all available studies, including contact with authors	10
10	Databases and registries searched	10
11	Search software used, name and version, including special features used (eg, explosion)	10
12	Use of hand searching (eg, reference lists of obtained articles)	10
13	List of citations located and those excluded, including justification	will provide if requested
14	Method of addressing articles published in languages other than English	10
15	Method of handling abstracts and unpublished studies	10
16	Description of any contact with authors	13
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	8-10
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	9
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	10
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	11
22	Assessment of heterogeneity	10-11
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	10-11
24	Provision of appropriate tables and graphics	Fig1-4, Tbl 1-2
Reporting of results should include		

25	Graphic summarizing individual study estimates and overall estimate	eApp 2
26	Table giving descriptive information for each study included	eTbl4
27	Results of sensitivity testing (eg, subgroup analysis)	eApp2, Fig3
28	Indication of statistical uncertainty of findings	Tbl2

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	eApp2
30	Justification for exclusion (eg, exclusion of non-English language citations)	na
31	Assessment of quality of included studies	Tbl2, 17-18
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	17-18
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	18
34	Guidelines for future research	18
35	Disclosure of funding source	4

eTable 4. Characteristics of Included Studies.

	POPULATION					ACETAZOLAMIDE/CONTROL			OUTCOMES		STUDY	
	Sleep Apnea Type	Mean Age (y)	Percent Female (%)	Mean BMI (kg/m^2)	Study Location	Dose (mg/day)	No. Days	Control Type	AHI/ AI	SpO_2 Nadir	Design	Risk of Bias Overall (Domains[n])
Sutton 1979[14]	CSA -HA		44.4		Canada	750	2	Baseline		Yes	RCT_{Cx}	High (U|H|L|L)
White 1982[19]	CSA -ID	57.7	0		USA	1000	7	Baseline	Yes		OBS	High (U|L|H)
Hackett 1987[13]	CSA -HA	30.5	0		USA	750	1	Placebo	[m]	[m]	RCT_{Cx}	Unclear (U|L|U|L)
Inoue 1987[35]	OSA [b]	55.4	13.4		Japan	375	7	Baseline	Yes		OBS	High (U|H|H)
Whyte 1988[3]	OSA	51.5	20		UK	1000	14	Placebo	Yes	Yes	RCT_{Cx}	Unclear (U|L|L|L)
Tojima 1988[22]	OSA	58	44.4	29.9	Japan	250	7.5	Baseline	Yes	Yes	OBS	High (U|L|H)
Chin 1992[36]	OSA				Japan	250	14	Baseline	Yes	Yes	OBS	High (L|H|H)
Sakamoto 1995[37]	OSA	54.6	0		Japan	399	52.4	Baseline	Yes		OBS	High (L|U|H)
DeBacker 1995[18]	CSA -ID	47.9	7.1	31.5	Belgium	250	30	Baseline	Yes		OBS	Unclear (U|L|U)
Inoue 1999[38]	OSA	55.2	12	25.6	Japan	351	39.5	Baseline	Yes	Yes	OBS	High (U|H|H)
Fischer 2004[9]	CSA -HA		0		Switzerland	500	4	Placebo	Yes		RCT_{Pa}	Unclear (U|L|L|L)
Verbraecken 2005[39]	CSA -ID	56.8		38.3	Belgium	250	1	Baseline	Yes	Yes	OBS	High (U|U|H)
Javaheri 2006[6]	CSA -CHF	66	0	26	USA	281[i]	6	Placebo	Yes	Yes	RCT_{Cx}	Unclear (U|L|L|L)
Belyavskiy 2010[40]	OSA (+CHF)[c]	57		28.2	Russia	36[j]	90	No AZM	Yes		OBS	High (H|U|U)
Rodway 2011[12]	CSA -HA	38.1			Nepal	125	1	No AZM	Yes		RCT_{Pa}	High (U|H|U|L)
Fontana 2011[41]	CSA -CHF	62	8.3	29	Italy	500	4	Baseline	Yes	Yes	OBS	High (U|H|U)
Latshang 2012[10]	CSA -HA[d]	63	5.9	33	Switzerland	750	3	Placebo	Yes		RCT_{Cx}	Low (L|L|L|L)
Edwards 2012[2]	OSA	50		34.2	USA	1000	6.5	Baseline	Yes	Yes	RCT_{Cx}	High (H|H|L|L)
Nussbaumer-Ochsner 2012[11]	OSA (+HA)[e]	64	6.7	31.7	Switzerland	500	3	Placebo	Yes	Yes	RCT_{Cx}	Unclear (U|L|L|L)
Apostolo 2014[42]	OSA (+CHF)[f]	69	0	24.5	Italy	1000	2	Baseline	Yes	Yes	OBS	High (U|H|H)
Pranathiageswaran 2014[43]	OSA	56	75	28	USA	1000	3	Placebo	Yes		RCT_{Cx}	Unclear (U|L|U|U)
Ulrich 2015[44]	CSA -Other[g]	66	65.2	26.6	Switzerland	500	7	Placebo[k]	Yes		RCT_{Cx}	Low (L|L|L|L)
Caravita 2015[8]	CSA -HA	36.1	48.8	21.9	Italy	500	4	Placebo	Yes	Yes	RCT_{Pa}	Unclear (U|L|L|L)
Eskandari 2018[45a]	OSA	64	0	29	Sweden	659	14	Baseline	Yes	Yes	OBS[a]	High (L|U|H)
Ginter 2018[46]	CSA -Other[h]	55.4		25.5	USA	1000	3	Placebo	Yes		RCT_{Cx}	High (U|U|U|H)
Adimi 2019[47]	CSA -Opioids	50.2	10	29.6	Iran	250	6	Placebo	Yes		RCT_{Cx}	Unclear (U|L|L|L)
Wellman NCT01377987[48]	OSA (+CHF)[f]	60	10.3		USA	300	7	Placebo	Yes		RCT_{Cx}	Unclear (U|L|U|L)
Strohl NCT00746954[49]	CSA -CHF	59.7	0		USA	250	1	Placebo	Yes		RCT_{Cx}	Unclear (U|U|U|L)

Abbreviations: AHI apnea-hypopnea index, AI apnea index, AZM acetazolamide, BMI body mass index, CSA central sleep apnea, CHF congestive heart failure, HA high altitude, ID idiopathic, $RCT_{Cx/Pa}$ randomized controlled trial (subscript Cx denotes cross-over trials; subscript Pa denotes parallel group trials).

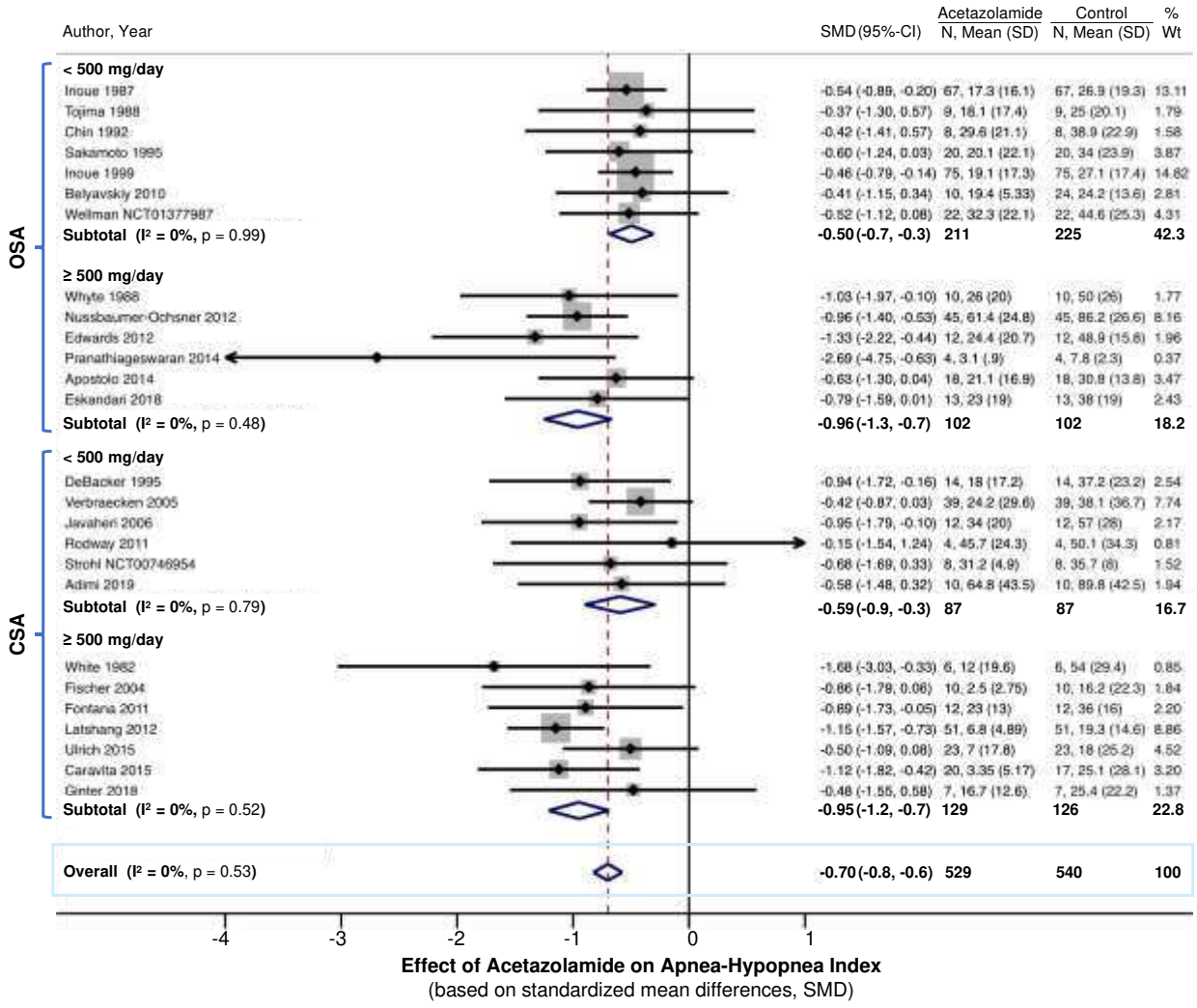
a This RCT has 3 arms: 1.) acetazolamide+CPAP; 2.) acetazolamide alone; 3.) CPAP alone. Subjects with CPAP alone had no sleep apnea (AHI<5), thus we could not compare the effect of acetazolamide+CPAP vs CPAP alone. However, this study also reported baseline values for each group allowing estimation of acetazolamide's effect in group 2 compared with untreated baseline values, which is a non-randomized comparison.
b Primarily OSA with some subjects having OSA+CSA, and very few CSA only (for primary analysis judged as OSA)
c Primarily OSA as per author clarification.
d OSA patients on CPAP were brought to high altitude to compare CPAP+acetazolamide vs CPAP alone; in the CPAP alone group OSA did not worsen, but high altitude CSA emerged, thus this study was judged as CSA-HA.
e OSA patients off CPAP were brought to high altitude to compare acetazolamide vs placebo; in the placebo group obstructive events were twice as frequent as central events, thus this study was judged as OSA.
f Unspecified sleep apnea in CHF patients (OSA tends to be more common than CSA even in CHF patients, thus for primary analysis judged as OSA)
g CSA in the setting of pre-capillary pulmonary hypertension
h CSA in the setting of spinal cord injury
i Subjects received 3.5 to 4mg/kg/day. Assuming an average weight of 75kg, we estimated the mean daily dose as 75kg x 3.75mg/kg/day = 281mg/day
j Subjects received 250mg/week. Thus, we estimated the mean daily dose as 250mg/7d = 36mg/d
k Placebo plus sham-oxygen
m Study reported outcome data for periodic breathing and mean SpO_2, thus it was included despite lacking data for primary outcomes
n Domains were (Selection|Performance|Detection|Attrition bias) for randomized studies, and (Selection|Comparability|Outcome bias) for observational studies; each domain was rated as low (L), high (H) or unclear (U).

eAppendix 2. Analyses Details

Apnea-Hypopnea Index (AHI)

Forest Plot

Due to the heterogeneity from widely varying AHI definitions and measurement techniques, changes in AHI were assessed using standardized mean differences (SMD), which expresses the mean differences as a proportion of the pooled standard deviations from the treatment and control groups (usual interpretation: 0.3 small, 0.5 moderate, 0.8 large effect size). Acetazolamide reduced the AHI significantly more in studies administering >500mg/day vs <500mg/day ("large" vs "moderate" effect sizes; P=0.003), but its effect on the AHI was similar in studies focusing on obstructive vs central sleep apnea (P=0.28).



Meta-Regression: Subgroup Analyses
Note, *negative* betas reflect greater reductions in AHI.

	Apnea-Hypopnea Index (AHI)		
	ß (95%-CI)	**N**	**P**
Intervention Characteristics			
Total Daily Dose, per 100mg	-0.08 (-0.14 to -0.03)	26	.005*
≥500mg/day vs <500mg/day	-0.43 (-0.70 to -0.16)	26	.003
Days of Acetazolamide, per 10d	0.05 (-0.02 to 0.12)	26	.15
Cumulative Dose, per 1000mg*d	0.01 (-0.02 to 0.03)	26	.62
Population Characteristics			
Type of Sleep Apnea, OSA vs CSA	0.15 (-0.13 to 0.44)	26	.28
Sensitivity Analysis, OSA vs CSA[a]	0.16 ((-0.14 to 0.47)	26	.28
Mean Age, per 10y	0.01 (-0.22 to 0.22)	24	.99
Mean BMI, per 10kg/m^2	-0.06 (-0.51 to 0.40)	17	.80
Percent Females, per 10%	0.01 (-0.09 to 0.10)	20	.87
Comorbid CHF vs no-CHF	0.02 (-0.39 to 0.44)	26	.93
Study Location, Asia vs no-Asia	0.35 (0.09 to 0.62)	26	.01*
High Altitude, yes vs no	-0.42 (-0.73 to -0.10)	26	.01*
Quality Indicators			
Overall Bias, Low/Unclear vs High	-0.34 (-0.61 to -0.08)	26	.01*
Overall Bias, Low vs Unclear/High	-0.26 (-0.66 to 0.14)	26	.20
Study-Design: RCT vs Observational	-0.34 (-0.60 to -0.07)	26	.02*
Industry Funded, yes vs no	0.24 (-0.04 to 0.51)	26	.09
Baseline Laboratory Values			
pH, per 0.01	-0.07 (-0.23 to 0.10)	10	.38
pCO_2, per 1mmHg	-0.02 (-0.07 to 0.04)	13	.53
pO_2, per 1mmHg	-0.00 (-0.03 to 0.03)	8	.92
Bicarbonate, per 1mmol/L	-0.02 (-0.18 to 0.14)	10	.76
Changes in Laboratory Values			
pH, per -0.01	-0.05 (-0.17 to 0.07)	10	.35
pCO_2, per -1mmHg	-0.08 (-0.16 to 0.01)	13	.08
pO_2, per +1mmHg	-0.01 (-0.10 to 0.09)	8	.83
Bicarbonate, per -1mmol/L	-0.06 (-0.19 to 0.07)	10	.30

a 5 studies[11,35,42,43,48] included patients, judged to have primarily OSA but (potentially) including also some patients with CSA; in sensitivity analysis these 5 studies were classified as CSA with similar results.

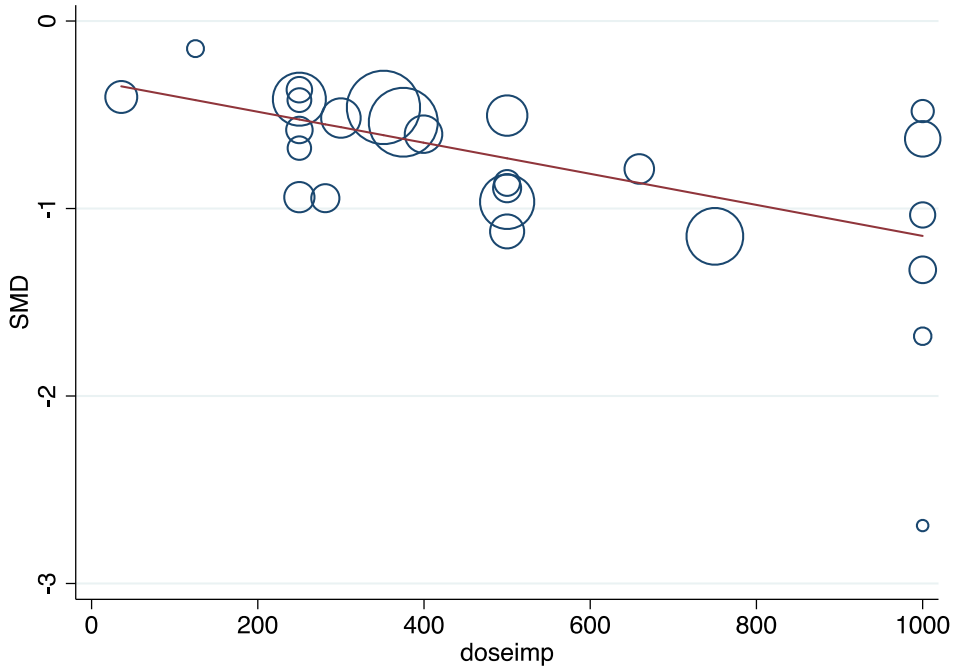
Sensitivity Analyses

	SMD	(95%-CI)	I^2	N	P
Primary Analysis Result (for comparison)[2,3,6,8-14,18,19,22,35-49]	-0.70	(-0.83 to -0.58)	0%	26	<.001*
Like primary analysis BUT…					
…using lower altitude data for 2 studies: 1630m (vs 2590m)[10], and 1860m (vs 2590m)[11]	-0.63	(-0.75 to -0.51)	0%	26	<.001*
…using outcome data from second rather than the first study night at high altitude[9]	-0.69	(-0.82 to -0.57)	0%	26	<.001*
…journal articles only (i.e. excluding conference abstracts[40,43,46] or clinicaltrials.gov records[48,49])	-0.71	(-0.85 to -0.58)	0%	21	<.001*
…excluding a study potentially not fully meeting eligibility criteria, because 4 of 23 subjects did not have sleep apnea,[44]	-0.71	(-0.84 to -0.58)	0%	25	<.001*
…excluding a study in which acetazolamide was administered once weekly and outcomes were assessed 1-2days after last administration[40]	-0.71	(-0.84 to -0.58)	0%	25	<.001*
…excluding a study only reporting apnea index (i.e. without hypopneas)[37]	-0.70	(-0.83 to -0.58)	0%	25	<.001*
…including only studies which clearly used nasal pressure transducer (i.e. not thermistor or other less sensitive device) for hypopnea detection[9-11,41,44,47]	-0.91	(-1.15 to 0.67)	0%	6	<.001*
…including only studies which clearly used inlab polysomnography (i.e. not home sleep apnea tests or similar devices) for sleep apnea assessment[2,3,6,9-11,18,19,22,35-39,43,44,46-49]	-0.69	(-0.83 to -0.56)	9%	20	<.001*

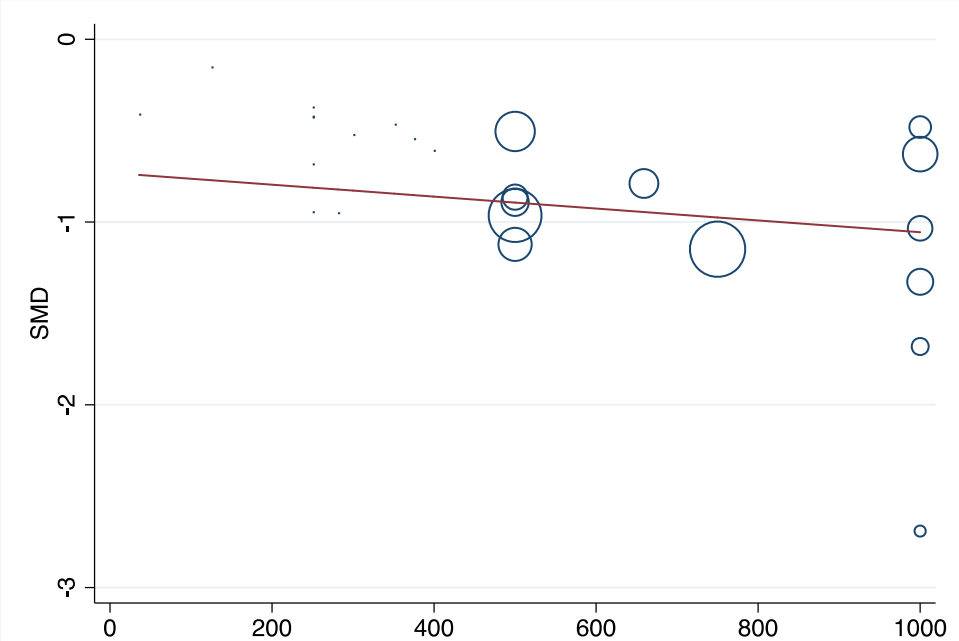
Judging by overlapping 95%-confidence intervals results from sensitivity analyses were similar as in the primary analysis.

Meta-Regression: Effect Modification by Total Daily Dose

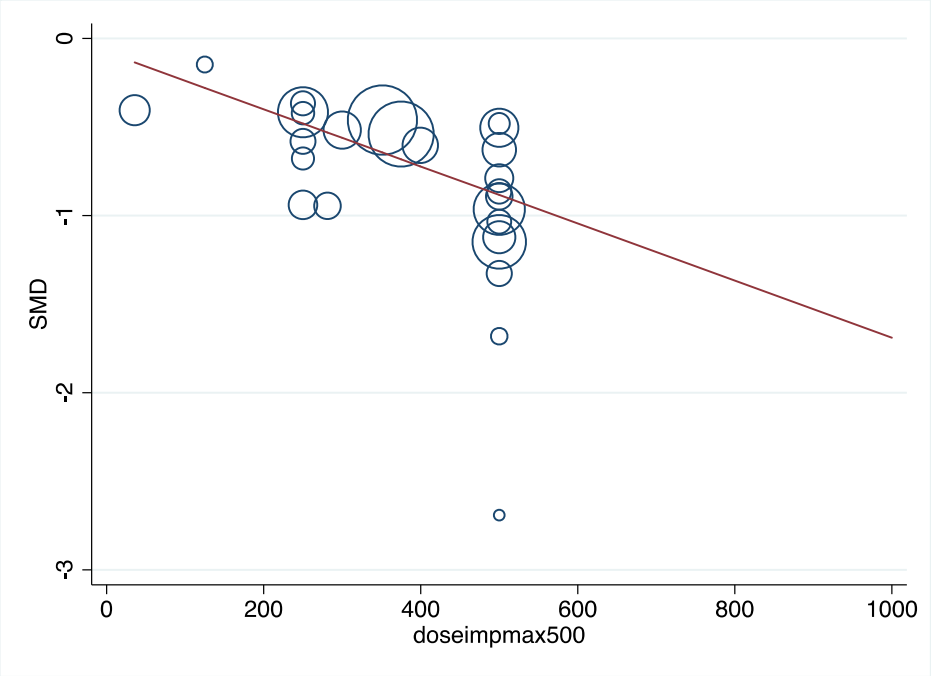
Initial meta-regression provided evidence for a significant linear dose-response $\beta_{per100mg}$ = -0.08 (95%-CI -0.14 to -0.03), P=0.005:



However, closer inspection (taking into account the relative weight of different studies denoted by the circles' areas) suggested that with doses greater than 500mg, there may be little change in acetazolamide's effect on the AHI. To explore this, we repeated the meta-regression, restricting the dataset to the studies which used acetazolamide of 500mg or greater:

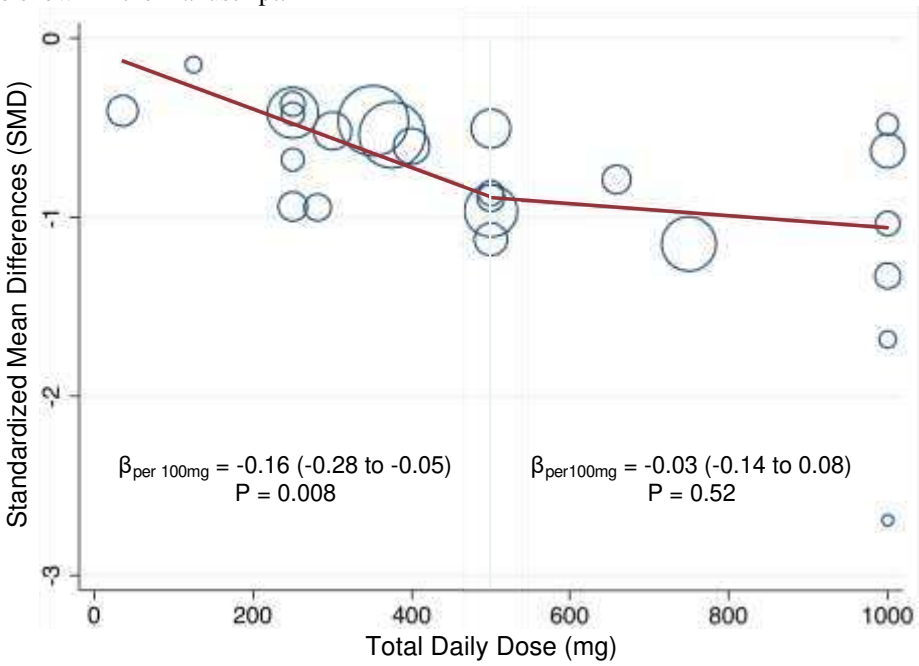


In this case $\beta_{per100mg}$ = -0.03 (95%-CI -0.14 to 0.08), P = 0.52, suggesting that doses beyond 500mg/day do not increase acetazolamide's effect on the AHI. Consequently, to get a more valid estimate for the dose range between 0-500mg/day, we performed a separate analysis including all studies, but setting the dose in studies that administered *greater than* 500mg/day *at* 500mg/day (i.e. we modelled that the effect of acetazolamide on the AHI is the same for all doses 500-1000mg/day):

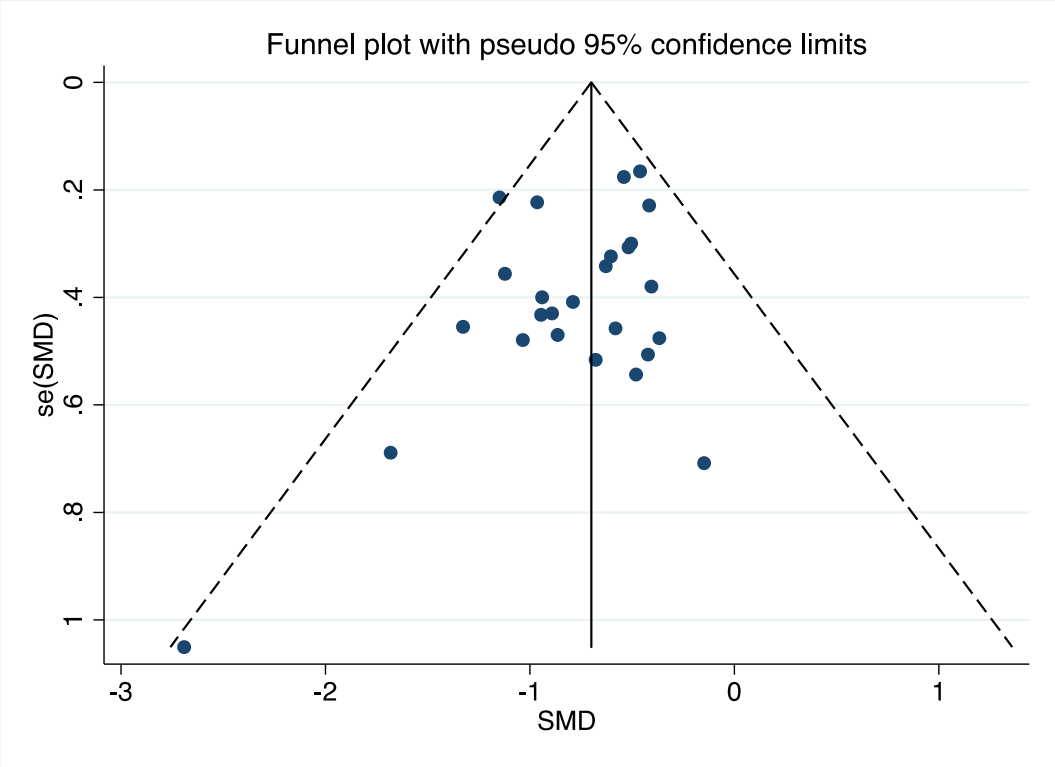


In that case the $\beta_{per100mg}$ = -0.16 (95%-CI -0.28 to -0.05), P = 0.008.

To better communicate these findings, we then combined the results from these 3 analyses in one figure, which is also shown in the manuscript:

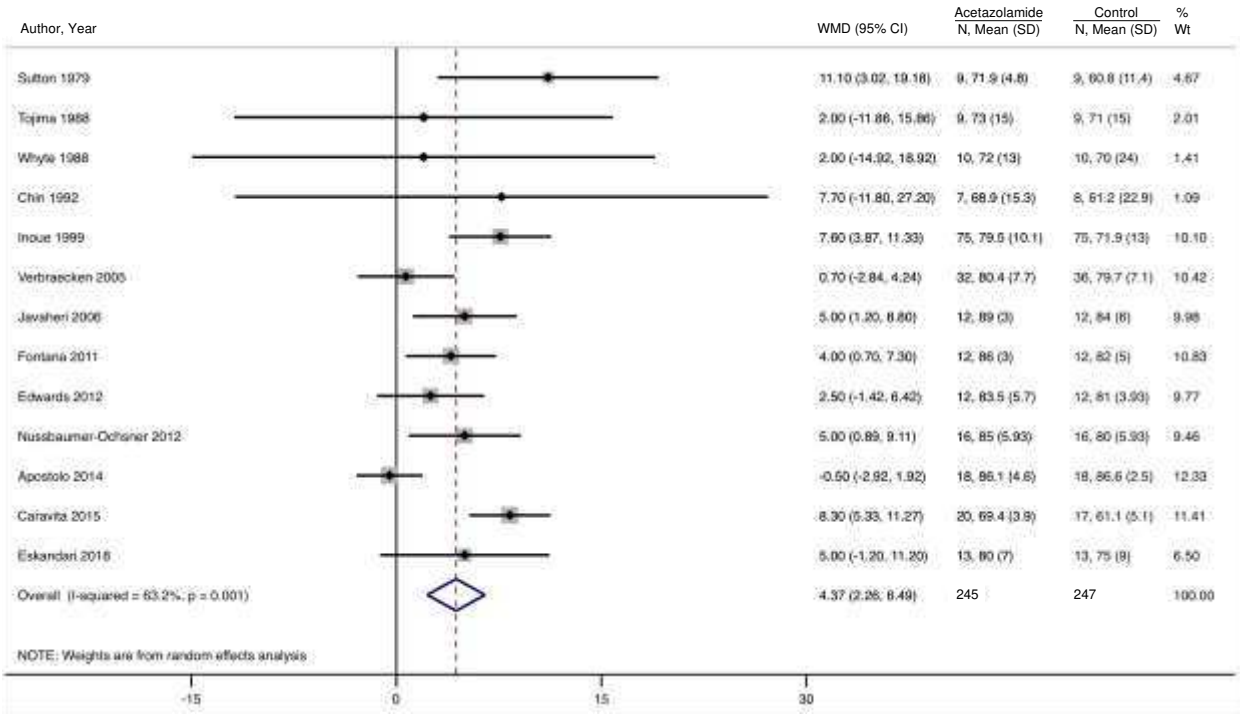


Funnel Plot



Egger's Test P=0.11

SpO_2 Nadir
Forest Plot



Change in SpO2 Nadir (%)
(analysis based on weighted mean differences, WMD)

Heterogeneity was high, but we were unable to identify a clear source of heterogeneity (see subgroup analyses).

Meta-Regression: Subgroup Analyses
Note, *positive* betas reflect greater increases in SpO_2 Nadir.

	SpO_2 Nadir		
	ß (95%-CI)	**N**	**P**
Intervention Characteristics			
Total Daily Dose, per 100mg	-0.4 (-1.2 to 0.4)	13	.29
≥500mg/day vs <500mg/day	0.03 (-5.1 to 5.1)	13	.99
Days of Acetazolamide, per 10d	1.1 (-0.9 to 3.1)	13	.25
Cumulative Dose, per 1000mg*d	0.2 (-0.3 to 0.7)	13	.44
Population Characteristics			
Type of Sleep Apnea, OSA vs CSA	-1.6 (-6.3 to 3.1)	13	.46
Sensitivity Analysis, OSA vs CSA[a]	+0.7 (-4.5 to 5.8)	13	.78
Mean Age, per 10y	-1.7 (-3.7 to 0.4)	11	.10
Mean BMI, per 10kg/m^2	-2.7 (-7.6 to 2.1)	10	.23
Percent Females, per 10%	1.2 (-0.1 to 2.4)	10	.06
Comorbid CHF vs no-CHF	-2.6 (-7.3 to 2.0)	13	.24
Study Location, Asia vs no-Asia	2.8 (-3.9 to 9.5)	13	.37
High Altitude, yes vs no	4.3 (-0.3 to 9.0)	13	.06
Quality Indicators			
Overall Bias, Low/Unclear vs High	2.6 (-1.9 to 7.2)	13	.23
Overall Bias, Low vs Unclear/High	na (no low risk studies)		
Study-Design: RCT vs Observational	2.7 (-1.6 to 7.1)	13	.19
Industry Funded, yes vs no	-0.2 (-5.2 to 4.7)	13	.92
Baseline Laboratory Values			
pH, per 0.01	na (insufficient n)		
pCO_2, per 1mmHg	-0.5 (-1.3 to 0.3)	8	.16
pO_2, per 1mmHg	na (insufficient n)		
Bicarbonate, per 1mmol/L	na (insufficient n)		
Changes in Laboratory Values			
pH, per -0.01	na (insufficient n)		
pCO_2, per -1mmHg	0.5 (-0.6 to 1.6)	8	.30
pO_2, per +1mmHg	na (insufficient n)		
Bicarbonate, per -1mmol/L	na (insufficient n)		

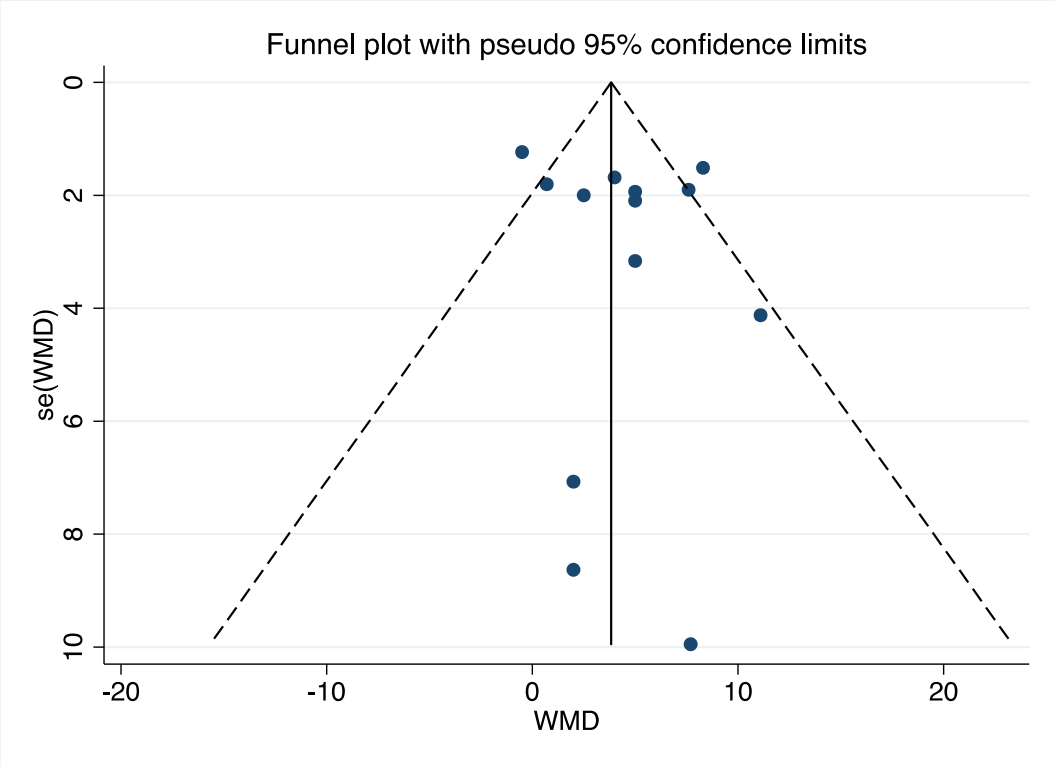
a 5 studies[11,35,42,43,48] included patients judged to have primarily OSA, but (potentially) including also some patients with CSA; in sensitivity analysis these 5 studies were classified as CSA with similar results.

Sensitivity Analyses

	WMD	(95%-CI)	I^2	N	P
Primary Analysis Result (for comparison)[2,3,6,8,11,14,22,36,38,39,41,42,45]	+4.4	(2.3 to 6.5)	63%	13	<.001*
Like primary analysis BUT…					
…using lower altitude data for one study: 1860m (vs 2590m)[11]	+4.0	(2.0 to 6.1)	64%	13	<.001*
…including only studies which clearly used inlab polysomnography (i.e. not home sleep apnea tests or similar devices) for sleep apnea assessment[2,3,6,11,22,36,38,39]	+4.1	(2.4 to 5.7)	15%	8	<.001*
…excluding a study which reported "average event SpO2 nadir"[11]	-4.3	(2.0 to 6.7)	66%	12	<.001*

Note, other sensitivity analyses performed for the AHI did not apply to the SpO2 nadir (e.g. all included studies were based on journal articles).

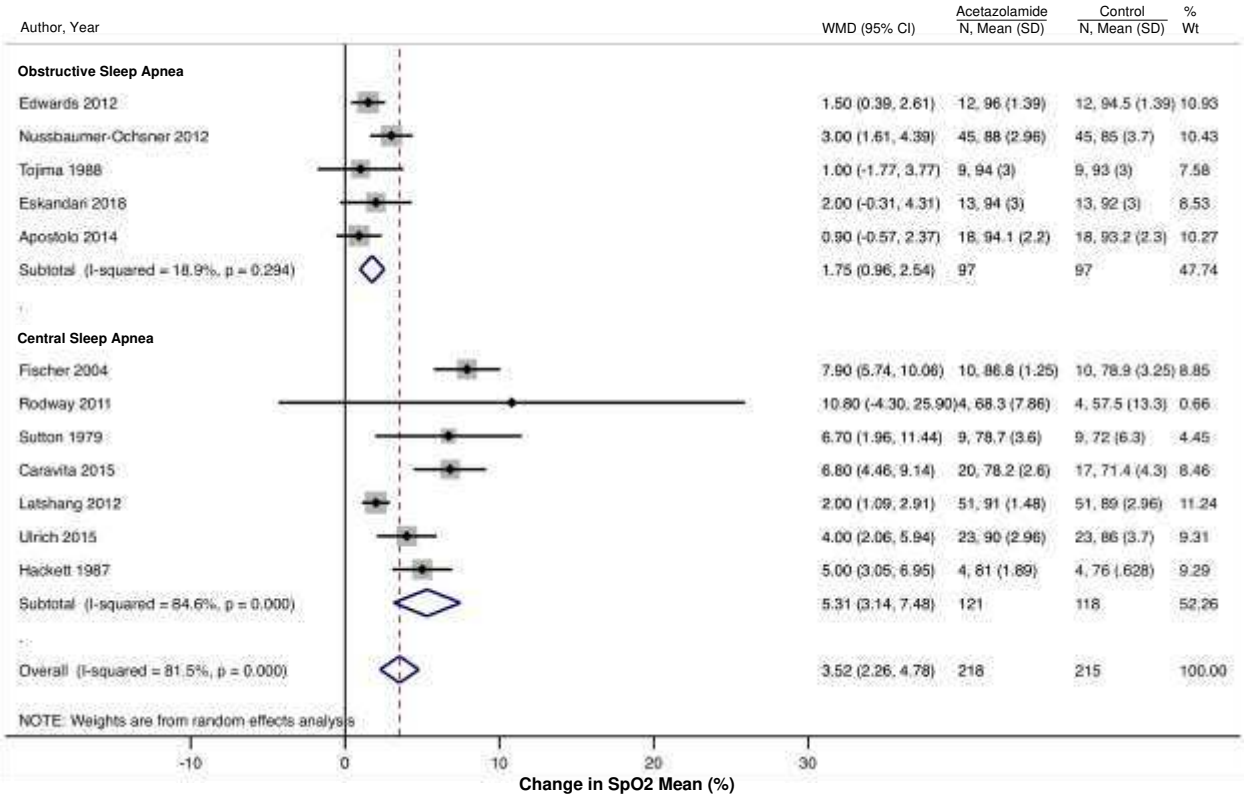
Funnel Plot



Egger's Test P=0.41

SpO_2 Mean
Forest Plot

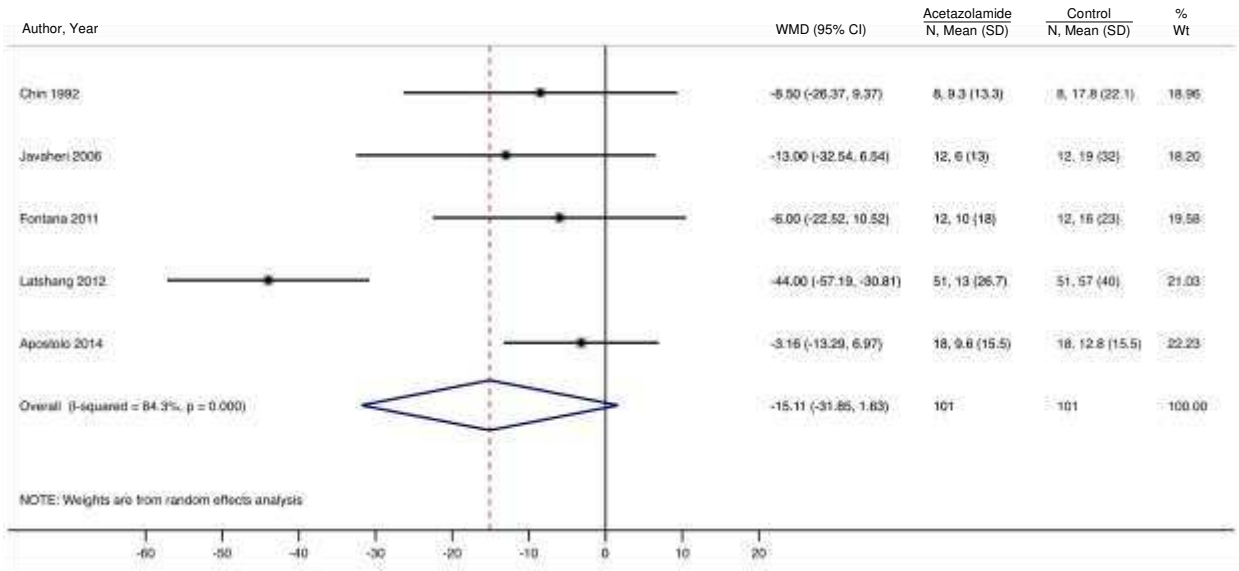
Initial analysis suggested high heterogeneity (I^2 = 82%). Exploration of potential sources via meta-regression suggested significant effect modification by obstructive vs central sleep apnea (P=0.01), thus we estimated acetazolamide's effect on SpO_2 mean separately for each group. In the subgroup of obstructive sleep apnea (OSA) heterogenetiy was low (I^2 = 19%). However, in the central sleep apnea (CSA) group heterogeneity remained high (I^2 = 85%). Except for the study by Ulrich 2015, all studies in CSA patients were performed at high altitude. Importantly, the mean SpO_2 in the control groups was much higher in studies with OSA vs CSA patients, suggesting that the observed effect modification is likely related to a.) ceiling effects, and b.) the sigmoid-shape of the oxygen dissociation curve (ODC; i.e. low baseline/control SpO_2 means are on a steeper part of the curve). Lastly note, that independent of sleep apnea type, acetazolamide consistently increased pO_2 by ~10mmHg (see the pO_2 section), but the resultant effect on the SpO_2 is in part countered by acetazolamide's effect on the pH, causing a right shift of the ODC; conceptually, the latter effect contributes relatively more to acetazolamide's net effect on the mean SpO_2 as the baseline/control pO_2 increases (i.e. flatter part of the ODC).



(analysis based on weighted mean differences, WMD)

Time with SpO_2 <90%
Forest Plot

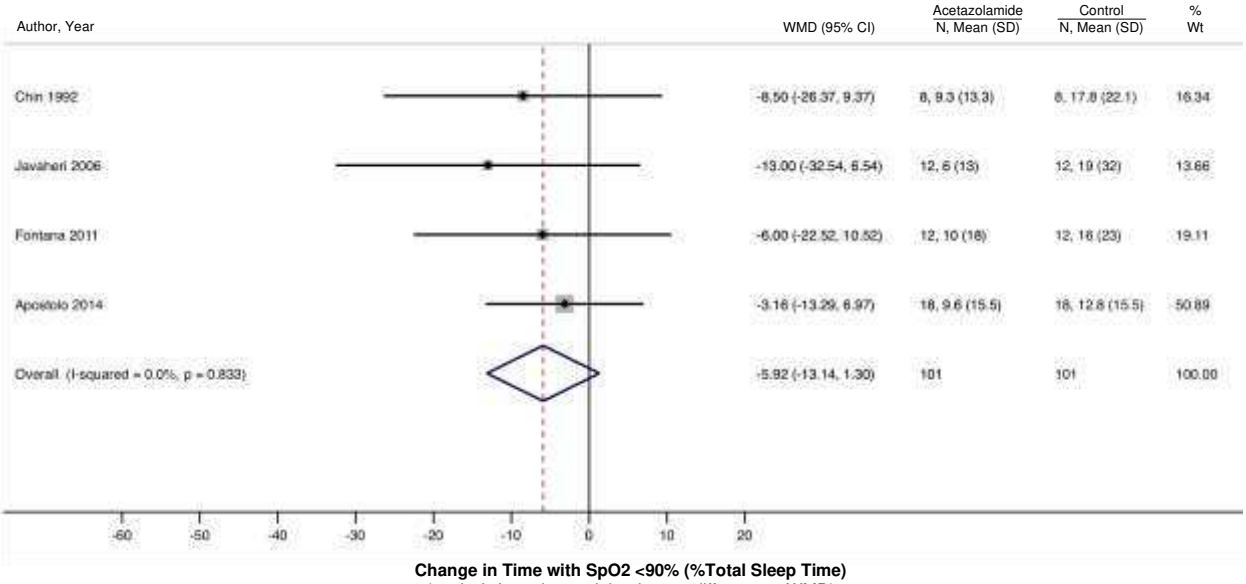
The primary analysis showed a high level of heterogeneity (I^2 = 84%):



Change in Time with SpO2 <90% (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

There were too few studies to explore potential effect modifiers via meta-regression. However, a closer inspection suggested that the main characteristic of the outlier study by Latshang 2012 was a 2-3 fold higher baseline/control of time with SpO2<90% than in any other study. Thus, we performed two *post hoc* analyses:

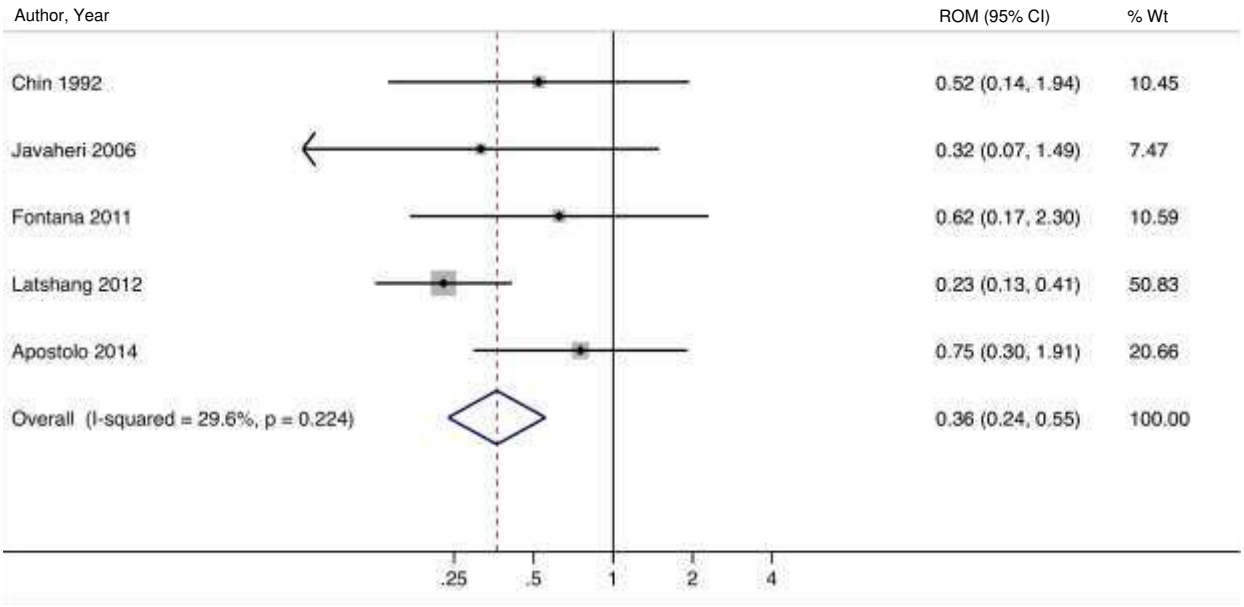
1.) Removing the study by Latshang 2012 suggested a relatively homogeneous but statistically non-significant effect in the remainder studies.



Change in Time with SpO2 <90% (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

2.) To explore, if changes in time with SpO2 <90% might better be described on a *relative* rather than on an *absolute* scale we analyzed the full dataset using the ratio of means method described by Friedrich et al 2008[50],

which suggested an overall decrease in total sleep time with SpO2<90% by 64% (95%-CI 45 to 76%) with acetazolamide vs control:



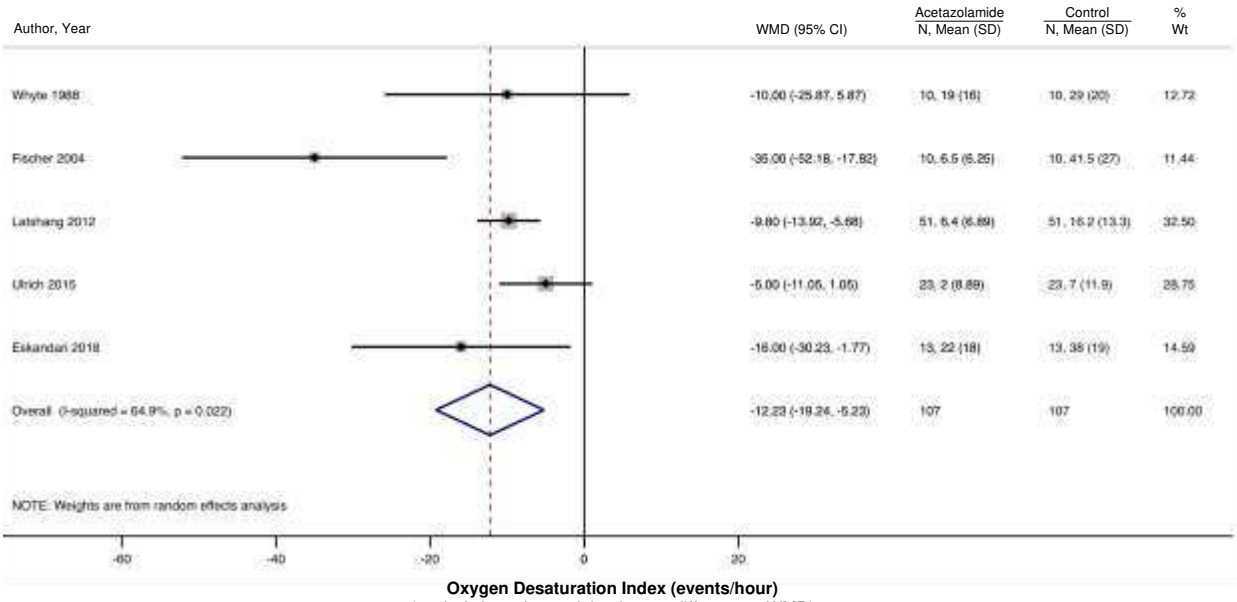
Percent of Total Sleep Time with SpO2 <90% Relative to Baseline/Control
(analysis based on weighted ratios of means, ROM)

Of note, the estimated *absolute* reduction by 15.1 %TST from the primary analysis is of similar magnitude, considering the weighted average time with SpO2 <90% in the control group was 24.8 %TST (15.1/24.8=61%).

Oxygen Desaturation Index

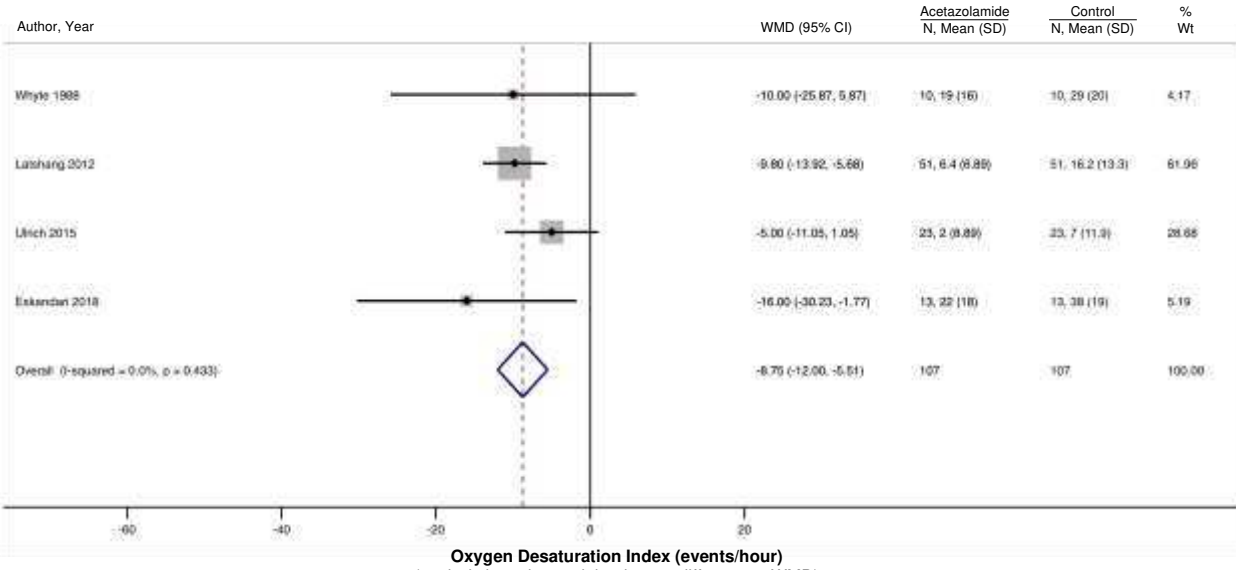
Forest Plot

In the primary meta-analysis, there was high heterogeneity (I^2=65%), which appeared to be primarily due to the outlier study by Fischer 2004. We could not identify any particular characteristic that set this study apart from the other ones included. Fischer and Whyte reported an ODI based on 4% oxygen desaturations, the other studies based on 3% oxygen desaturations.



Oxygen Desaturation Index (events/hour)
(analysis based on weighted mean differences, WMD)

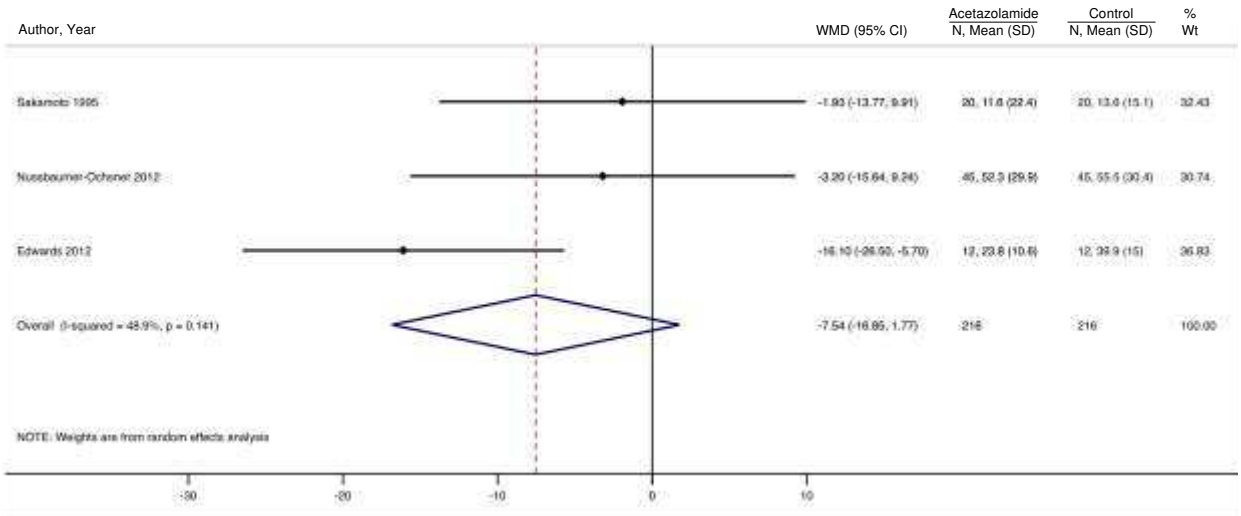
A sensitivity analysis excluding the Fischer 2004 study showed a similar reduction in ODI as in the primary analysis without heterogeneity (I^2=0%), suggesting robustness of this result.



Oxygen Desaturation Index (events/hour)
(analysis based on weighted mean differences, WMD)

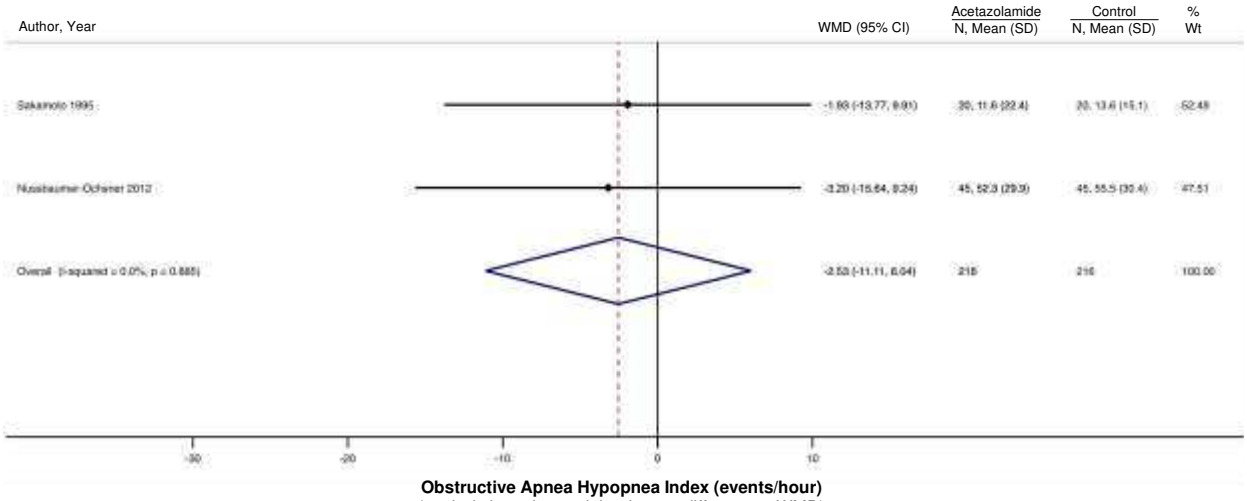
Obstructive AHI
Forest Plot

In the primary meta-analysis, there was moderate heterogeneity (I^2=49%), which appeared to be primarily due to the outlier study by Edwards 2012. In this study subjects received a higher dose of acetazolamide (1000mg/d in Edwards vs 500mg/d in Nussbaumer-Ochsner vs 399mg/d in Sakamoto), otherwise we could not identify any particular characteristic that set this study apart from the other ones included. Sakamoto reported an obstructive apnea index, whereas the other studies reported an obstructive apnea-hypopnea index. A meta-analysis based on standardized mean differences had similar results and level of heterogeneity (I^2 64%; analysis not shown).



Obstructive Apnea Hypopnea Index (events/hour)
(analysis based on weighted mean differences, WMD)

A sensitivity analysis excluding the study by Edwards 2012 resulted in a change of the effect estimate by 66% (2.53 vs 7.54), but overall results were similar in that neither analysis showed a statistically significant effect.



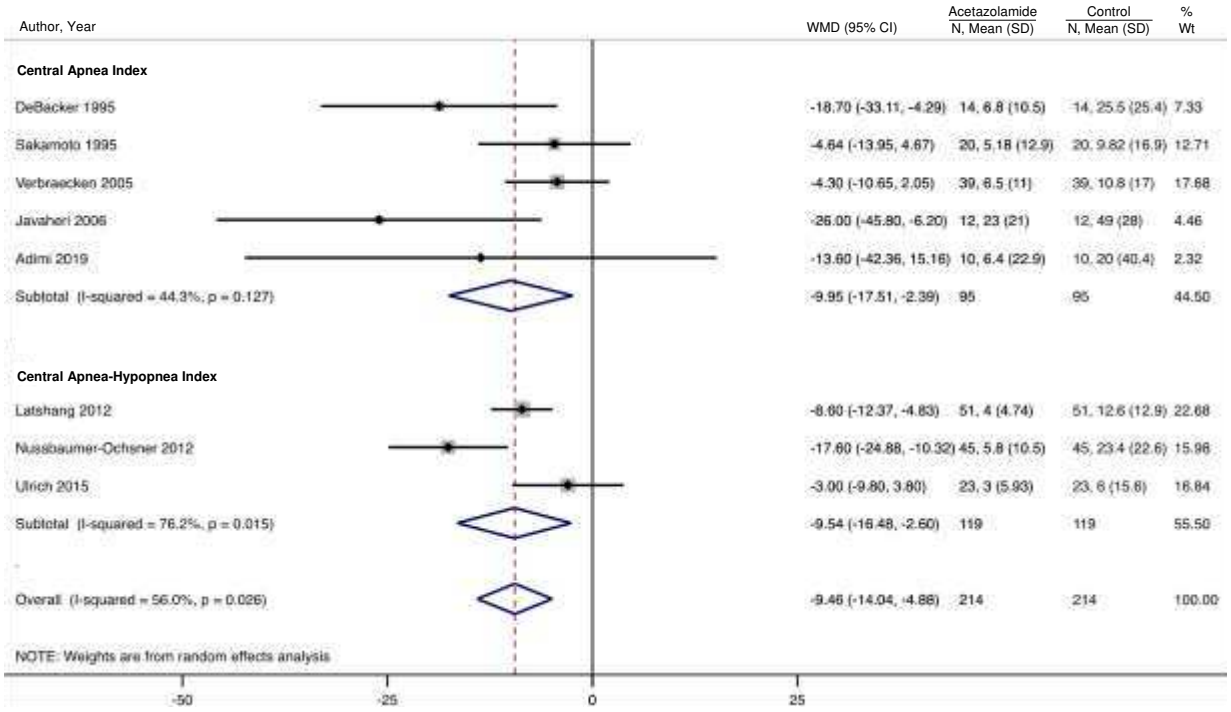
Obstructive Apnea Hypopnea Index (events/hour)
(analysis based on weighted mean differences, WMD)

Central AHI

Forest Plot

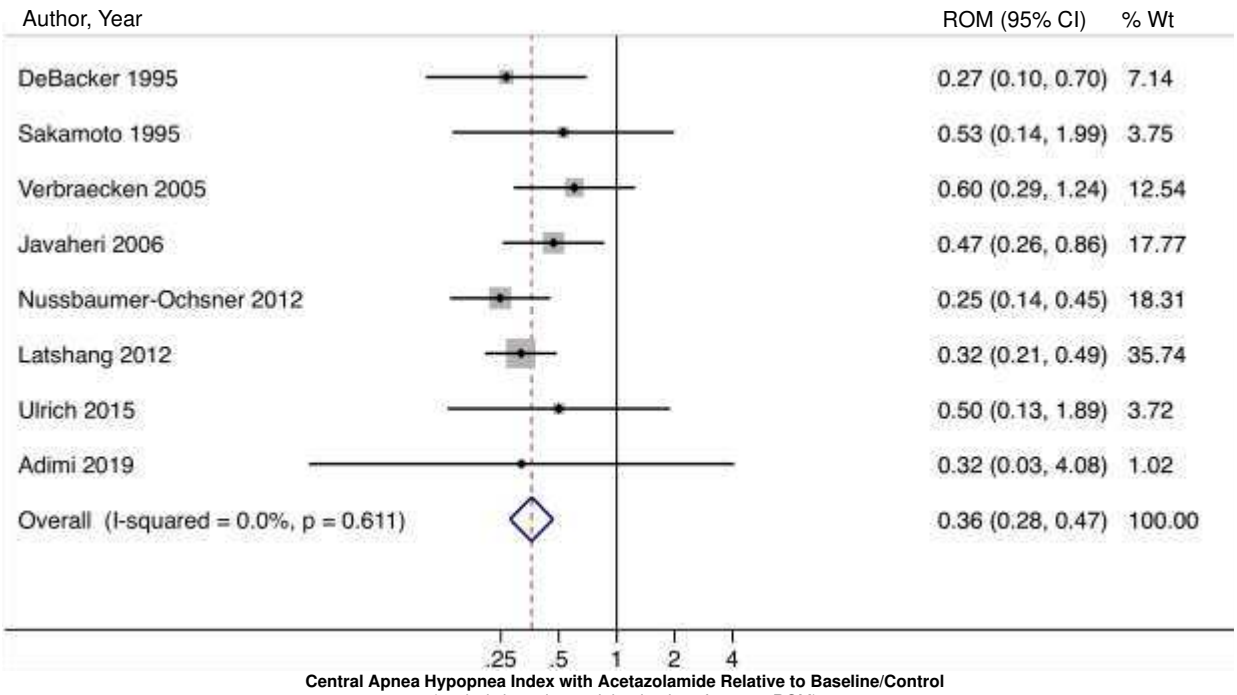
In the primary meta-analysis, there was high heterogeneity (I^2=56%).

Based on exploratory meta-regression, there was no effect modification by acetazolamide dose, days of administration or obstructive vs central sleep apnea (P>0.6 for all). Further, there was no difference between studies reporting a central apnea index vs a central apnea-hypopnea index, with high heterogeneity within both subgroups:



Furthermore, use of standardized mean difference (to take into account variations in AHI definitions) showed similar results with only a small decrease in heterogeneity (I^2 = 34.6; analysis not shown).

Reductions in CAHI seemed to be closely related to baseline CAHI levels (i.e. consistent *percent* changes rather than *absolute* changes). Formal exploration, using the ratio of means method described by Friedrich et al 2008[50], suggested a consistent overall reduction of CAHI by 64% (95%-CI 53 to 72%; I^2=0%; P<.001) by acetazolamide vs control:



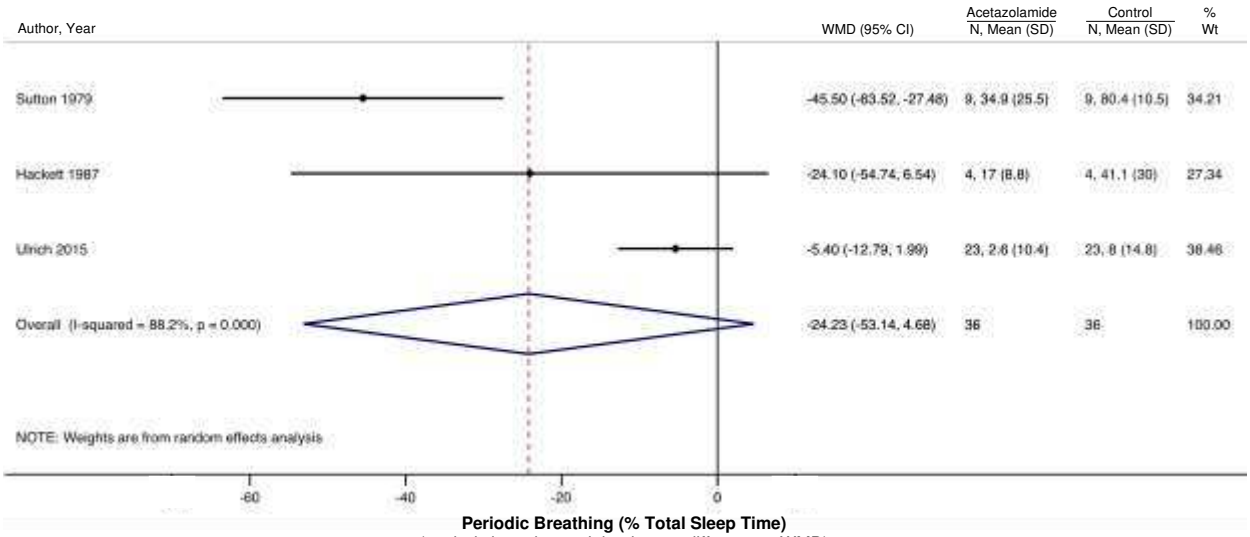
Central Apnea Hypopnea Index with Acetazolamide Relative to Baseline/Control
(analysis based on weighted ratios of means, ROM)

Of note, the estimated *absolute* reduction by 9.4 events/hour from the primary analysis is of similar magnitude considering the weighted average CAHI in the control group was 15.3 events/hour (9.4/15.3=61%).

Periodic Breathing

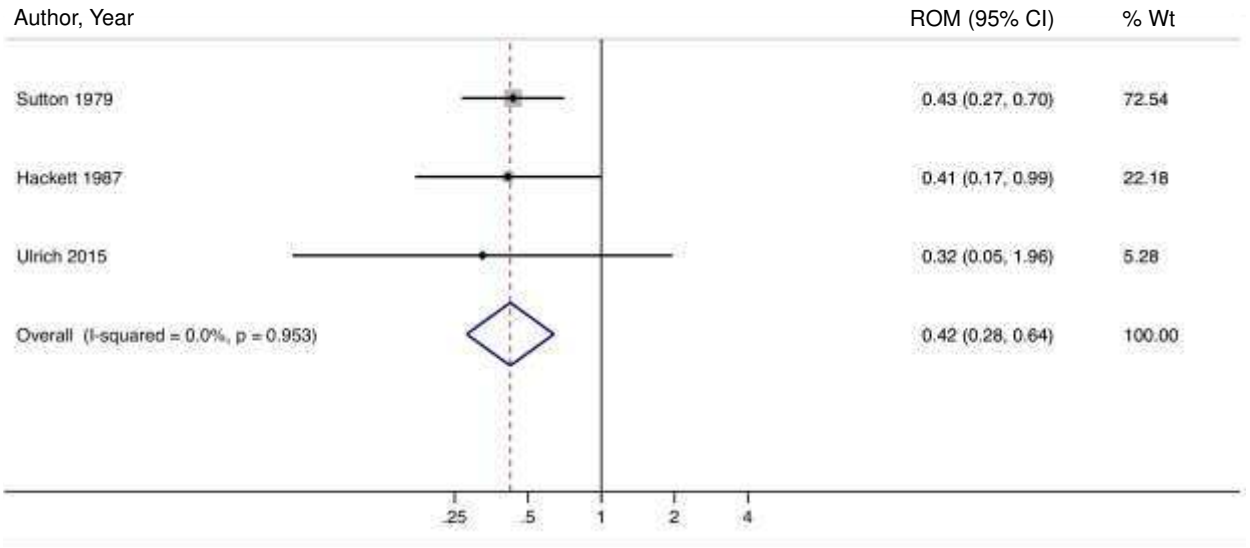
Forest Plot

Primary analysis revealed high heterogeneity (I^2=88%). Unlike the studies by Sutton and Hackett, the study by Ulrich was not performed at high altitude and used full inlab polysomnography to assess sleep disordered breathing.



Periodic Breathing (% Total Sleep Time)
(analysis based on weighted mean differences, WMD)

Further, reductions in periodic breathing appeared to be closely related to baseline levels (i.e. consistent *percent* changes rather than *absolute* changes). Formal exploration using the ratio of means method described by Friedrich et al 2008[50], suggested a consistent overall reduction of periodic breathing by 58% (95%-CI 56 to 72%; I^2=0%; P<.001) with acetazolamide vs baseline/control:



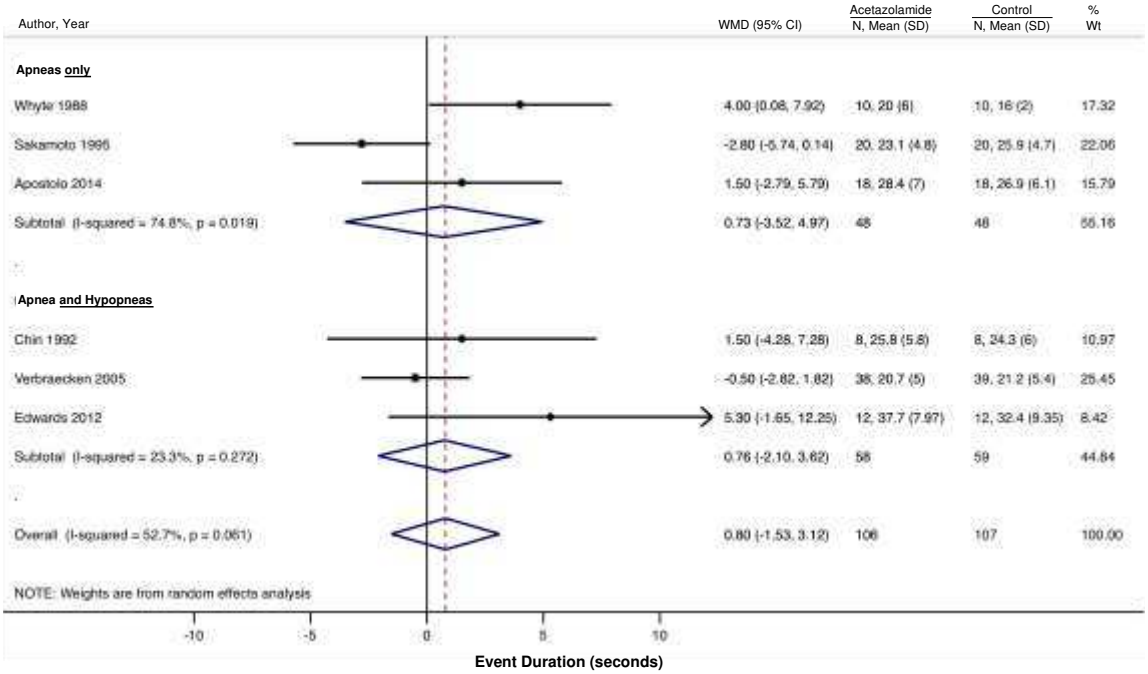
Periodic Breathing with Acetazolamide Relative to Baseline/Control
(analysis based on weighted ratios of means, ROM)

Of note, the estimated *absolute* reduction by 24.2 %TST from the primary analysis is of similar magnitude, considering the weighted average of periodic breathing in the control group was 41.8 %TST (24.2/41.8=58%).

Apnea-Hypopnea Duration

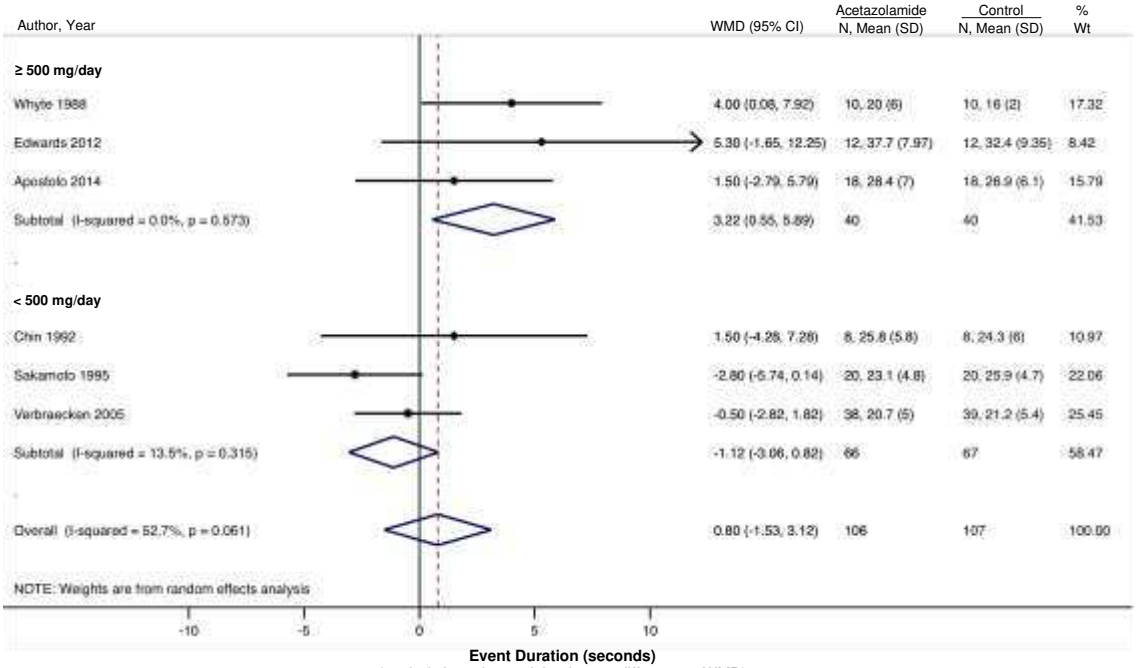
Forest Plot

Primary analysis revealed high heterogeneity (I^2=53%). Some studies reported event duration based on apneas only vs apneas+hypopneas, but heterogeneity was high within both groups.



(analysis based on weighted mean differences, WMD)

Exploratory meta-regression failed to show clear effect modification by acetazolamide dose (P=0.053). However, sample size was small and inspection of the forest plot suggested that much of the heterogeneity was explained by dose; in the subgroup of studies administering ≥500mg/day of acetazolamide there was a significant increase of event duration, whereas event duration did not change in the subgroup of studies administering <500mg/day:

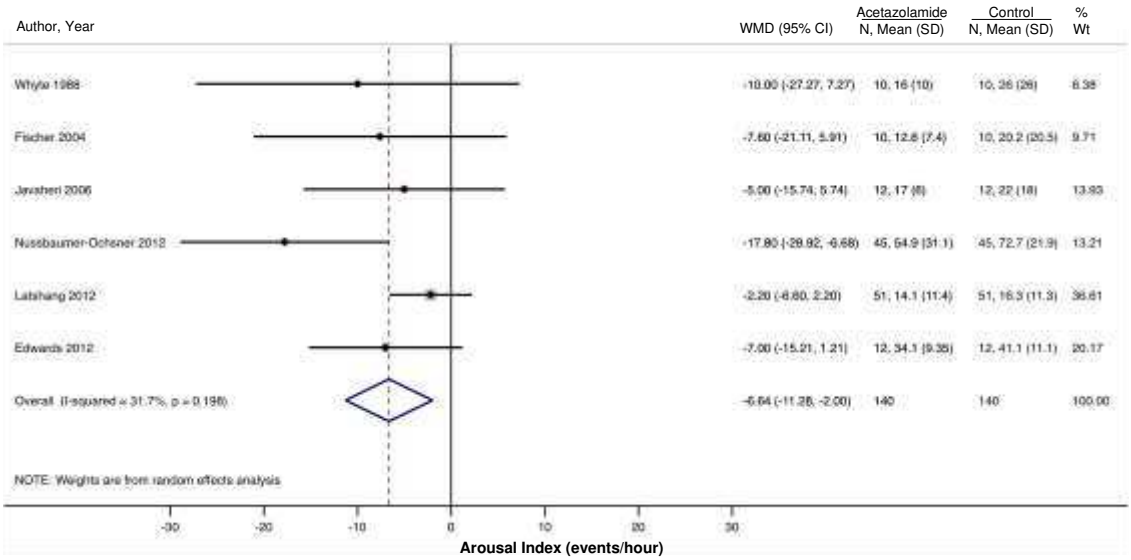


(analysis based on weighted mean differences, WMD)

Arousal Index

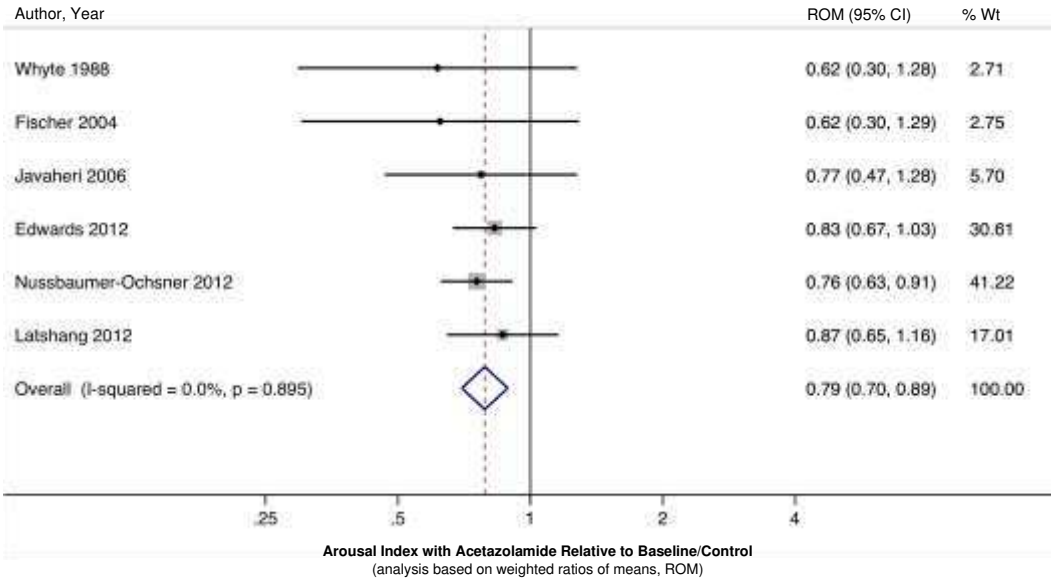
Forest Plot

Primary analysis revealed moderate heterogeneity (I^2=32%). We did not identify any significant effect modifier (e.g. except for Javaheri all studies administered ≥500mg/day).



(analysis based on weighted mean differences, WMD)

But reductions in arousal index appeared to be closely related to baseline levels (i.e. consistent *percent* changes rather than *absolute* changes). Formal exploration using the ratio of means method described by Friedrich et al 2008[50], suggested a consistent overall reduction of arousal indices by 21% (95%-CI 11 to 30%; I^2=0%; P<.001) with acetazolamide vs control:

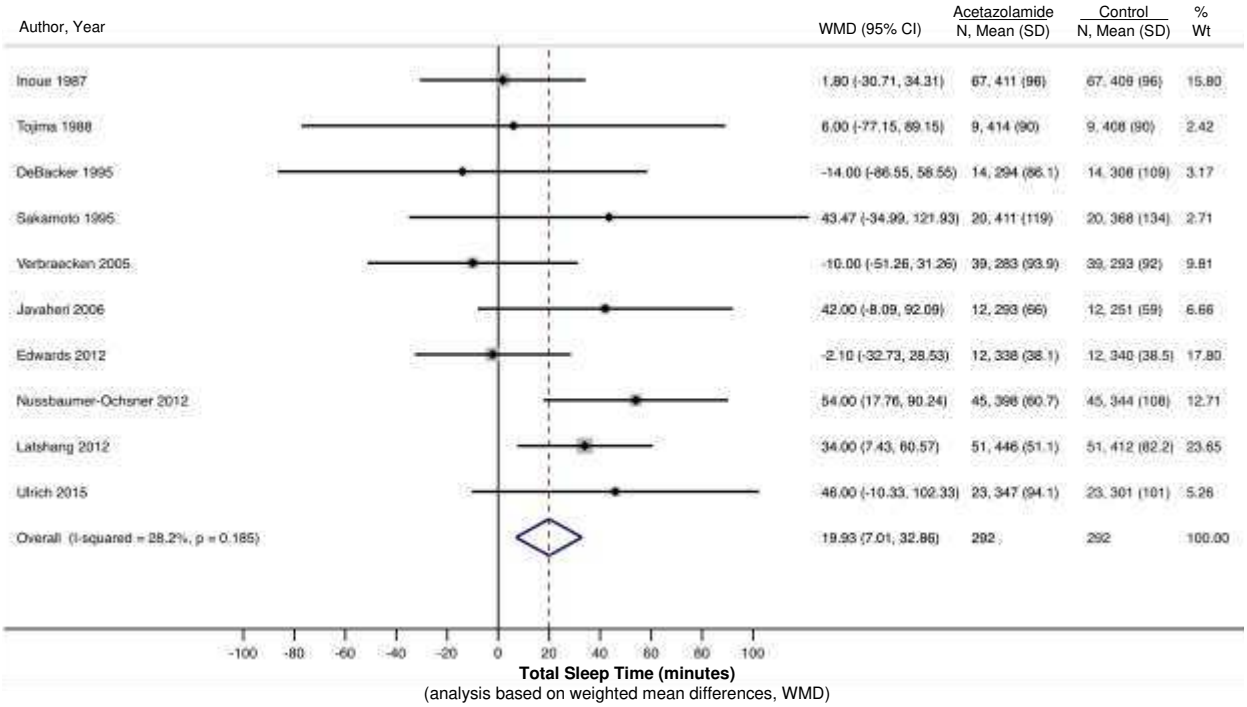


(analysis based on weighted ratios of means, ROM)

Of note, the estimated *absolute* reduction by 6.6/h from the primary analysis is of similar magnitude, considering the weighted average arousal index in the control group was 30.5/h (6.6/30.5=22%). Lastly, note that all included studies were randomized trials, suggesting that the improvement in arousal indices was not due to confounding by first night effects (i.e. control during first night & acetazolamide during subsequent night).

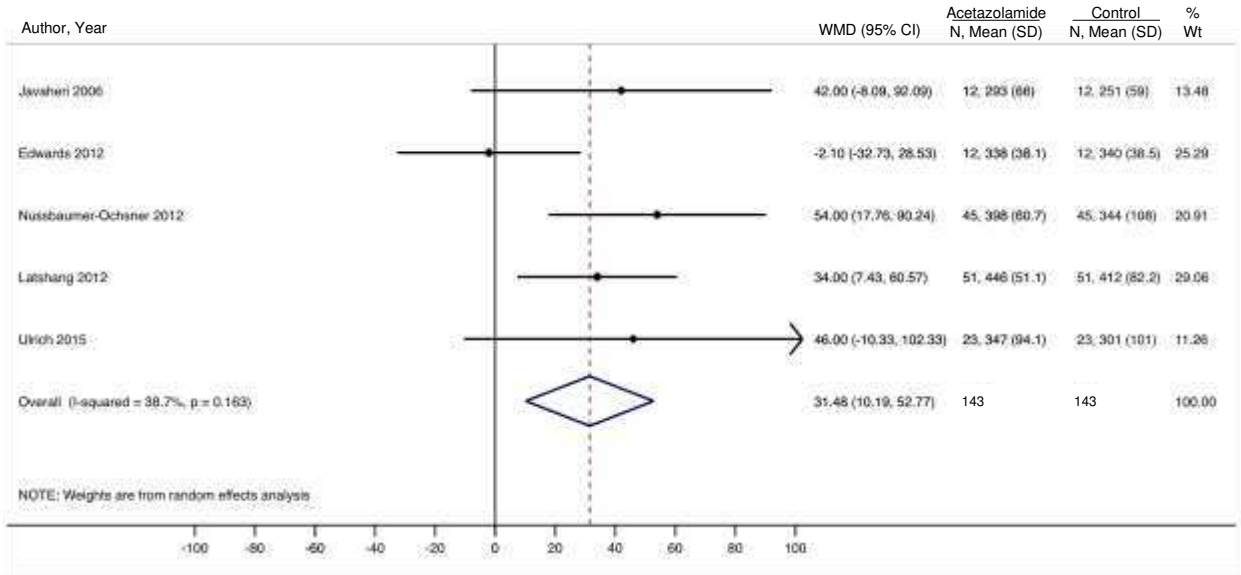
Total Sleep Time
Forest Plots

Primary analysis showed low heterogeneity (I^2=28%):



(analysis based on weighted mean differences, WMD)

Results were similar when including only randomized trials suggesting that the increase in total sleep time was not due to confounding by first night effects (i.e. baseline/control during first night & acetazolamide during subsequent night):

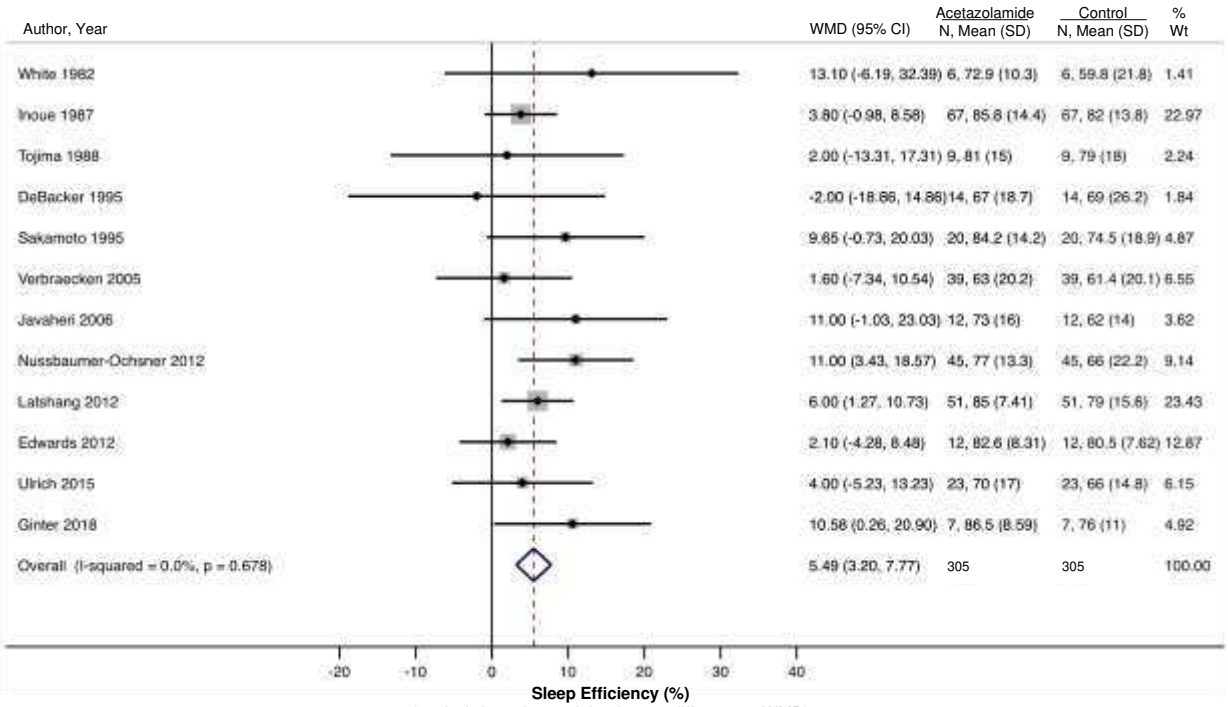


(analysis based on weighted mean differences, WMD)

Sleep Efficiency

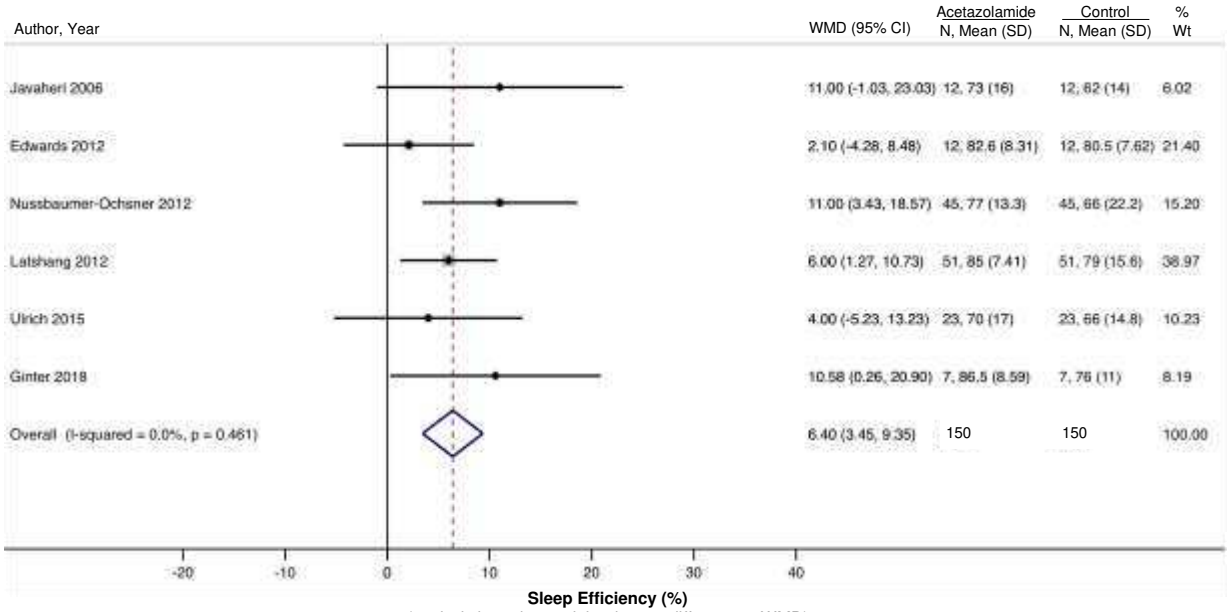
Forest Plot

Primary analysis showed low heterogeneity (I^2=0%):



(analysis based on weighted mean differences, WMD)

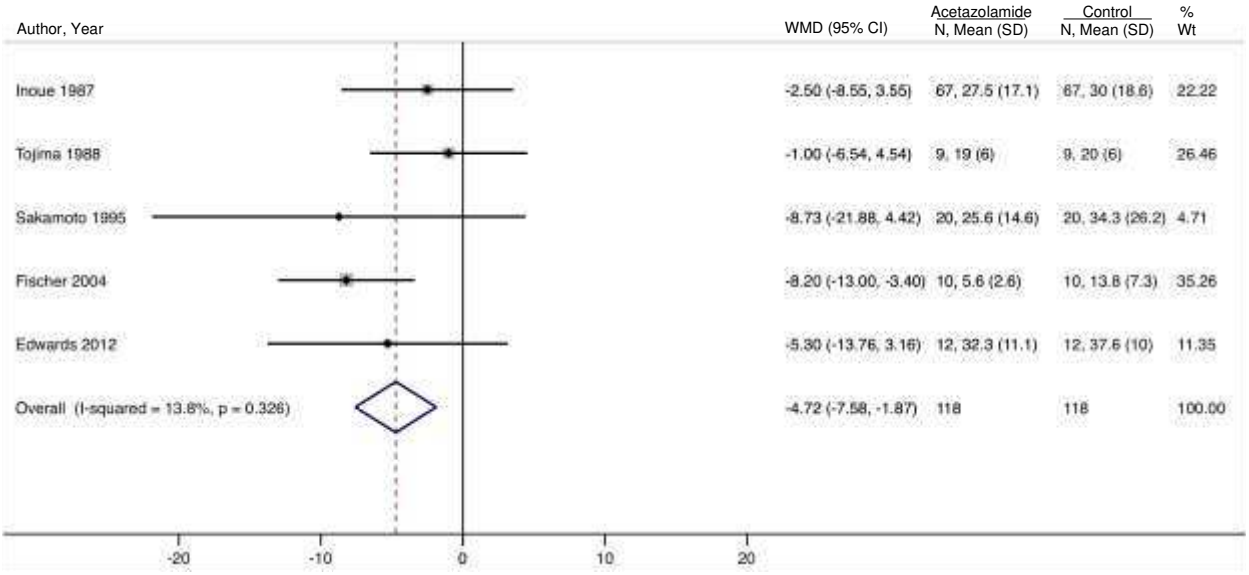
Results were similar when including only randomized trials, suggesting that the improvement in sleep efficiency was not due to confounding by first night effects (i.e. baseline/control during first night & acetazolamide during subsequent night):



(analysis based on weighted mean differences, WMD)

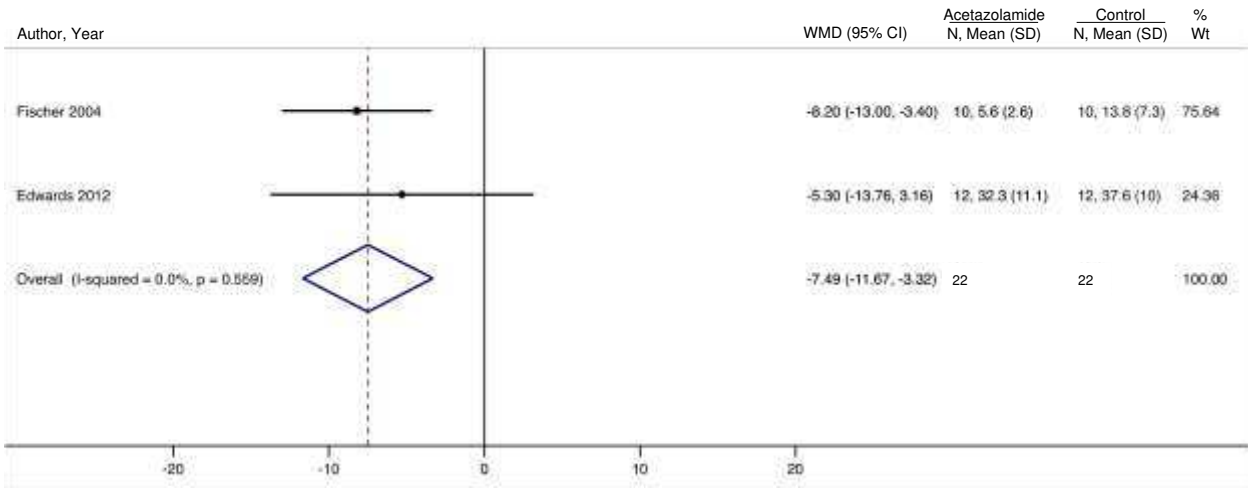
Stage N1
Forest Plots

Primary analysis showed low heterogeneity (I^2=14%):



Stage N1 (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

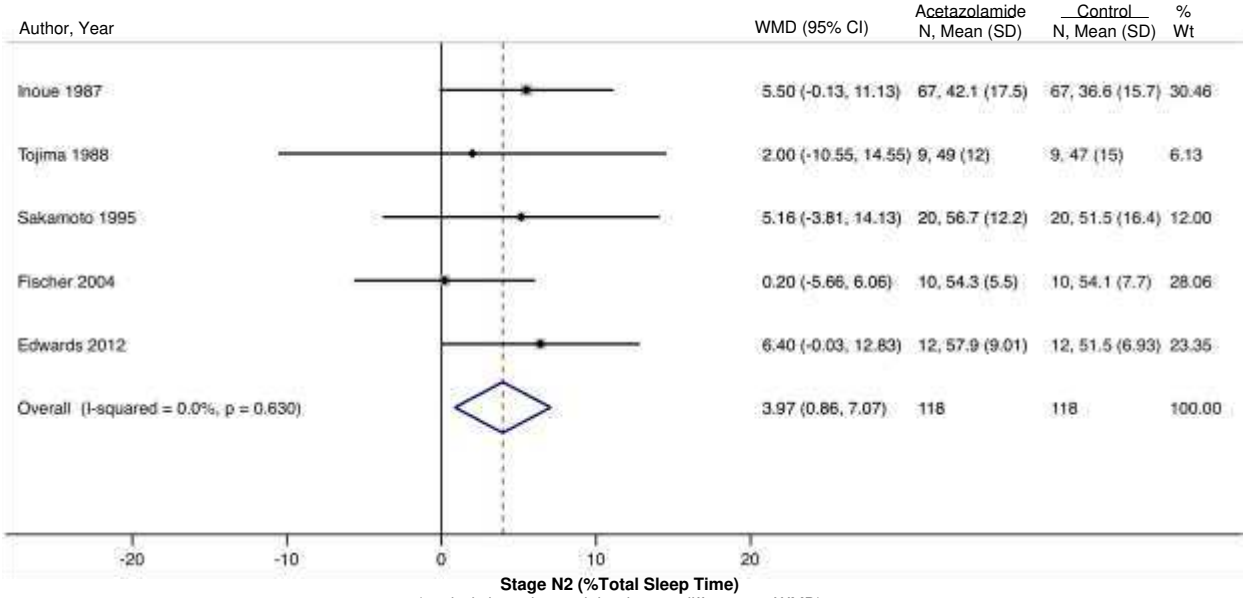
Results were similar when including only randomized trials, suggesting that the reduction in stage 1 sleep was not due to confounding by first night effects (i.e. baseline/control during first night & acetazolamide during subsequent night):



Stage N1 (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

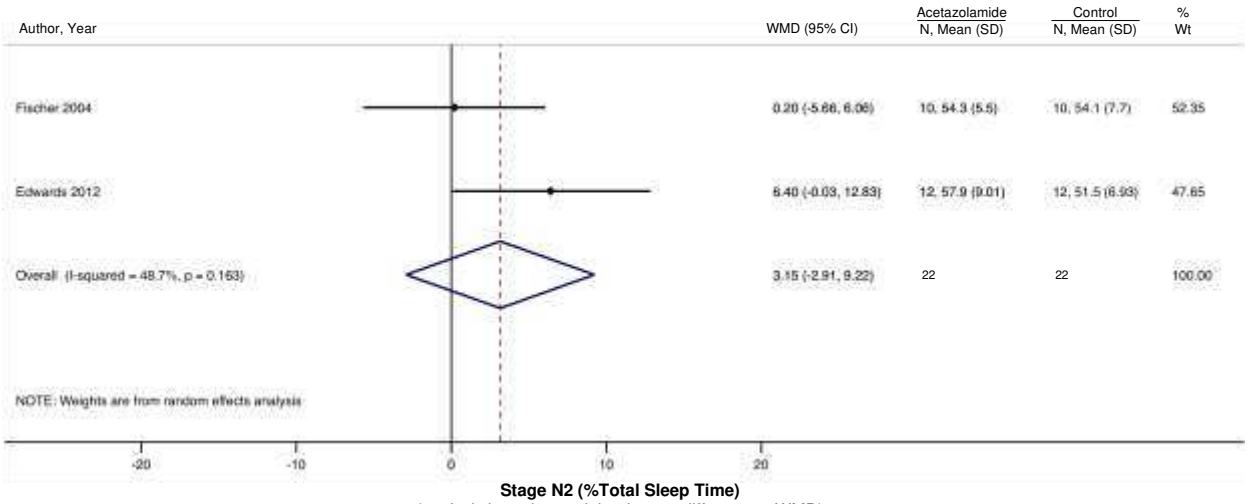
Stage N2
Forest Plot

Primary analysis showed low heterogeneity (I^2=0%):



Stage N2 (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

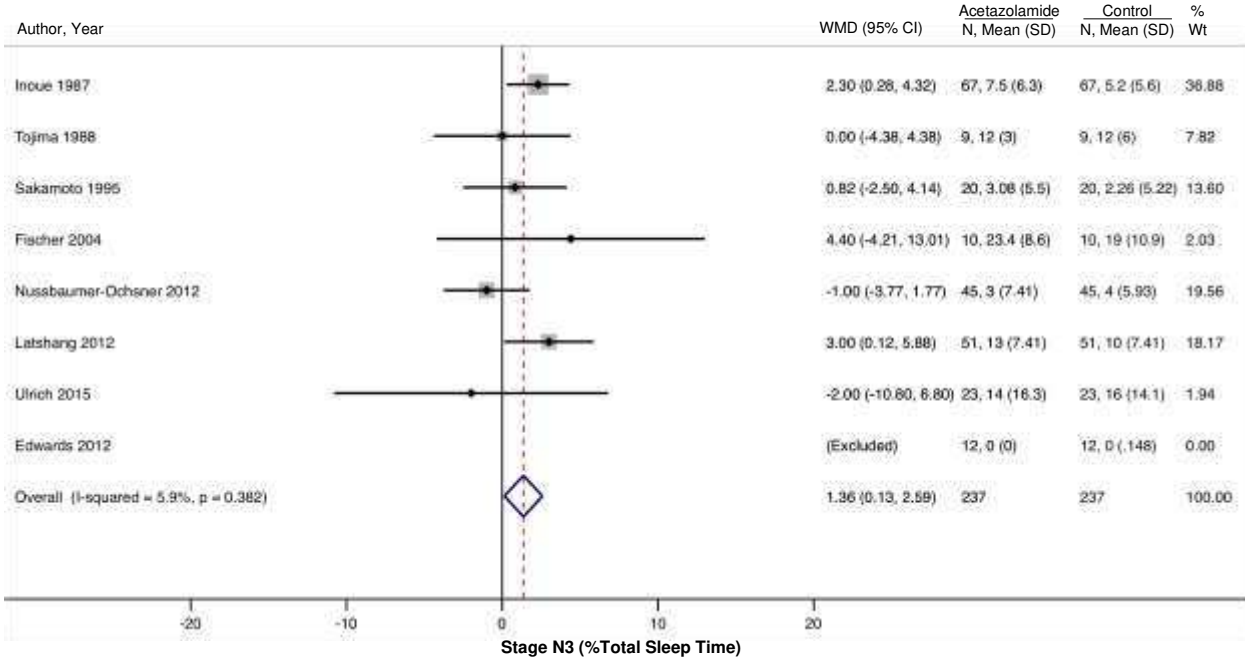
In a sensitivity analysis including only randomized trials, the effect estimate was similar, but results were statistically non-significant and heterogeneity was high based on I^2=49%:



Stage N2 (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

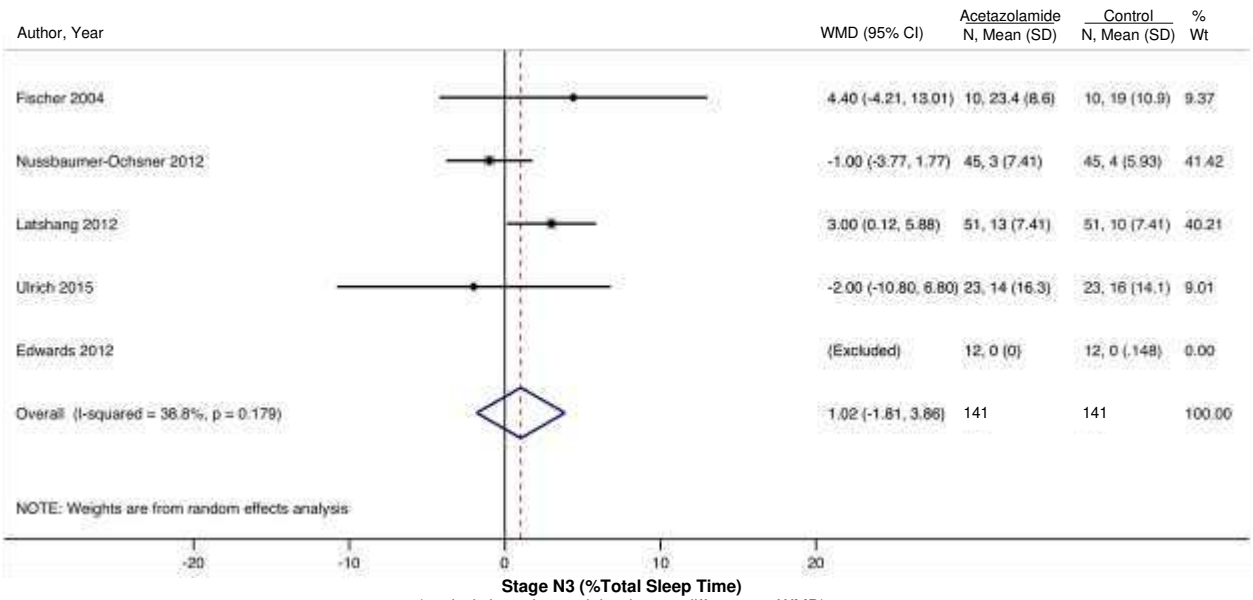
Stage N3
Forest Plot

Primary analysis showed low heterogeneity (I^2=6%):



Stage N3 (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

In a sensitivity analysis including only randomized trials, the effect estimate was similar, but results were statistically non-significant and heterogeneity was high based on I^2=39%.

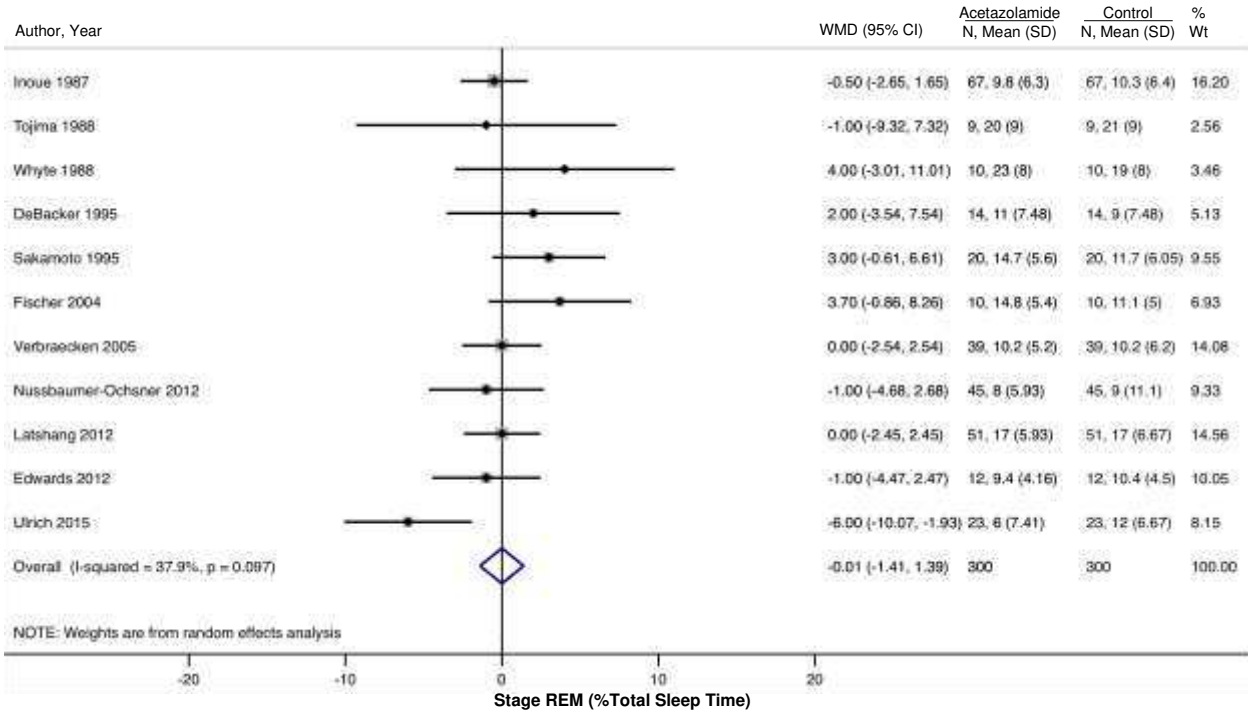


Stage N3 (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

Stage REM

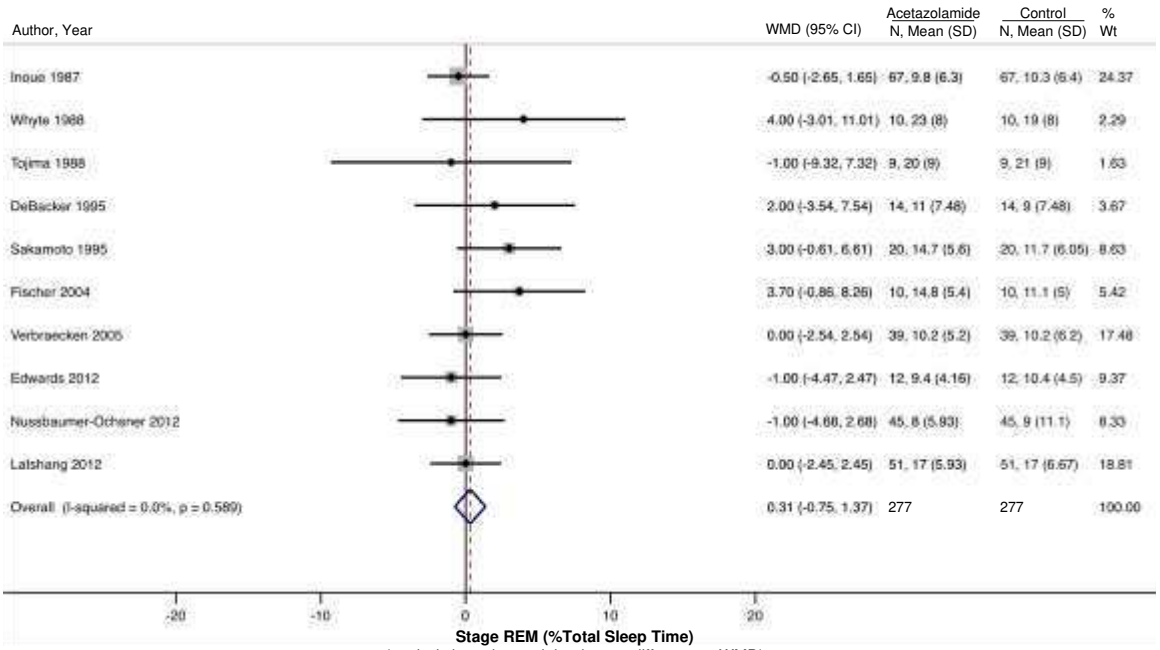
Forest Plot

Primary analysis showed moderate heterogeneity (I^2=38%):



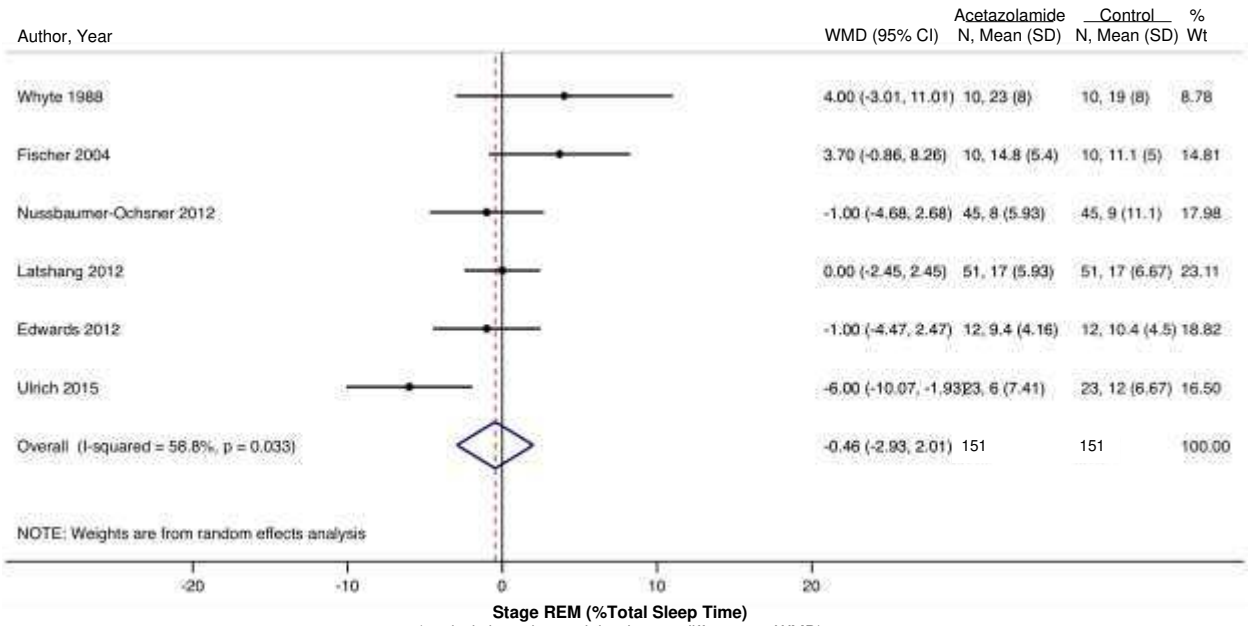
(analysis based on weighted mean differences, WMD)

Based on meta-regression, there was no effect modification by acetazolamide dose (P=.94), days of administration (P=.16) or obstructive vs central sleep apnea (P=.75). Heterogeneity was primarily due to the study by Ulrich – we did not identify any clear reason that would explain the reduction in REM sleep in the study by Ulrich, but when removing it in a sensitivity analysis then the results were similar as in the primary analysis but with low heterogeneity (I^2=0%):



(analysis based on weighted mean differences, WMD)

Results were also similar in another sensitivity analysis when including only randomized trials, suggesting that the results from the primary analysis were not confounded by first night effects (i.e. baseline/control during first night & acetazolamide during subsequent night):

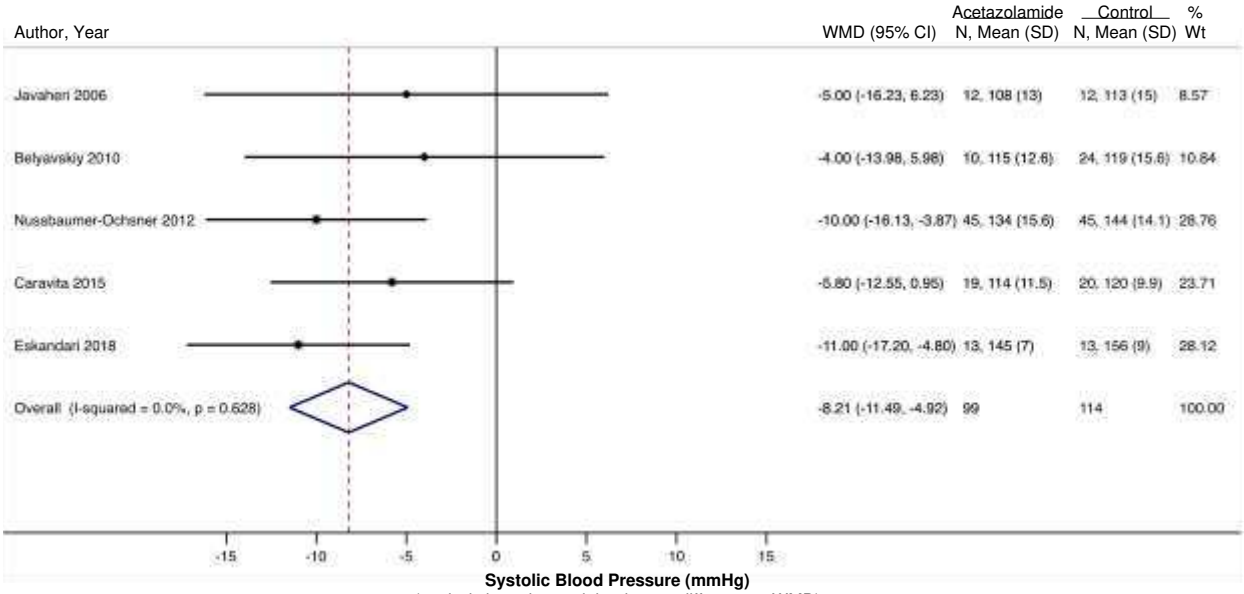


Stage REM (%Total Sleep Time)
(analysis based on weighted mean differences, WMD)

Systolic Blood Pressure

Forest Plot

Primary analysis showed low heterogeneity (I^2=0%):

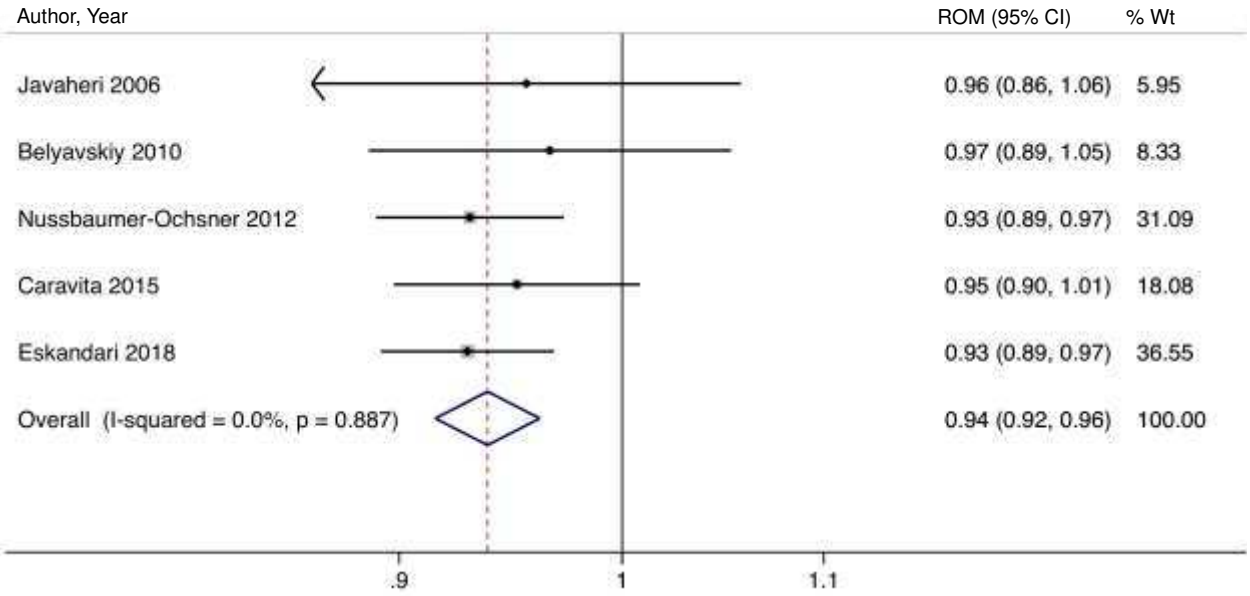


In three studies the control blood pressure was within the normal range 113-120mmHg, whereas in two studies the control blood pressure was in the hypertensive range (144-156mmHg). In the latter two studies (Nussbaumer & Eskandari), the reduction in BP appeared to be more pronounced (10-11mmHg vs 4-6mmHg). The number of studies was too small to test for effect modification via meta-regression; a qualitative assessment of different study characteristics demonstrated that in these two studies the majority of hypertensive subjects were untreated. Otherwise we did not identify any other potential modifying factor:

Study	Sleep Apnea Type	Dose	% HTN Diagnosis	% On Anti-hypertensives
Javaheri	CHF+CSA	281mg/d (3.5-4mg/kg/d)	na	83% ACE; 33% BB
Belyavskiy	CHF+OSA	36mg/d (250mg/wk)	na	100% ACE; ?87% BB
Nussbaumer	OSA+CSA-HA	500mg/d	69%	29%
Caravita	CSA-HA	500mg/d	na (healthy subjects)	na (healthy subjects)
Eskandari	OSA	659mg/d (500-750mg/d)	100% (by design)	0% (by design)

Abbreviations: CHF congestive heart failure, CSA central sleep apnea, OSA obstructive sleep apnea, HA high altitude, HTN systemic hypertension, ACE angiotensin converting enzyme inhibitor, BB beta blocker

Since reductions in systolic blood pressure appeared to be related to baseline levels (i.e. consistent *percent* changes rather than *absolute* changes), we performed a sensitivity analysis based on the ratio of means method described by Friedrich et al 2008[50], which suggested a consistent overall reduction of systolic blood pressure by 6% (95%-CI 4 to 8%; I^2=0%; P<.001) with acetazolamide vs control:



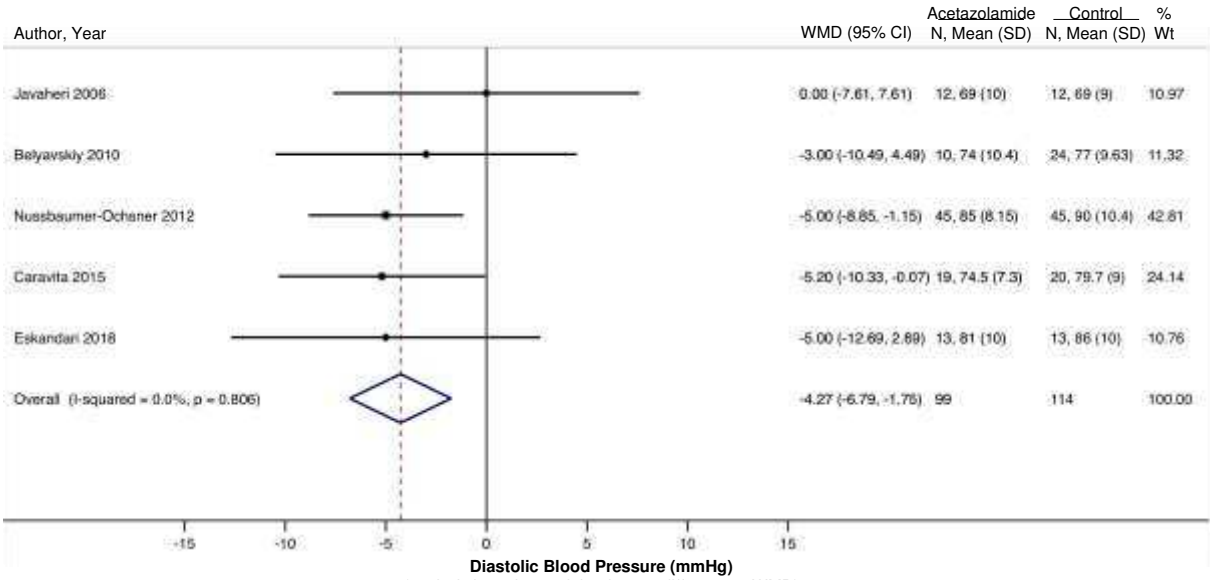
Systolic Blood Pressure with Acetazolamide Relative to Baseline/Control
(analysis based on weighted ratios of means, ROM)

Of note, the estimated *absolute* reduction by 8.2mmHg from the primary analysis is of similar magnitude, considering the weighted average systolic blood pressure in the control group was 136.2mmHg (8.2/136.2=6%).

Diastolic Blood Pressure

Forest Plot

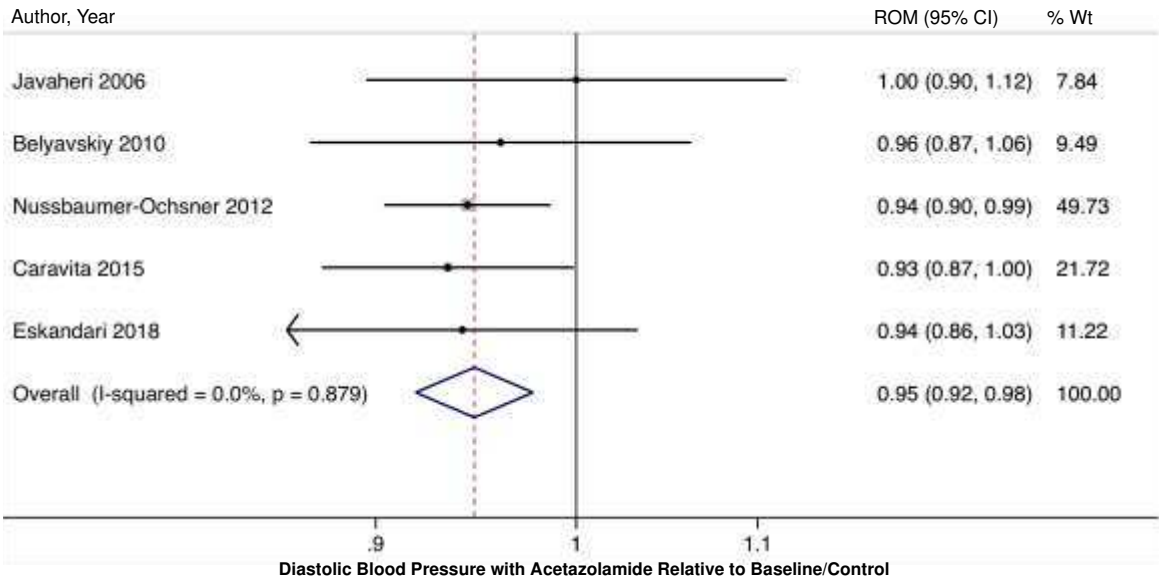
Primary analysis showed low heterogeneity (I^2=0%):



(analysis based on weighted mean differences, WMD)

Of note, the only study with a non-negative effect estimate (by Javaheri) had the lowest baseline/control diastolic blood pressure (69mmHg vs 77-90mmHg).

A sensitivity analysis based on the ratio of means method described by Friedrich et al 2008[50], which takes into account the baseline blood pressure, suggested a consistent overall reduction of diastolic blood pressure by 5% (95%-CI 2 to 8%; I^2=0%; P=.001) with acetazolamide vs control:

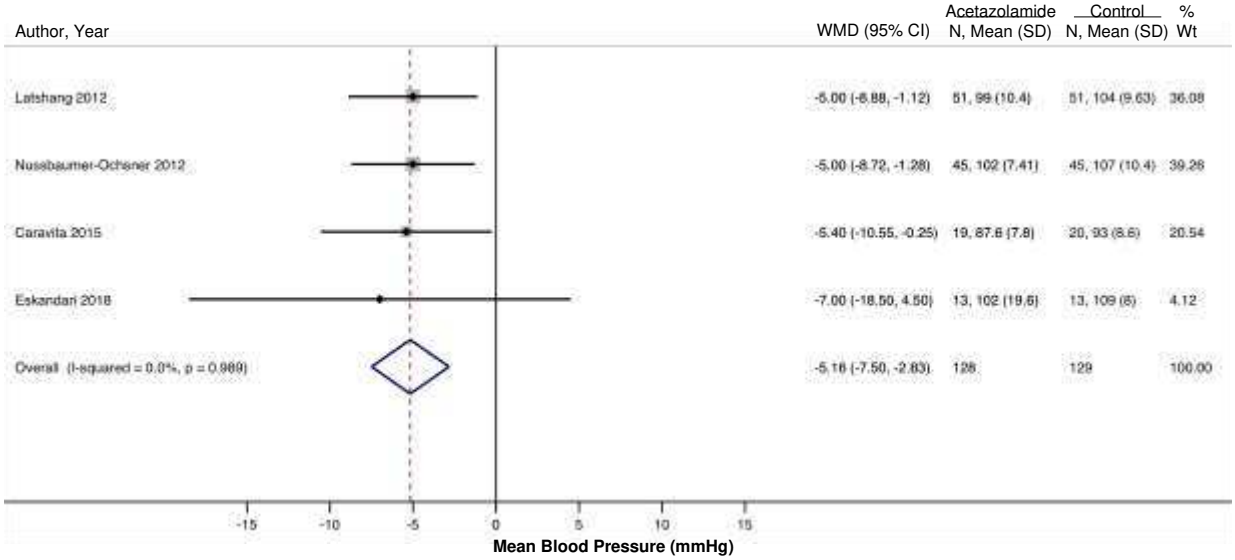


(analysis based on weighted ratios of means, ROM)

Of note, the estimated *absolute* reduction by 4.3mmHg from the primary analysis is of similar magnitude, considering the weighted average diastolic blood pressure in the control group was 83.3mmHg (4.3/83.3=5%).

Mean Blood Pressure
Forest Plot

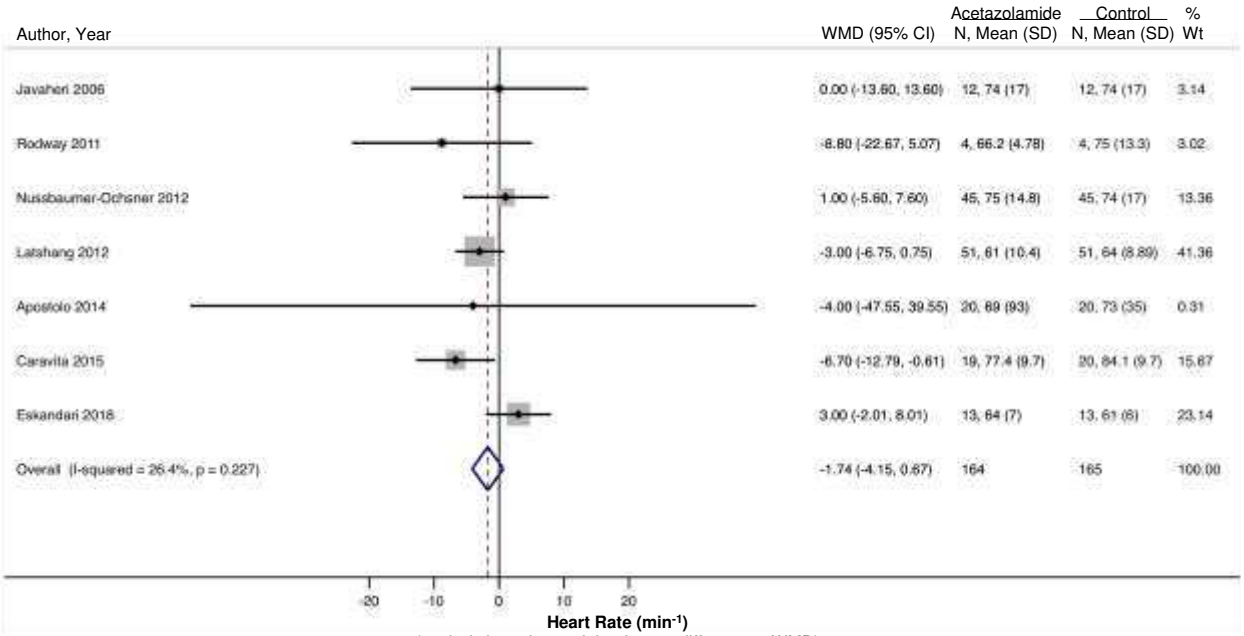
Primary analysis showed low heterogeneity (I^2=0%):



(analysis based on weighted mean differences, WMD)

Heart Rate
Forest Plot

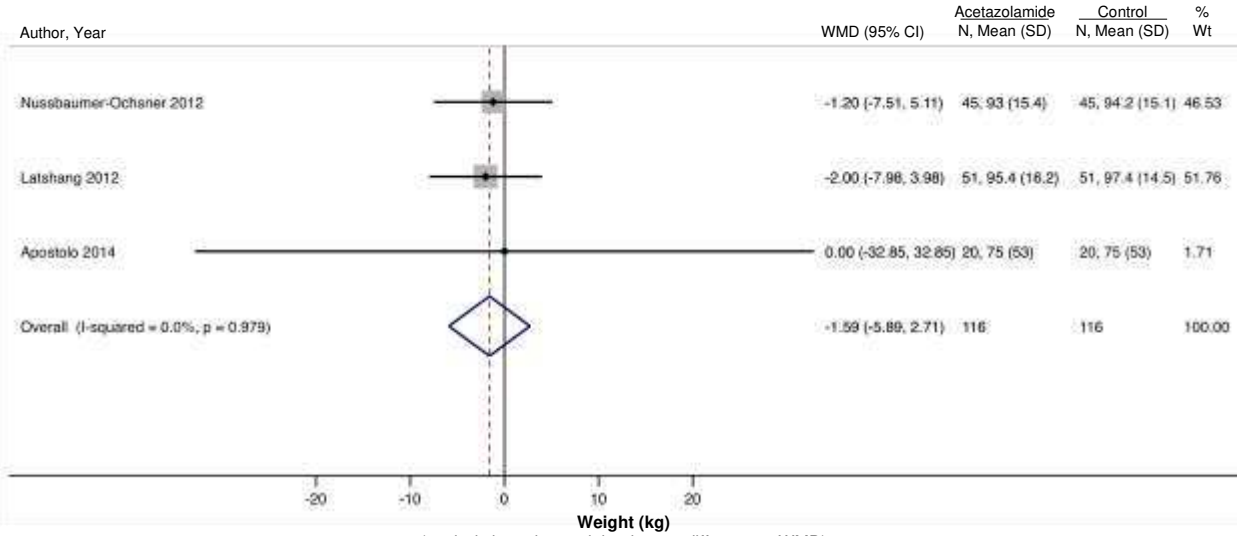
Primary analysis showed low heterogeneity (I^2=26%):



(analysis based on weighted mean differences, WMD)

Weight
Forest Plot

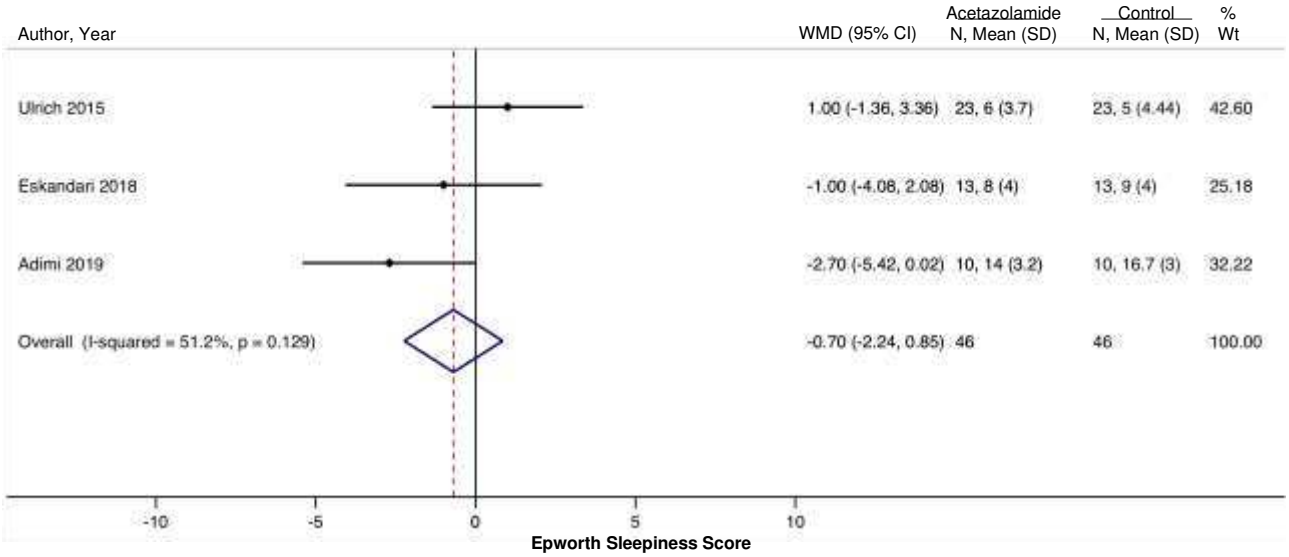
Primary analysis showed low heterogeneity (I^2=0%):



(analysis based on weighted mean differences, WMD)

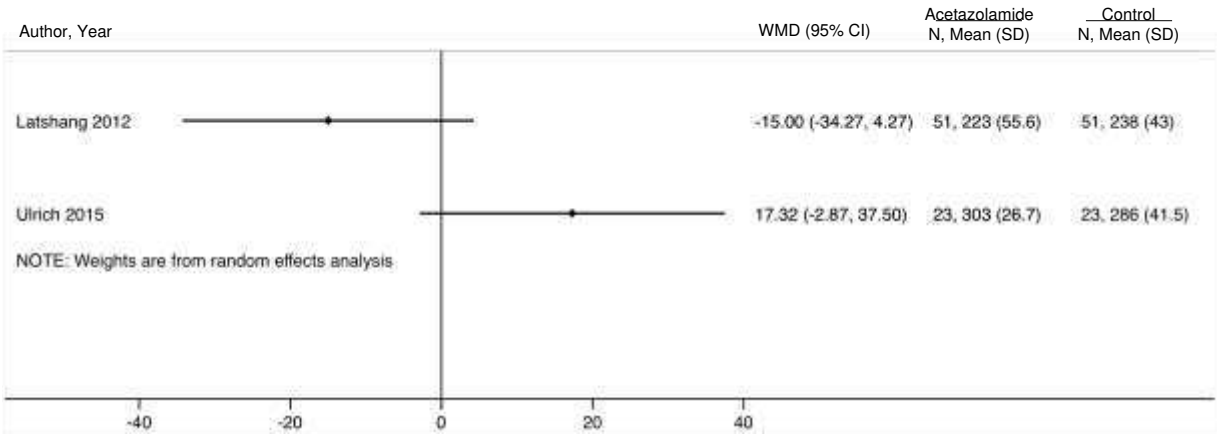
Epworth Sleepiness Score (ESS)
Forest Plot

Primary analysis showed high heterogeneity (I^2=51%):



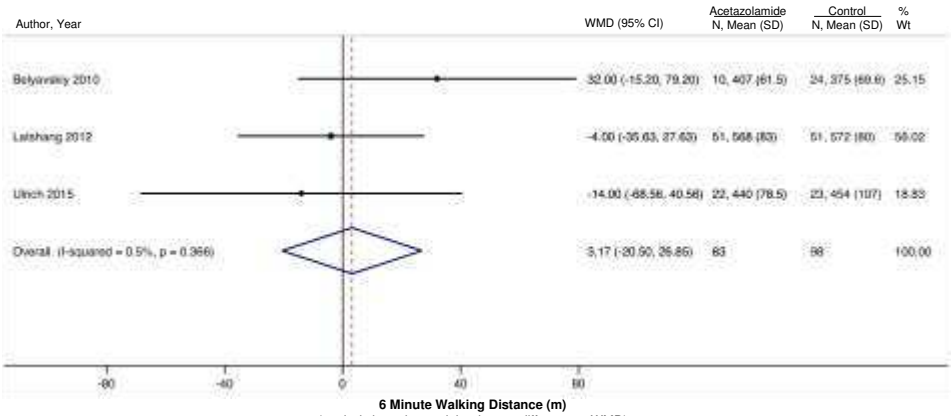
Of note, the only study with a baseline ESS within the abnormal range (>10) was the study by Adimi; one may speculate that the varying baseline scores may be the primary source of heterogeneity.

Psychomotor Vigilance Test (PVT)
Forest Plot



Psychomotor Vigilance Test (reaction speed in ms)
(analysis based on weighted mean differences, WMD)

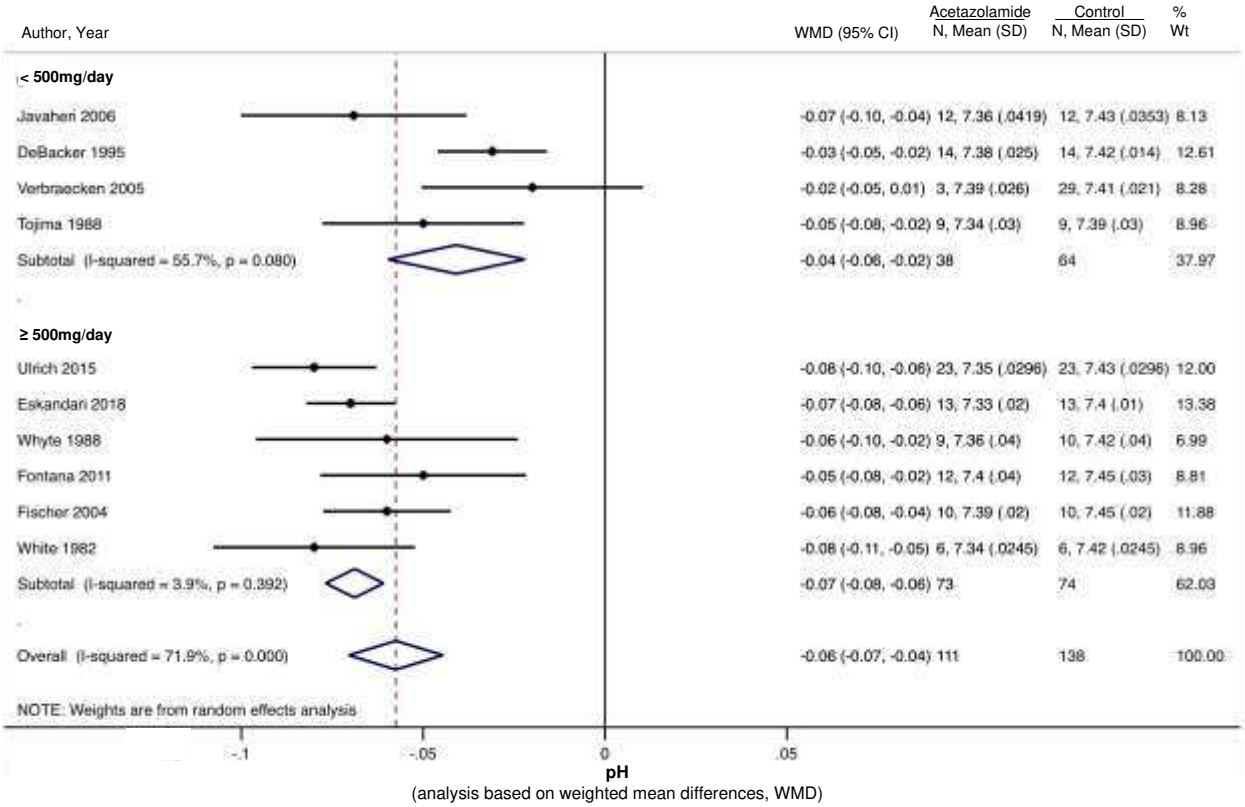
6-Minute Walking Distance
Forest Plot



(analysis based on weighted mean differences, WMD)

PH
Forest Plot

Primary analysis showed high heterogeneity (I^2=72%). Based on meta-regression there was no significant effect modification by duration of acetazolamide administration (P=.41), obstructive vs central sleep apnea (P=.72) or acetazolamide dose (P=0.053). Exploration of dose as a potential effect modifier suggested larger pH reductions in studies which administered higher acetazolamide doses:



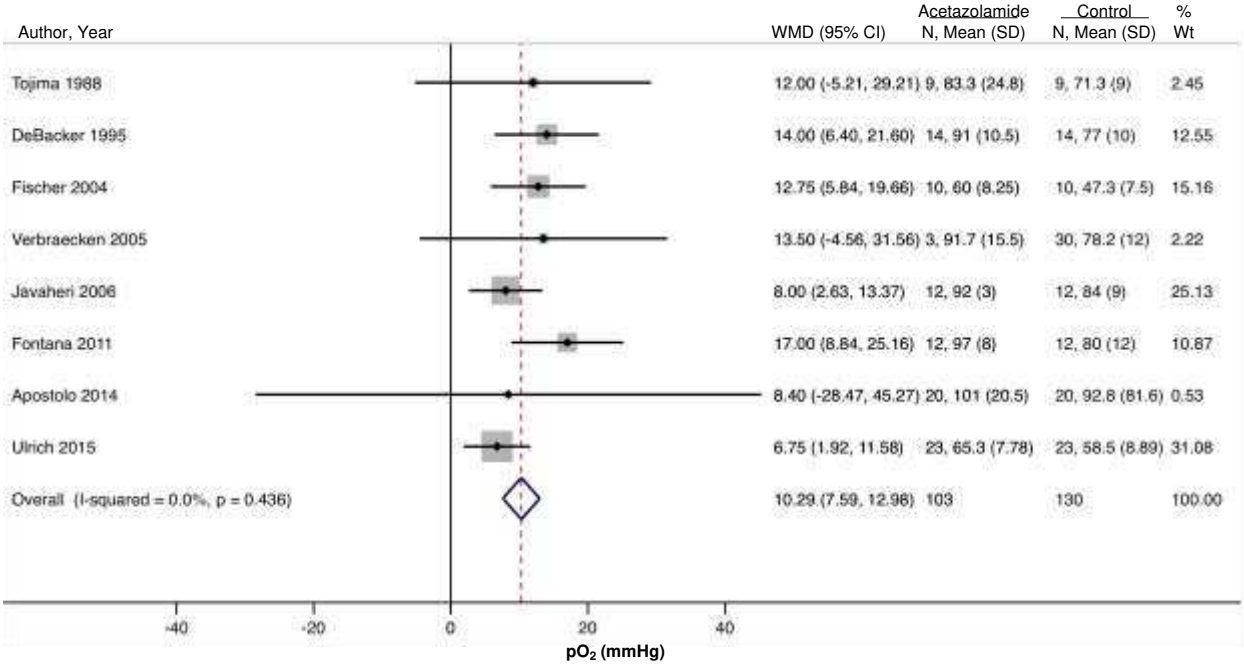
(analysis based on weighted mean differences, WMD)

However, within the low-dose (<500mg/day) subgroup heterogeneity remained high (I^2=56%), and closer inspection suggested that the difference in effects was primarily due to higher baseline/control levels of pH in the high-dose studies red (i.e. the mean AHI with Acetazolamide was similar in both subgroups green)

						Acetazolamide			Control		
	ES (95%-CI)	I^2	N	P	Type	M	SD	N	M	SD	N
pH (primary analysis)	-0.06 (-0.07 to -0.04)	72%	10	<.001*	W_{rand}	7.36	(0.03)	111	7.42	(0.03)	138
<500mg/day	-0.04 (-0.06 to -0.02)	56%	4	<.001*	W_{rand}	7.37	(0.03)	38	7.41	(0.03)	64
≥500mg/day	-0.07 (-0.08 to -0.06)	4%	6	<.001*	W_{rand}	7.36	(0.03)	73	7.43	(0.03)	74

PO_2
Forest Plot

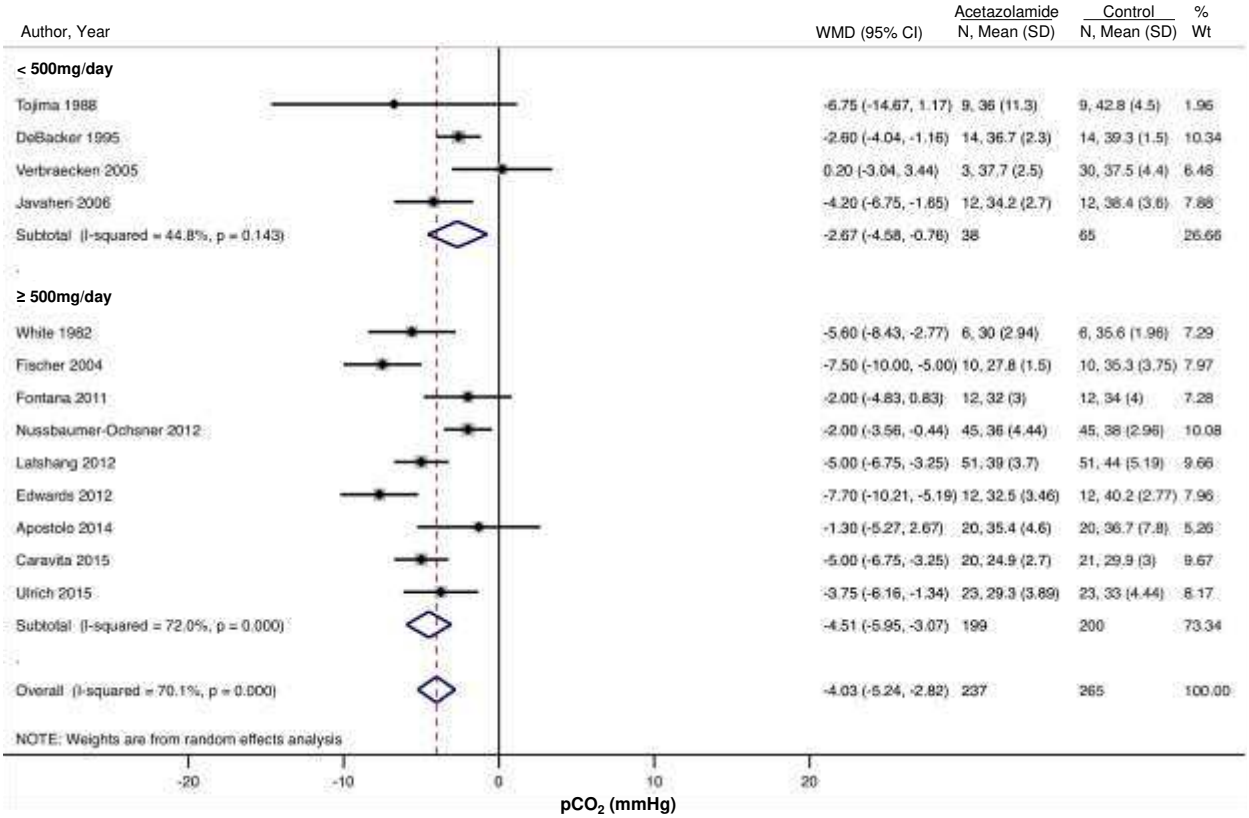
Primary analysis showed low heterogeneity (I^2=0%):



(analysis based on weighted mean differences, WMD)

PCO_2
Forest Plot

Primary analysis showed high heterogeneity (I^2=70%). Based on meta-regression, there was no significant effect modification by duration of acetazolamide administration (P=.84), obstructive vs central sleep apnea (P=.98) or acetazolamide dose (P=0.15). Visual exploration confirmed lack of effect modification by dose, with high residual heterogeneity in both subgroups:

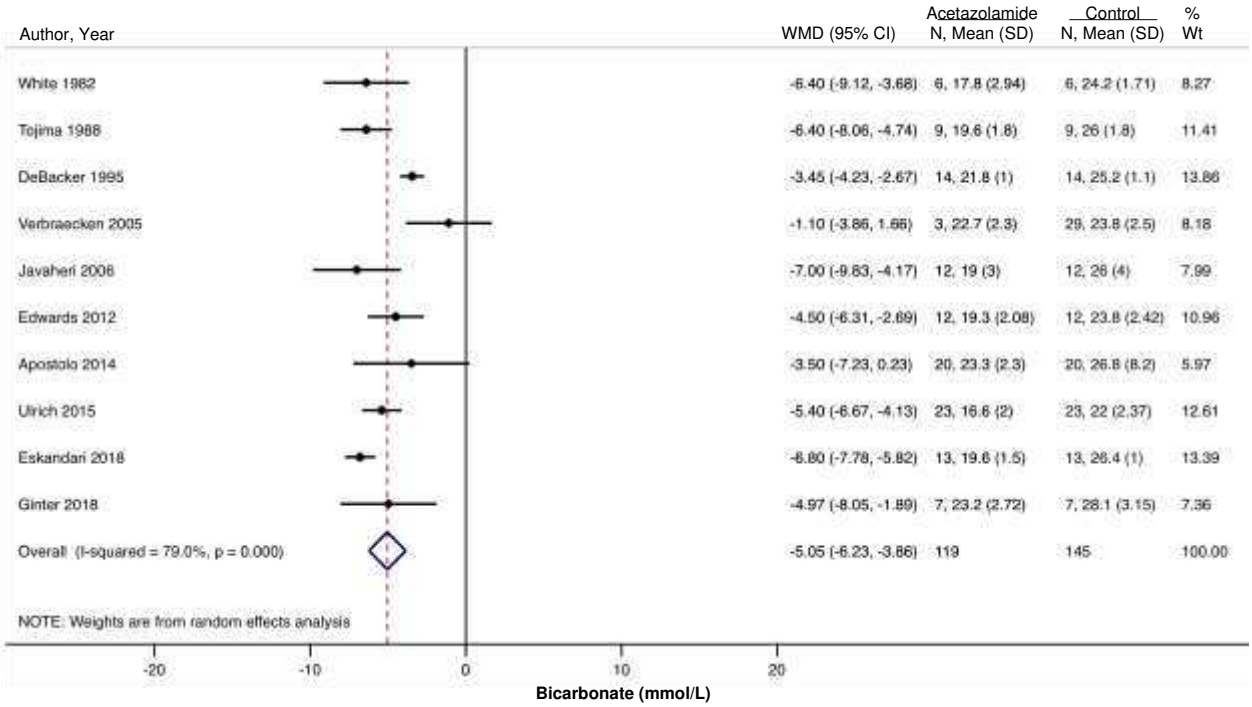


(analysis based on weighted mean differences, WMD)

Bicarbonate

Forest Plot

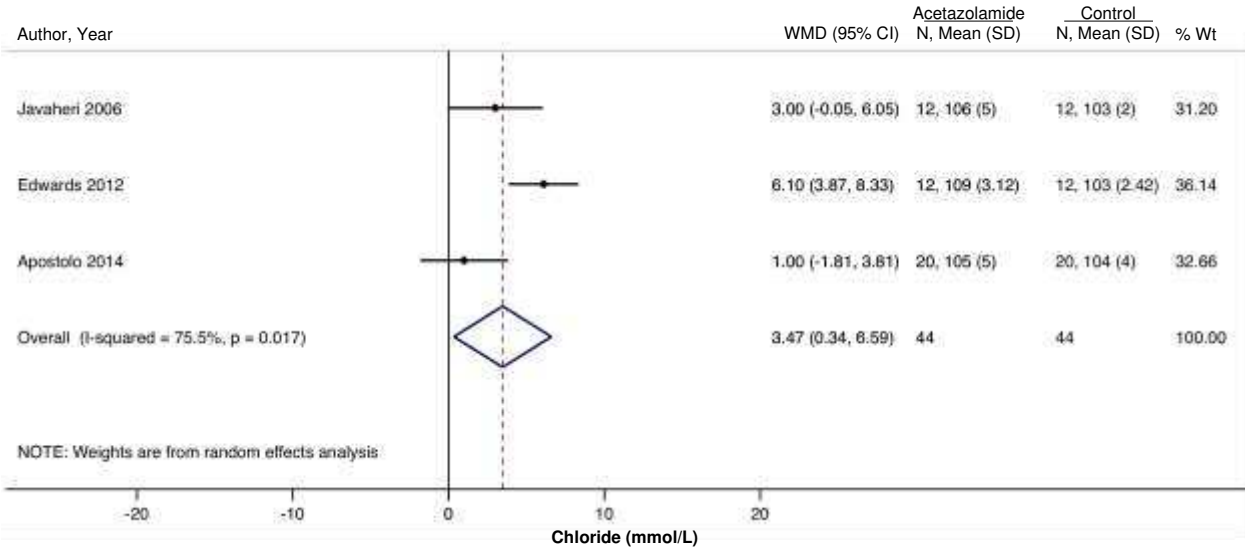
Primary analysis showed high heterogeneity (I^2=79%). Based on meta-regression, there was no significant effect modification by acetazolamide dose, duration, or obstructive vs central sleep apnea (P >0.3 for all).



(analysis based on weighted mean differences, WMD)

Chloride
Forest Plot

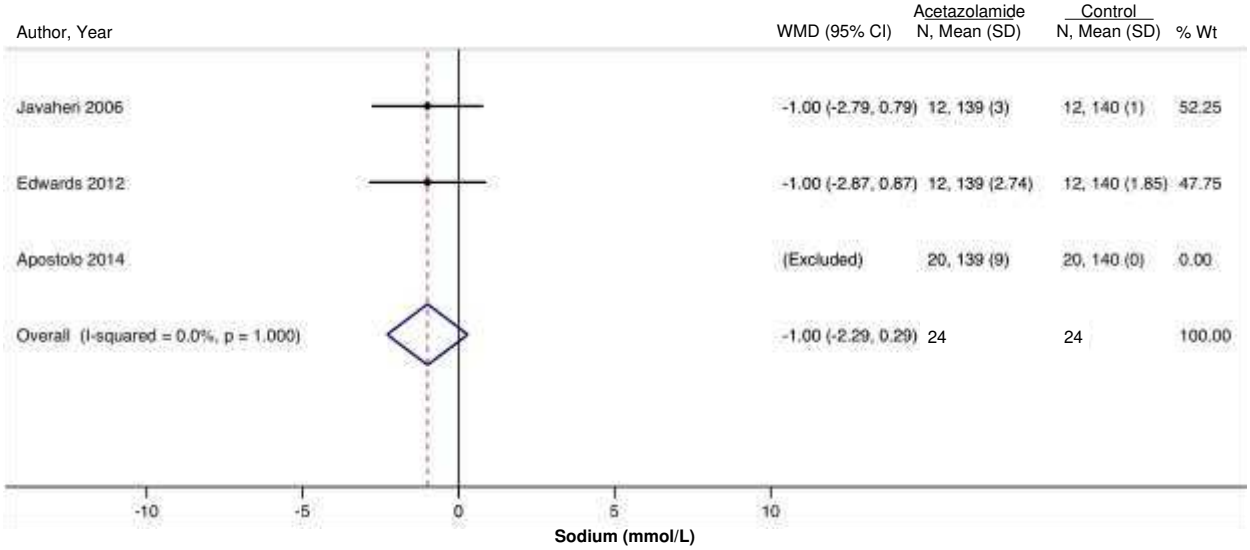
Primary analysis showed high heterogeneity (I^2=76%). There were too few studies to assess for effect modifiers via meta-regression. Qualitative assessment did not reveal any likely reasons for the observed heterogeneity. Note, both Apostolo and Edwards administered 1000mg/day.



(analysis based on weighted mean differences, WMD)

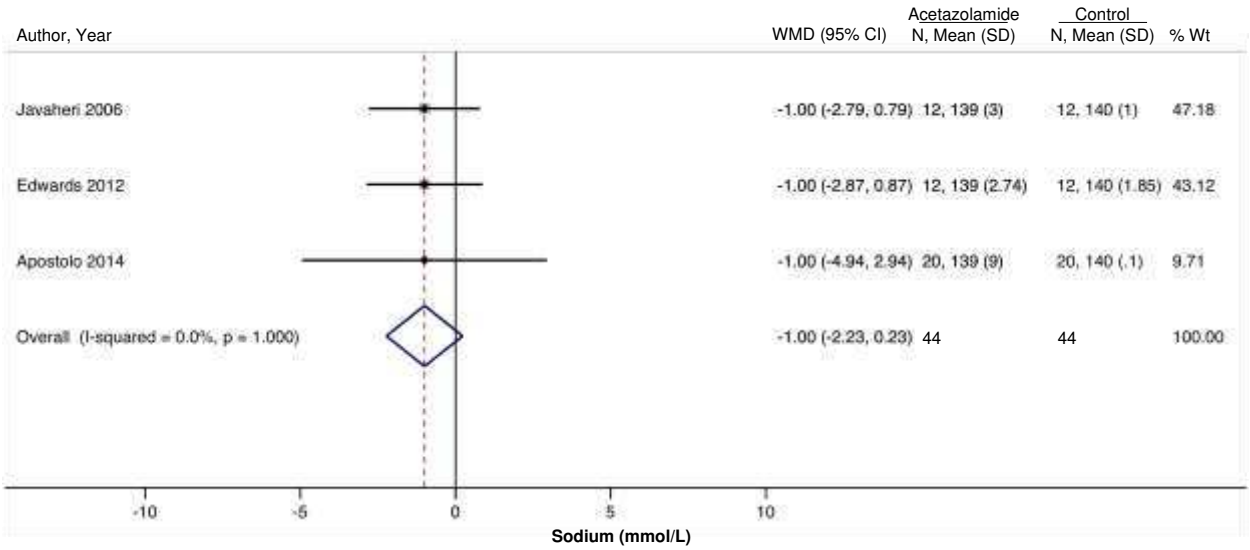
Sodium
Forest Plot

Primary analysis showed low heterogeneity (I^2=0%).



(analysis based on weighted mean differences, WMD)

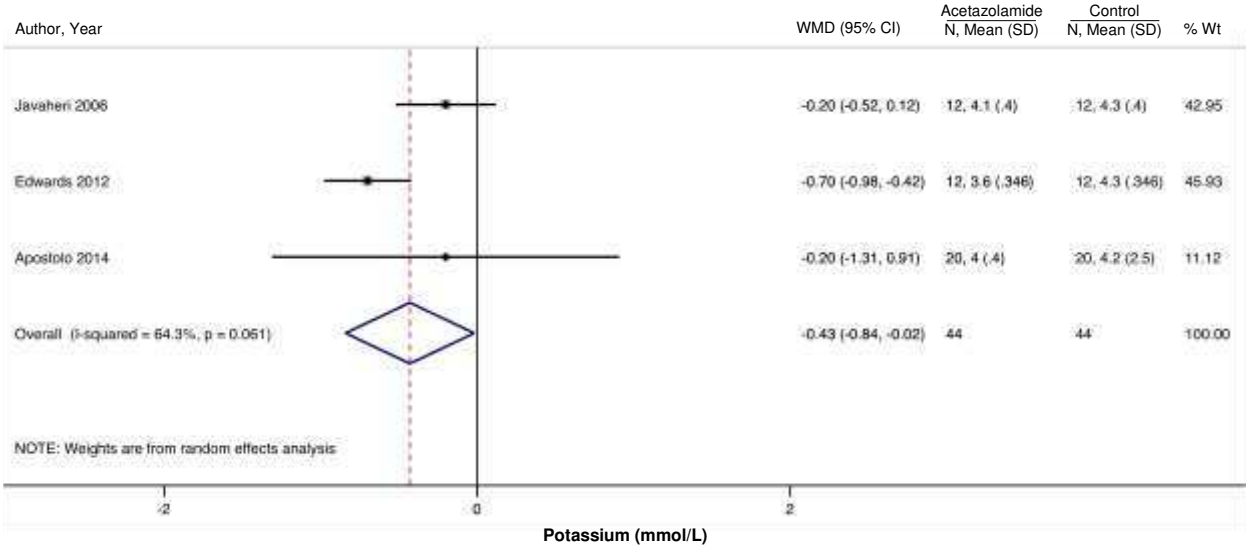
The study by Apostolo was excluded due to reporting a standard deviation of "zero" in the control group. A sensitivity analysis assuming that this reflected a rounding error (setting the standard deviation to 0.1) showed near-identical results as in the primary analysis:



(analysis based on weighted mean differences, WMD)

Potassium
Forest Plot

Primary analysis showed high heterogeneity (I^2=64%).



(analysis based on weighted mean differences, WMD)

There were too few studies to assess for effect modifiers via meta-regression. Qualitative assessment did not reveal any likely reasons for the observed heterogeneity:

Study	Sleep Apnea Type	Dose x Duration	K-Supplement	Excluded Renal Dysfct?
Javaheri	CHF+CSA	281mg/d (3.5-4mg/kg/d) x1wk	Yes	Yes
Edwards	OSA	1000mg/d x1wk	No	Yes
Apostolo	CHF+OSA/CSA	1000mg/d x2d	No	No

Of note, in the study by Edwards one subject had to be excluded because of hypokalemia in the setting of concomitant use of a thiazide diuretic (subject is not included in the data entered into the meta-analysis above).

eTable 5. Summary of Evidence (based on GRADE)

Certainty assessment							№ of patients			Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acetazolamide	control		Absolute (95% CI)		
Apnea-Hypopnea Index (follow up: range 1 days to 90 days)												
26	randomised trials [a]	serious [b]	not serious	not serious	not serious [c]	none	529	540	-	SMD 0.7 SD lower (0.83 lower to 0.58 lower)	⨁⨁⨁◯ MODERATE	
SpO2 Nadir												
13	randomised trials [d]	serious [e]	very serious [f]	not serious	serious [g]	none	245	247	-	MD 4.4 % higher (2.3 higher to 6.5 higher)	⨁◯◯◯ VERY LOW	
SpO2 Mean												
12	randomised trials [d]	serious [b]	serious [h]	not serious	not serious	none	218	215	-	MD 3.5 % higher (2.3 higher to 4.8 higher)	⨁⨁◯◯ LOW	
Time with SpO2<90%												
5	observational studies [i]	serious [j]	serious [h]	not serious	serious [k]	none	101	101	-	MD 15.1 %TST lower (31.9 lower to 1.6 higher)	⨁◯◯◯ VERY LOW	
Oxygen Desaturation Index (ODI)												
5	randomised trials [d]	serious [l]	serious [h]	not serious	not serious	none	107	107	-	MD 12.2 per hour lower (19.2 lower to 5.2 higher)	⨁⨁◯◯ LOW	
Obstructive AHI												
3	randomised trials [d]	serious [e]	serious [m]	not serious	serious [k]	none	77	77	-	MD 7.5 per hour lower (16.9 lower to 1.8 higher)	⨁◯◯◯ VERY LOW	
Central AHI												
8	randomised trials [d]	serious [b]	serious [h]	not serious	serious [n]	none	204	204	-	MD 9.4 per hour lower (14.2 lower to 4.6 lower)	⨁◯◯◯ VERY LOW	
Periodic Breathing												
3	randomised trials [o]	serious [j]	serious [h]	not serious	serious [k,p]	none	36	36	-	MD 24.2 %TST lower (53.1 lower to 4.7 higher)	⨁◯◯◯ VERY LOW	
Apnea-Hypopnea Duration												
6	observational studies [i]	serious [e]	serious [h]	not serious	serious [p,q]	none	106	107	-	MD 0.8 seconds higher (1.5 lower to 3.1 higher)	⨁◯◯◯ VERY LOW	
Arousal Index												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acetazolamide	control		Absolute (95% CI)		
6	randomised trials [o]	serious [j]	not serious	not serious	serious [n]	none	140	140	-	MD 6.6 per hour lower (11.3 lower to 2 lower)	⨁⨁◯◯ LOW	
Total Sleep Time												
10	randomised trials [d]	serious [b]	not serious	not serious	serious [n,p]	none	292	292	-	MD 20 minutes higher (7.1 higher to 32.9 higher)	⨁⨁◯◯ LOW	
Sleep Efficiency												
12	randomised trials [d]	serious [b]	not serious	not serious	serious [p]	none	305	305	-	MD 5.5 % higher (3.2 higher to 7.8 higher)	⨁⨁◯◯ LOW	
Stage N1												
5	randomised trials [r]	serious [e]	not serious	not serious	serious [n,p]	none	118	118	-	MD 4.7 %TST lower (7.6 lower to 1.9 lower)	⨁⨁◯◯ LOW	
Stage N2												
5	observational studies [i]	serious [e]	not serious	not serious	serious [n,p]	none	118	118	-	MD 4 %TST higher (0.9 higher to 7.1 higher)	⨁◯◯◯ VERY LOW	
Stage N3												
7	randomised trials [d]	serious [b]	not serious	not serious	serious [n]	none	237	237	-	MD 1.4 %TST higher (0.1 higher to 2.6 higher)	⨁⨁◯◯ LOW	
Stage REM												
11	randomised trials [d]	serious [b]	not serious	not serious	not serious	none	300	300	-	MD 0 %TST (1.4 lower to 1.4 higher)	⨁⨁⨁◯ MODERATE	
Systolic Blood Pressure												
5	randomised trials [d]	serious [e]	not serious	not serious	serious [g]	none	99	114	-	MD 8.2 mmHg lower (11.5 lower to 4.9 lower)	⨁⨁◯◯ LOW	
Diastolic Blood Pressure												
5	randomised trials [d]	serious [e]	not serious	not serious	serious [n,p]	none	99	114	-	MD 4.3 mmHg lower (6.8 lower to 1.8 lower)	⨁⨁◯◯ LOW	
Mean Blood Pressure												
4	randomised trials [d]	serious [b]	not serious	not serious	serious [g]	none	128	129	-	MD 5.2 mmHg lower (7.5 lower to 2.8 lower)	⨁⨁◯◯ LOW	
Heart Rate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acetazolamide	control		Absolute (95% CI)		
7	randomised trials [d]	serious [b]	not serious	not serious	serious [p,s]	none	164	165	-	MD 1.7 per minute lower (4.2 lower to 0.7 higher)	⨁⨁◯◯ LOW	
Weight												
3	randomised trials [d]	serious [b]	not serious	not serious	very serious [p,t]	none	116	116	-	MD 1.6 kilograms lower (5.9 lower to 2.8 higher)	⨁◯◯◯ VERY LOW	
Epworth Sleepiness Score												
3	randomised trials [d]	serious [b]	serious [h]	not serious	serious [p,s]	none	46	46	-	MD 0.7 lower (2.2 lower to 0.9 higher)	⨁◯◯◯ VERY LOW	

GRADE: Grading of Recommendations Assessment, Development and Evaluation; **CI:** Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Majority of included studies were randomized controlled trials (RCTs); the effect estimate was significantly greater in randomized vs observational studies
b. Most studies rated as high/unclear risk of bias, but no significant effect modification by risk of bias
c. Assumed minimal clinically important difference (MCID) = 10 events/hour
d. Majority of included studies were RCTs and there was no significant evidence that effect estimates were different in randomized vs observational studies
e. All of the included studies were judged to be of high/unclear risk of bias
f. I^2 >50% and no clear explanation of heterogeneity identified
g. 95%-Confidence Interval (CI) excludes values less than the minimal clinically important difference (MCID), but optimal information size (OIS) is not met
h. I^2>50%, but possible explanation of heterogeneity identified
i. <50% of studies were RCTs and within the RCT subgroup the effect was not significant
j. Most studies rated as high/unclear risk of bias; too few studies to assess for effect modification by risk of bias
k. 95%-CI includes both large beneficial and null effects (but excludes substantial harmful effects)
l. Most studies rated as high/unclear risk of bias, but effect similar and significant in low/unclear vs high risk subgroups
m. I^2 <50%, but there was a big difference in effect sizes between studies without clear explanation for these differences
n. 95%-CI includes values less than the minimal clinically important difference (MCID)
o. All studies were RCTs
p. Did not meet Optimal Information Size (OIS) criteria
q. 95%-CI includes potentially "harmful" effects above the minimal clinically important difference (MCID) and null effects
r. Less than 50% of studies were RCTs, but results were similar in the subgroup of RCTs
s. 95%-CI includes potentially "beneficial" effects above the minimal clinically important difference (MCID) and null effects
t. 95%-CI includes both potentially "harmful" and "beneficial" effects above the minimal clinically important difference (MCID)

eTable 6. Overview of Data concerning Subjective Symptoms

Javaheri[6]

Cross-over RCT of acetazolamide (4mg/kg ~280mg/day) vs placebo for 6 days in 10 subjects with CSA-CHF.

With acetazolamide (N=10) vs placebo (N=10), more patients reported subjective improvement in
- Sleep quality: 7 vs 1 (P = 0.003)
- Daytime fatigue: 7 vs 2 (P = 0.02)
- Waking up rested: 8 vs 2 (P = 0.007)
- Falling asleep unintentionally: 5 vs 0 (P = 0.002)

Whyte[3]

Cross-over RCT of acetazolamide 1000mg/day vs placebo for 14 days in 10 subjects with symptomatic OSA.

"Daytime somnolence, morning headache, and sleep disturbance, as assessed by visual analog scale, were not significantly altered by [acetazolamide] compared to placebo for the whole group. […] Patients felt no more rested In the morning with [acetazolamide]."

Sakomoto[37]

Case series of 20 OSA patients who received on average 399mg/day of acetazolamide for a mean duration of 52.4 days.

With acetazolamide there was an improvement in:
- 9/15 who had complained of insomnia at baseline
- 12/17 who had complained of excessive daytime sleepiness at baseline
- 12/19 who had complained of snoring at baseline

DeBacker[18]

Case series of 14 patients with idiopathic CSA treated with acetazolamide 250mg/day for 30days.

Compared with baseline, at 30days significantly less patients reported symptoms:
- Feeling sleepy during the day: 12 vs 1 (P<0.01)
- Falling asleep during the day: 10 vs 2 (P<0.01)
- Memory Losses: 10 vs 2 (P<0.01)
- Alert in the morning: 6 vs 14 (P<0.01)

Compared with baseline, at 30days a similar number of patients reported snoring:
- Snoring: 14 vs 13 (P>0.05)

Tojima[22]

Case series of 9 sleep apnea patients (8OSA/1CSA) treated with 250mg for 7-8 days.

Subjective improvement "to some degree" in
- 5/7 with excessive daytime sleepiness at baseline
- 4/4 with morning inertia at baseline
- 3/4 with insomnia at baseline

White[19]

Case series of CSA patients (5 idiopathic; 1 mild CHF) treated with acetazolamide 1000mg/day for 7 days.

5 of 6 patients reported some improved daytime symptoms with acetazolamide:
- 2 believed to be "cured" with no awakenings during sleep and a disappearance of fatigue during the day
- 1 patient who was hypersomnolent reported decreased daytime lethargy and improved job performance
- 2 others stated their condition improved but still had a few nocturnal awakenings and a less than normal energy level during the day
- 1 patient noted no change, but had originally reported the fewest symptoms of all patients studied

eTable 7. Effects of Acetazolamide on Laboratory Tests

						Acetazolamide			Control		
	Δ (95%-CI)	**I^2**	**$N_{Studies}$**	**$P_{A=0}$**	**Δ Type**	**$Mean_{wt}$**	**SD_{wt}**	**N_{Subj}**	**$Mean_{wt}$**	**SD_{wt}**	**N_{Subj}**
pH[a]	-0.06 (-0.07 to -0.04)	72%	10	<.001*	W_R	7.36	(0.03)	111	7.42	(0.03)	138
pO_2 (mmHg)	+10.3 (7.6 to 13.0)	0%	8	<.001*	W_F	79.1	(8.7)	103	68.8	(11.1)	130
pCO_2 (mmHg)	-4.0 (-5.2 to -2.8)	70%	13	<.001*	W_R	33.0	(3.6)	237	37.0	(3.9)	265
Bicarbonate (mmol/L)	-5.1 (-6.2 to -3.9)	79%	10	<.001*	W_R	20.0	(2.1)	119	25.1	(3.0)	145
Chloride (mmol/L)	+3.5 (0.3 to 6.6)	76%	3	.03*	W_R	106.6	(4.4)	44	103.2	(2.9)	44
Sodium (mmol/L)	-1.0 (-2.3 to 0.3)	0%	2	.13	W_F	138.8	(2.9)	44	139.8	(1.5)	44
Potassium (mmol/L)	-0.43 (-0.84 to -0.02)	64%	3	.04*	W_F	3.9	(0.4)	44	4.3	(0.9)	44

a pH reductions were greater in studies which administered higher doses of acetazolamide but this difference did not reach statistical significance (P=.053) and these studies also tended to have higher control pHs (i.e. the mean pH values with acetazolamide was similar in high vs low dose studies).

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