SUPPLEMENTAL MATERIALS
Treatment of Central Sleep Apnea in Adults

All Literature Search Terms

((("sleep"[MeSH Terms] AND "apnea"[MeSH Terms]) OR "central sleep apnea"[All Fields] OR "central sleep apnoea"[All Fields] OR "CSA"[All Fields] AND ("heart failure"[All Fields] OR "reduced ejection fraction"[All Fields] OR "Cheyne Stokes"[All Fields] OR "Cheyne Stokes Respiration"[All Fields] OR "medication"[All Fields] OR "substance"[All Fields] OR "narcotics"[All Fields] OR "opioids"[All Fields] OR "medical condition"[All Fields] OR "condition"[All Fields] OR "disorder"[All Fields] OR "stroke"[All Fields] OR "end-stage renal disease"[All Fields] OR "spinal cord injury"[All Fields] OR "neurologic disorder"[All Fields] OR "traumatic brain injury"[All Fields] OR "high altitude"[All Fields] OR "high altitude periodic breathing"[All Fields] OR "hypoxia"[All Fields] OR "hypoxemic"[All Fields] OR "treatment emergent"[All Fields] OR "therapy emergent"[All Fields])) AND ("carbonic anhydrase inhibitors"[All Fields] OR "zolpidem"[All Fields] OR "triazolam"[All Fields] OR "temazepam"[All Fields] OR "hypnotics"[All Fields] OR "intervention"[All Fields] OR "treatment"[All Fields] OR "pharmacological"[All Fields] OR "medication"[All Fields] OR "pharmacotherapy"[All Fields] OR "positive airway pressure"[All Fields] OR "PAP"[All Fields] OR "APAP"[All Fields] OR "automatic positive airway pressure"[All Fields] OR "bilevel pressure"[All Fields] OR "BPAP"[All Fields] OR "continuous positive airway pressure"[All Fields] OR "CPAP"[All Fields] OR "Adaptive Servo-Ventilation"[All Fields] OR "oxygen"[All Fields] OR "oxygen therapy"[All Fields] OR "phrenic nerve stimulation"[All Fields] OR "positional therapy"[All Fields])) AND (Adult[MeSH Terms] OR Adult[All Fields]) *Filters applied: Clinical Study, Clinical Trial, Controlled Clinical Trial, Multicenter Study, Observational Study, Randomized Controlled Trial, Humans, English*

Exclusion Criteria

Exclusion criteria are applied during the abstract review of all retrieved publications. Studies that meet any of the exclusion criteria are rejected from the systematic review.

A. Publication type
   a. Book and book chapters
   b. Conference abstracts
   c. Dissertations
   d. Editorials
   e. Letters to the editor
   f. Methods papers
   g. Case reports or case series
   h. Single case design or pilot
   i. Review papers (systematic reviews, narrative reviews, and meta-analysis)
B. Study type
   a. animal research
C. Language
   a. non-English
D. Patients
   a. Did not undergo treatment for central sleep apnea
   b. Not adults (anyone under 18 years of age)

Inclusion Criteria

Inclusion criteria are applied during the full publication review of all publications that were not rejected during the abstract review. Studies that **meet all inclusion criteria will be accepted as evidence to use in the systematic review.**

A. Outcomes of interest (must meet at least 1)
   a. Apnea-hypopnea index
   b. Daytime functioning or work performance
   c. Disease severity
   d. Fatigue
   e. Insomnia
   f. Vigilance/alertness
   g. Overall quality of life
   h. Oxygen desaturation index
   i. Sleep quality (patient reported)
   j. Sleepiness during the day
   k. Cardiovascular disease/stroke
   l. Cognitive functioning
   m. Hospitalization
   n. Mortality
   o. Sleep quality (psg)
   p. Cycle length
   q. Mental quality of life
   r. Vigilance/alertness, wakefulness

B. Publication type
   a. RCTs:
      i. Intervention vs placebo
      ii. Intervention vs no treatment
      iii. Intervention vs standard of care
      iv. Intervention vs sham

   b. Observational studies: longitudinally/cross-sectionally examines the effect(s) of the intervention

C. Patients

   a. Adults with a diagnosis of central sleep apnea

D. Interventions (must include at least 1)
   a. Acetazolamide
   b. Triazolam
   c. Hypnotics
   d. Zolpidem
   e. PAP therapy
   f. APAP
   g. BPAP

h. CPAP
i. ASV
j. Oxygen therapy
k. Phrenic nerve stimulation
l. Positional therapy

Abbreviations:

6MWD – 6-minute walk distance
AHI – Apnea hypopnea index
ASV – Adaptive servo ventilation
BNP – B-type natriuretic peptide
BPAP – Bilevel positive airway pressure
BPAP-ST – Bilevel positive airway pressure-spontaneous time
CAHI – Central apnea hypopnea index
CAI – Central apnea index
CSA – Central sleep apnea
CST – Clinical significance threshold
CPAP – Continuous positive airway pressure
DBP - Diastolic blood pressure
ESS – Epworth Sleepiness Scale
GRADE – Grading of Recommendations, Assessment, Development and Evaluation
HR - Heart rate
LVEF - Left ventricular ejection fraction
MLHFQ – Minnesota living with heart failure questionnaire
MWT – Maintenance of wakefulness test
NT pro-BNP - N-terminal pro-B-type natriuretic peptide
NYHA - New York Heart Association classification
ODI – Oxygen desaturation index
PAP – Positive airway pressure
PASAT - Paced auditory serial addition task
PICO – Patient, intervention, comparator, outcome
POMS-A – Profile of moods-adolescent
PSG – Polysomnography
PSQI – Pittsburgh sleep quality index
PVT – Psychomotor vigilance test
RCT – Randomized controlled trial
REM – Rapid eye movement
SD – Standard deviation
SF-36 – Short form 36 health questionnaire
SMD – Standardized mean-difference
SBP - Systolic blood pressure
SSS - Stanford Sleepiness Scale
SWS – Slow-wave sleep
TIB – Time in bed

PICO 1: Adults with primary CSA, CSA due to heart failure, CSA due to a medical condition or disorder, CSA due to a medication or substance, treatment- emergent CSA

CPAP

Summary of Findings (GRADE)

Table S1 CPAP in adults with CSA

References: Bradley 2005, Granton 1996, Kasai 2010, Kasai 2013, Köhnlein 2002, Naughton 1994, Naughton 1995, Naughton 1995 (Am J Resp), Philippe 2006, Sin 2000, Teschler 2001

Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **CPAP vs. baseline or control**	**No of Participants (studies)**
Excessive sleepiness [ESS]	⨁◯◯◯ **VERY LOW**[a, b]	The mean difference in the CPAP group was **1.86 points fewer (3.71 fewer to 0.0 fewer)** compared to baseline	42 (3 RCTS)
Disease severity [AHI]	⨁⨁⨁⨁ **HIGH**	The mean difference in the CPAP group was **17.43 events/ hour fewer (21.01 fewer to 13.86 fewer)** compared to control	363 (6 RCTs)
Disease severity [CAI]	⨁⨁◯◯ **LOW**[b,c]	The mean difference in the CPAP group was **17.3 events/hour lower (25.76 lower to 8.84 lower)** compared to control	28 (1 RCTs)
Cardiovascular disease [6MWD]	⨁⨁⨁◯ **MODERATE**[c]	The mean difference in the CPAP group was **20.8 meters more (6.14 more to 35.46 more)** compared to control	258 (1 RCT)
Hospitalizations [Hospitalizations per patient per year]	⨁⨁⨁◯ **MODERATE**[d]	The mean difference in the CPAP group was **0.05 events higher (0.11 lower to 0.21 higher)** compared to control	258 (1 RCT)
Mortality [reported deaths]	⨁⨁◯◯ **LOW**[e]	The risk ratio in the CPAP group was **0.87 (0.58 to 1.28)** with an absolute risk of **19 fewer per 1,000 (63 fewer to 42 more)** compared to control	324 (2 RCTs)

a. Downgraded quality of evidence due to RCT data analyzed using pre- and posttreatment values
b. Imprecision due to small sample size (<200 participants)
c. Imprecision due to the 95% CI includes possibility for important benefit and no effect
d. Imprecision is present because of a small number of events leading to wide confidence intervals
e. Imprecision due to the 95% CI includes possibility for important benefit and harm

Critical Outcomes

Figure S1. CPAP vs. Baseline (Excessive sleepiness, ESS) [CST= -2 pts], RCTs (single-arm pre-posttreatment data)

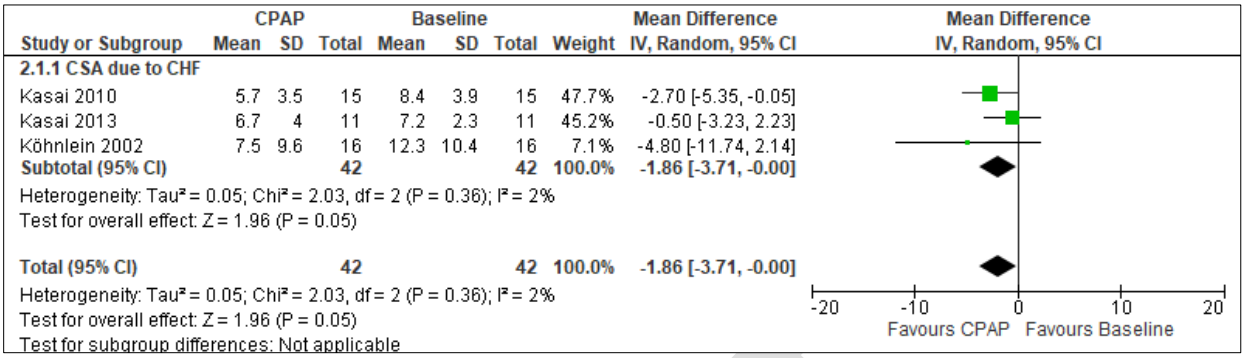
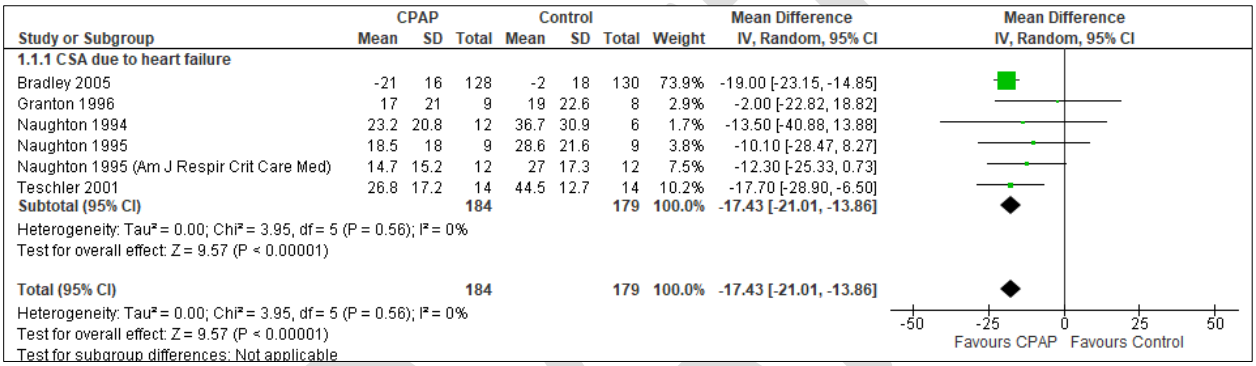
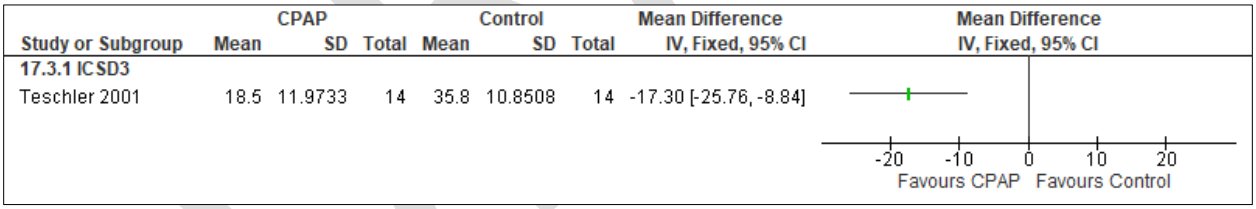


Figure S2. CPAP vs. Control (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCTs



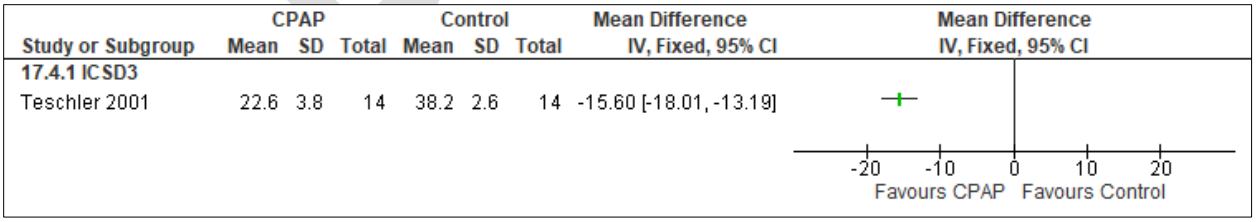
Teschler 2001, Naughton 1994, Granton 1996, Naughton 1995, Naughton (Am J Respir Crit Care Med) 1995: SEM converted to SD; Bradley 2005: data reported as change from baseline.

Figure S3. CPAP vs. Control (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCT



Teschler 2001: SEM converted to SD

Figure S4. CPAP vs. Control (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCT



*Teschler 2001: Change from baseline

Figure S5. CPAP vs. Control (Cardiovascular disease, 6MWD (change score) [CST= +32 meters], RCT

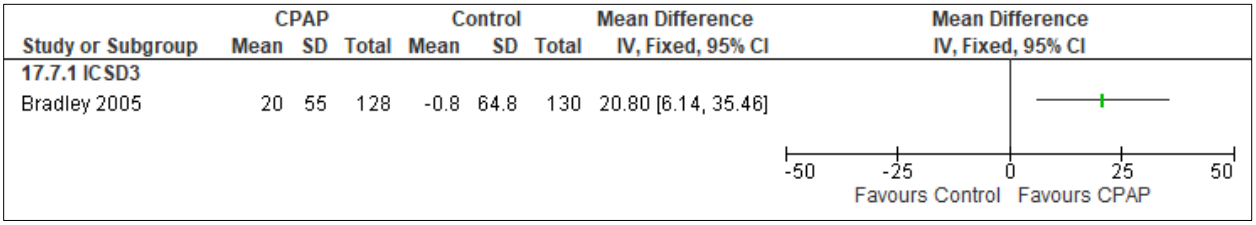


Figure S6. CPAP vs. Control (Cardiovascular disease, LVEF (%)) [CST= +5%], RCTs

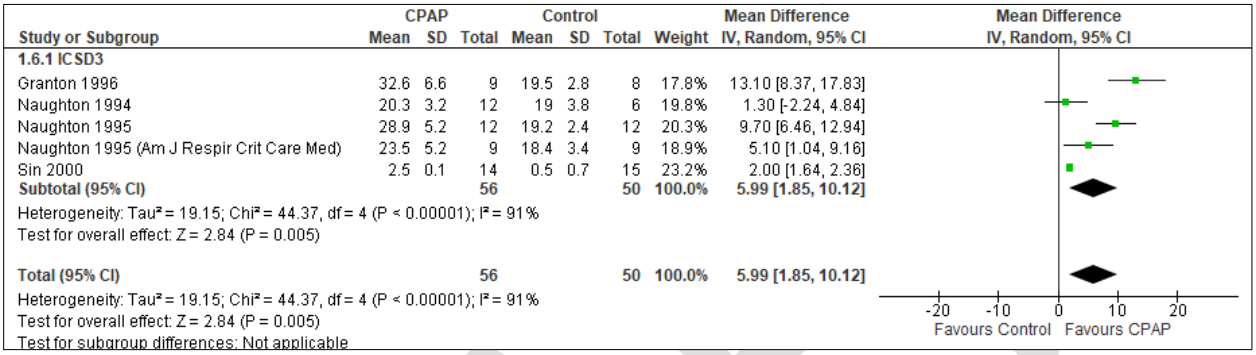


Figure S7. CPAP vs. Control (Cardiovascular disease, Systolic BP (mmHg)) [CST= - 2 mmHg], RCT

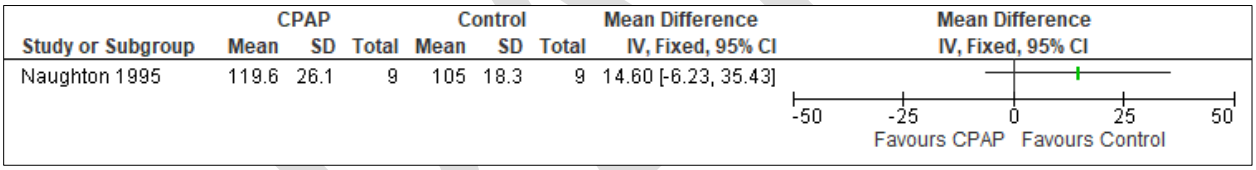


Figure S8. CPAP vs. Control (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCT

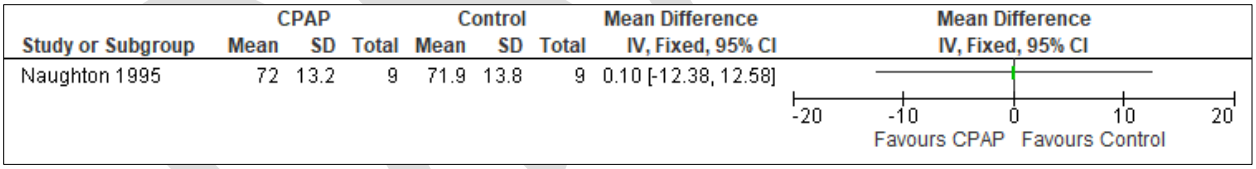


Figure S9. CPAP vs. Control (Cardiovascular disease, HR (beats/min)) [No CST], RCT

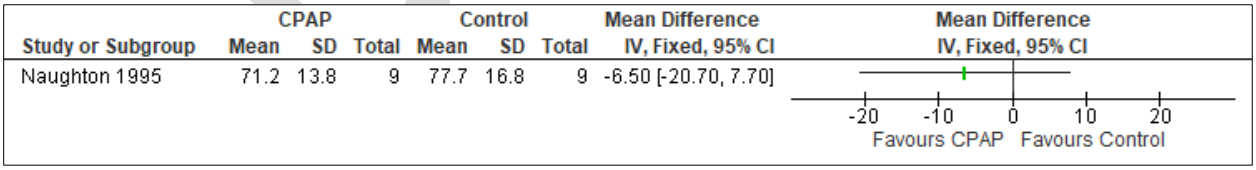


Figure S10. CPAP vs. Control (Hospitalizations, Hospitalizations per patient per year) [No CST], RCT

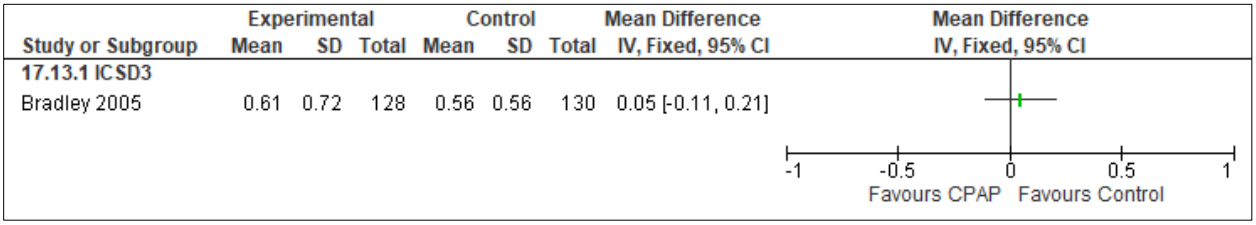


Figure S11. CPAP vs. Control (Mortality, reported deaths) [CST= 0.8], RCTs

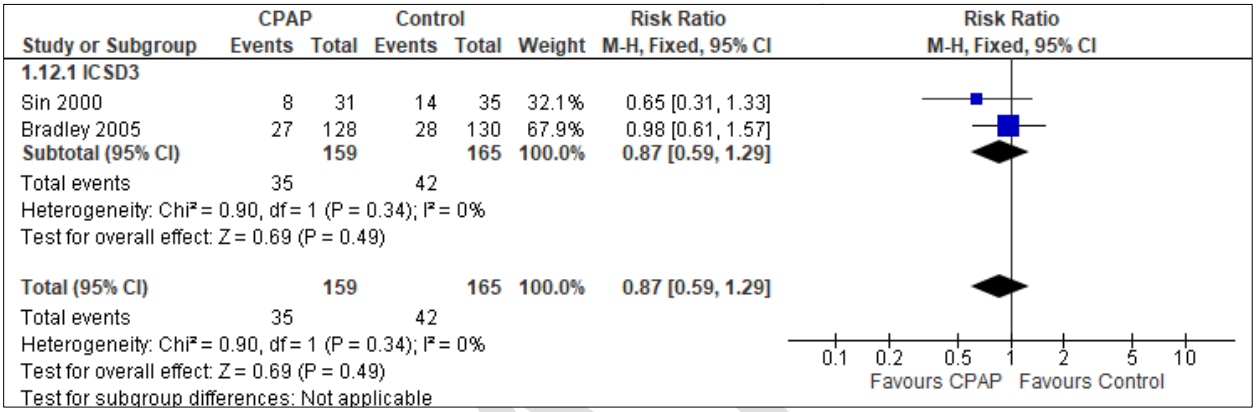
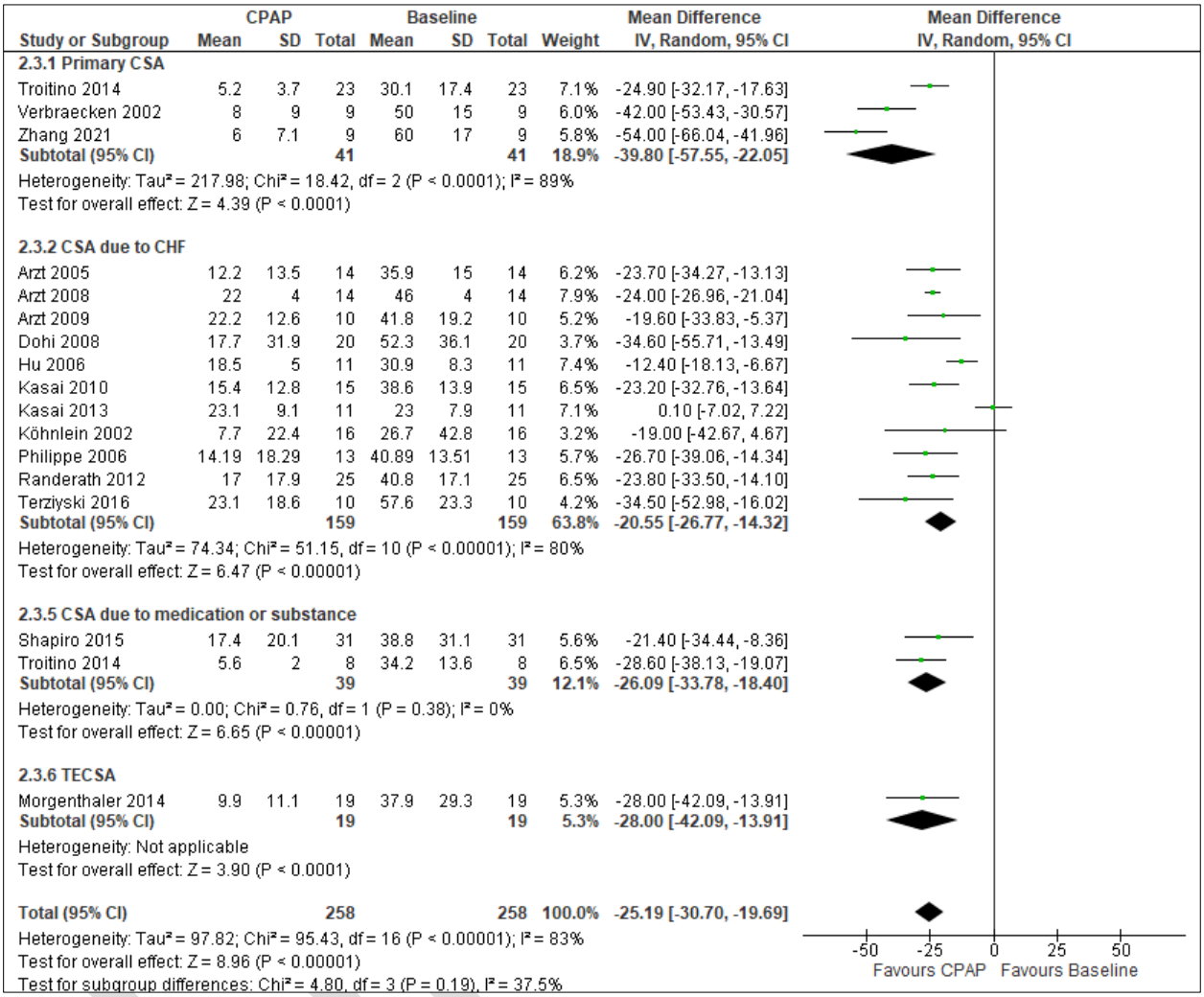


Figure S12. CPAP vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



Kohnlein 2002: SEM converted to SD; Philippe 2006: data extracted from graph; Dohi 2008: data from responders and non-responders pooled, SEM converted to SD; Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD.

Figure S13. CPAP vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCTs (single-arm pre- posttreatment data) and observational studies

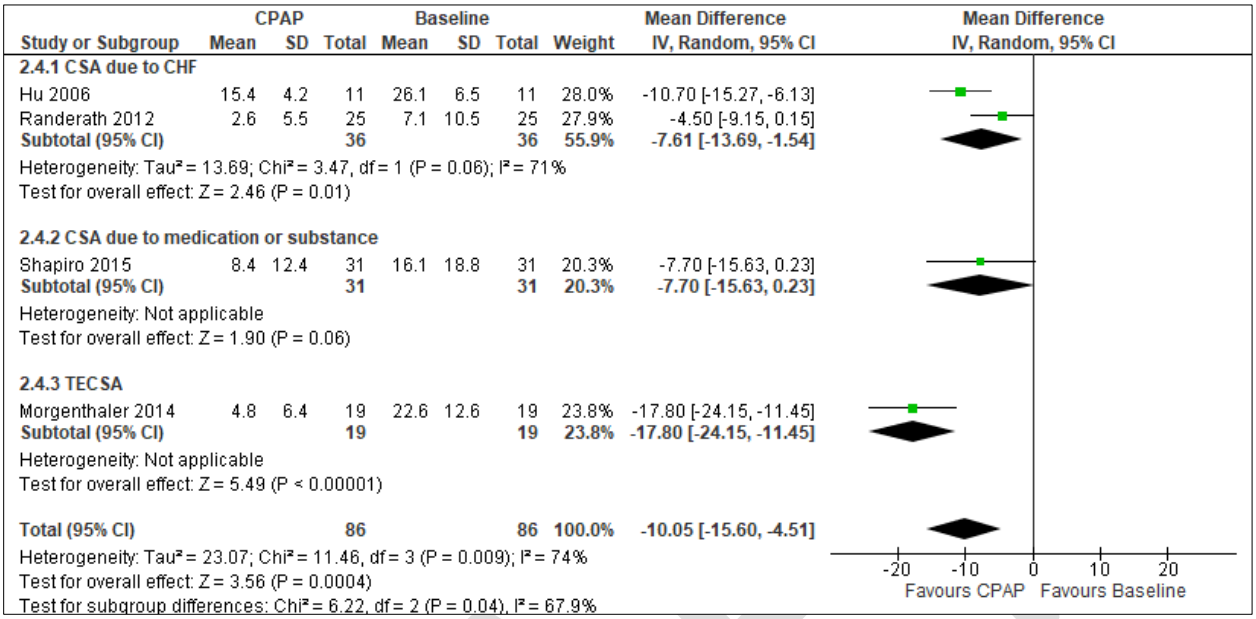


Figure S14. CPAP vs. Baseline (Disease Severity, CAHI) [CST= ≥ 50% change from baseline], RCTs (single-arm pre- posttreatment data) and observational studies

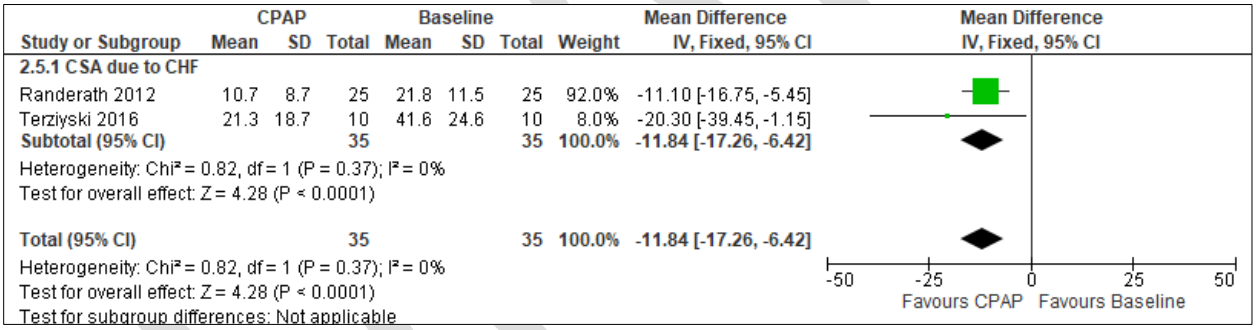
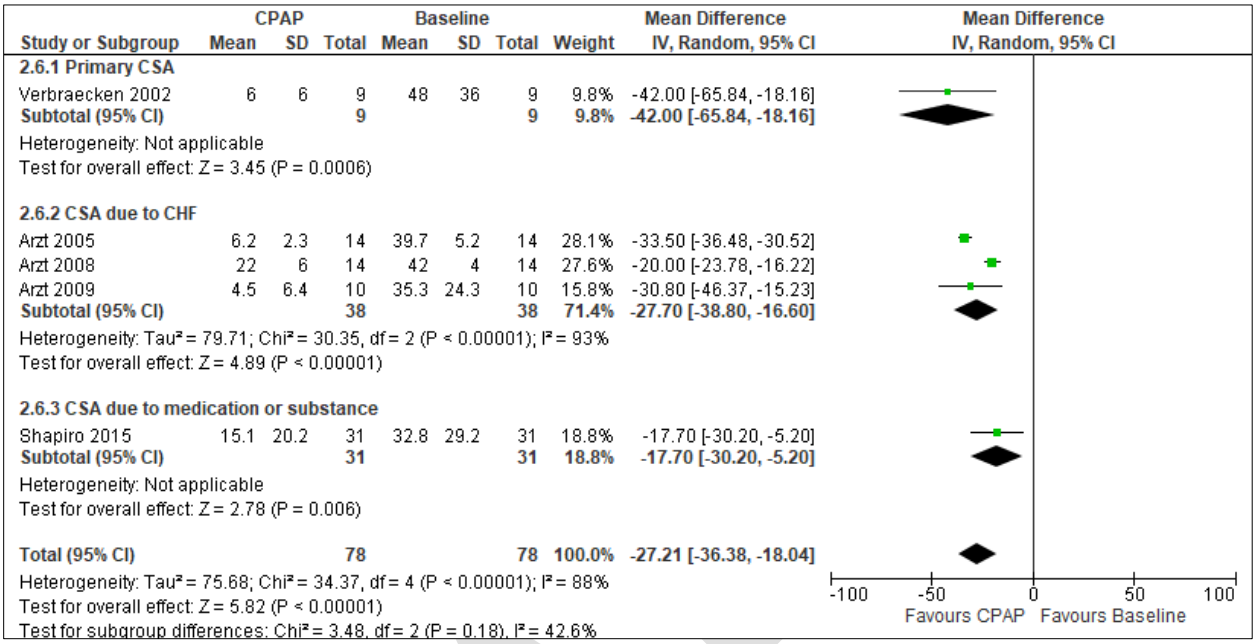
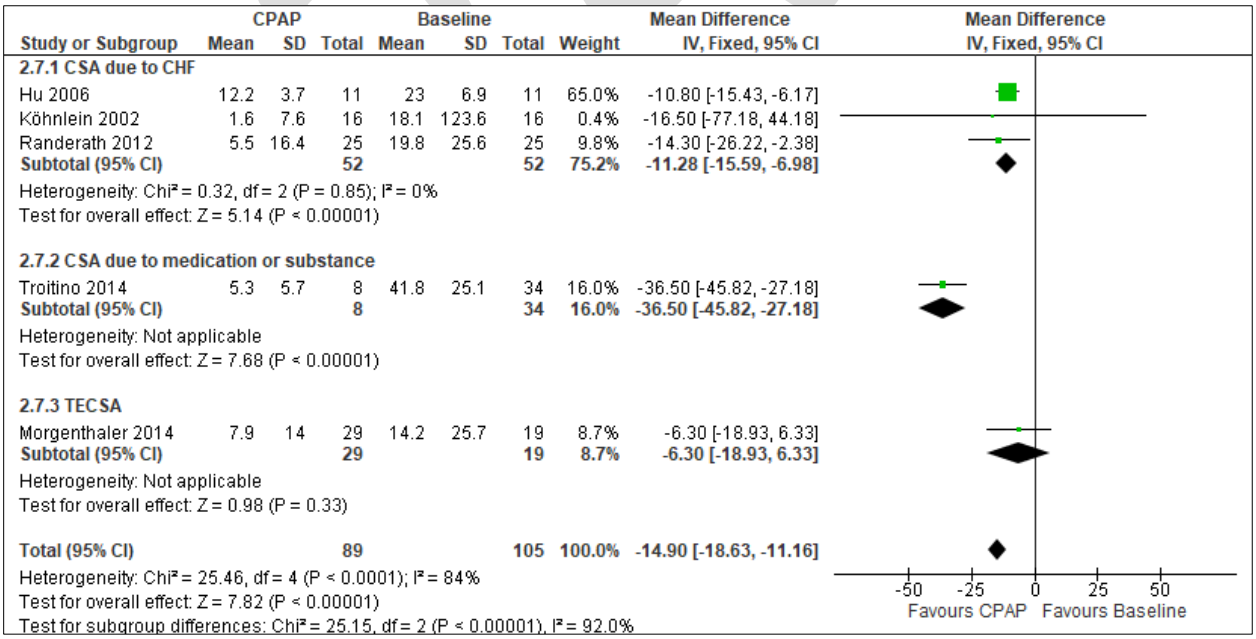


Figure S15. CPAP vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCT (single-arm pre- posttreatment data) and observational studies



* Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S16. CPAP vs. Baseline (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% change from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



Kohnlein: data extracted from the graph; SEM converted to SD

Figure S17. CPAP vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= 5%], RCTs (single-arm pre-posttreatment data) and observational studies

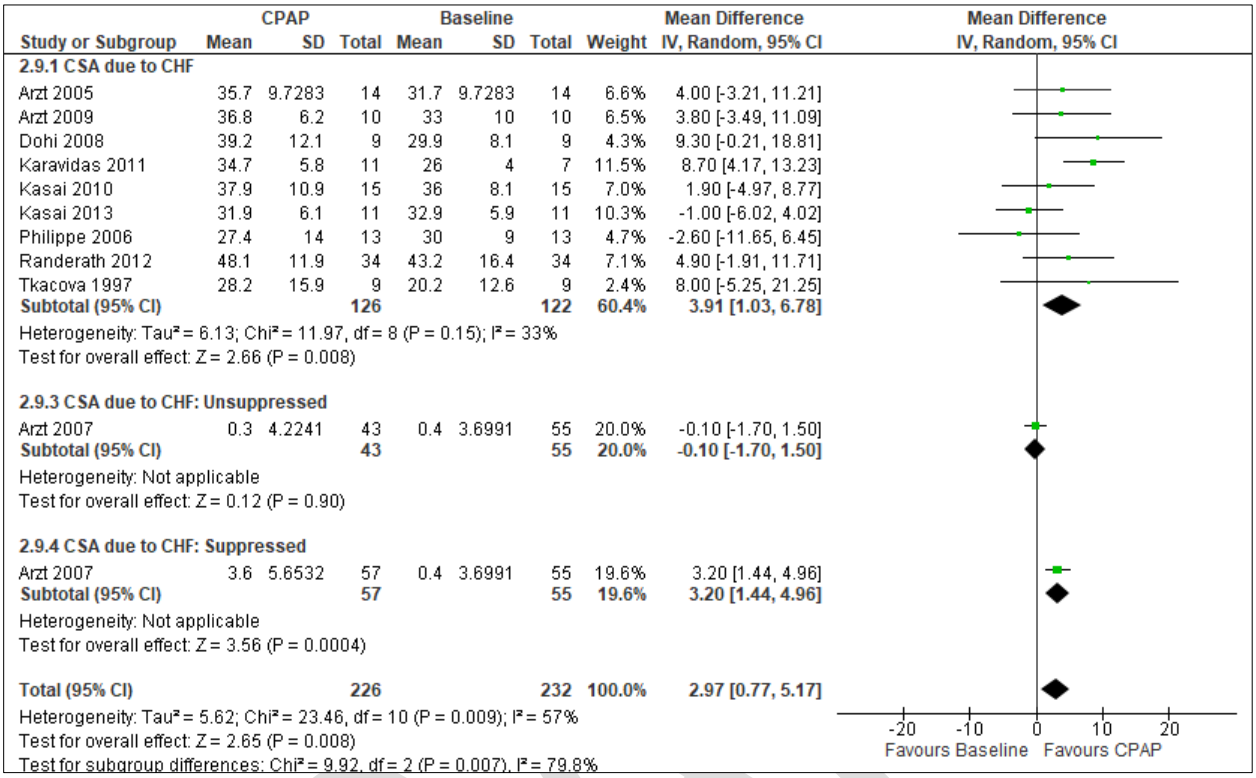


Figure S18. CPAP vs. Baseline (Cardiovascular disease, Systolic BP (mmHg)) [CST= - 2 mmHg], RCTs (single-arm pre- posttreatment data) and observational studies

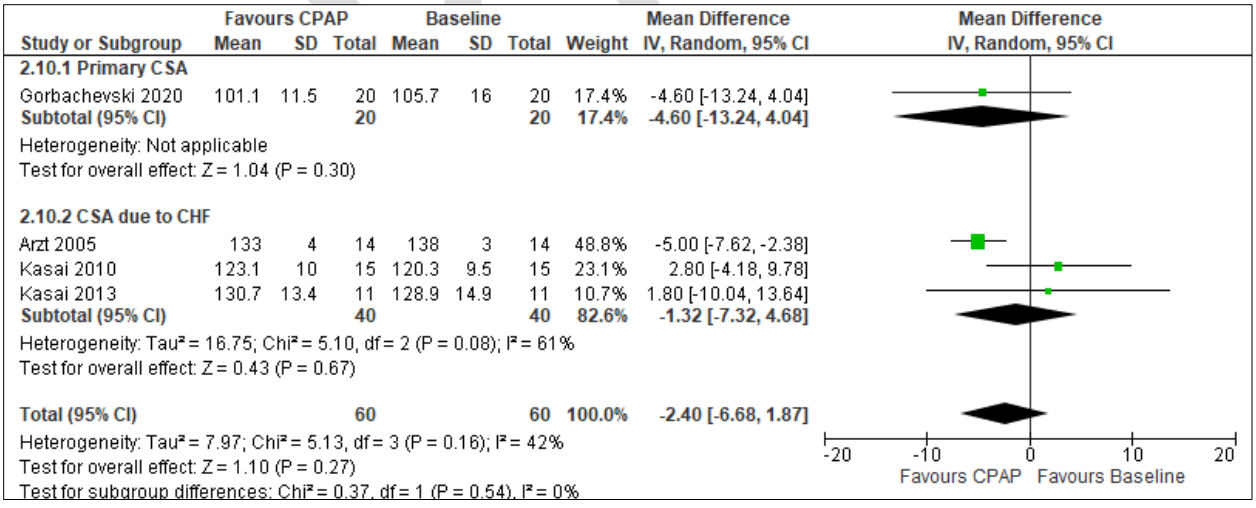


Figure S19. CPAP vs. Baseline (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCTs (single-arm pre- posttreatment data) and observational studies

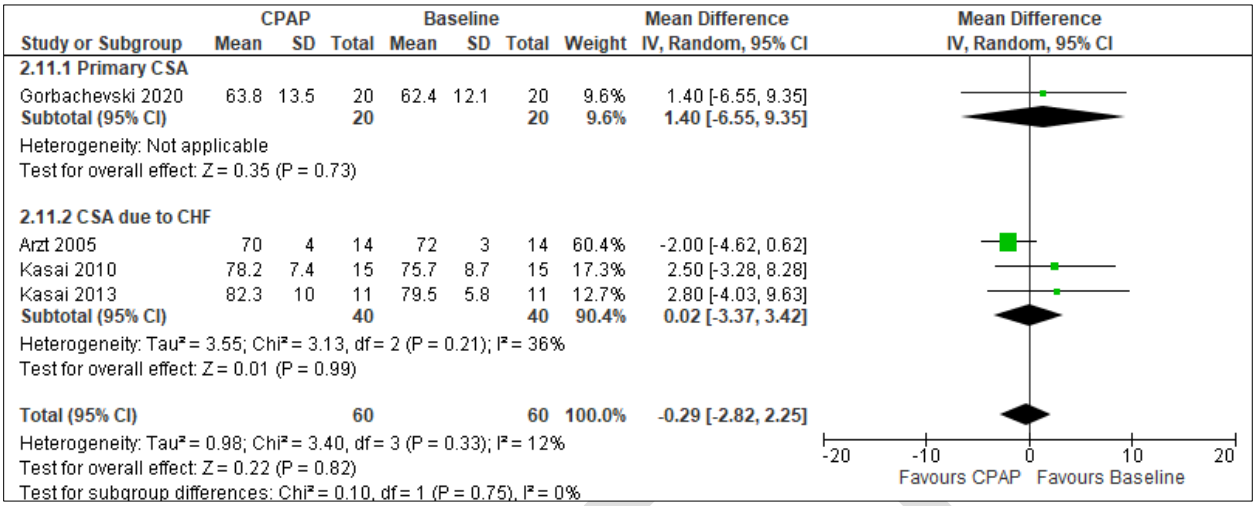


Figure S20. CPAP vs. Baseline (Cardiovascular disease, HR (beats/min)) [No CST], RCTs (single-arm pre-posttreatment data) and observational studies

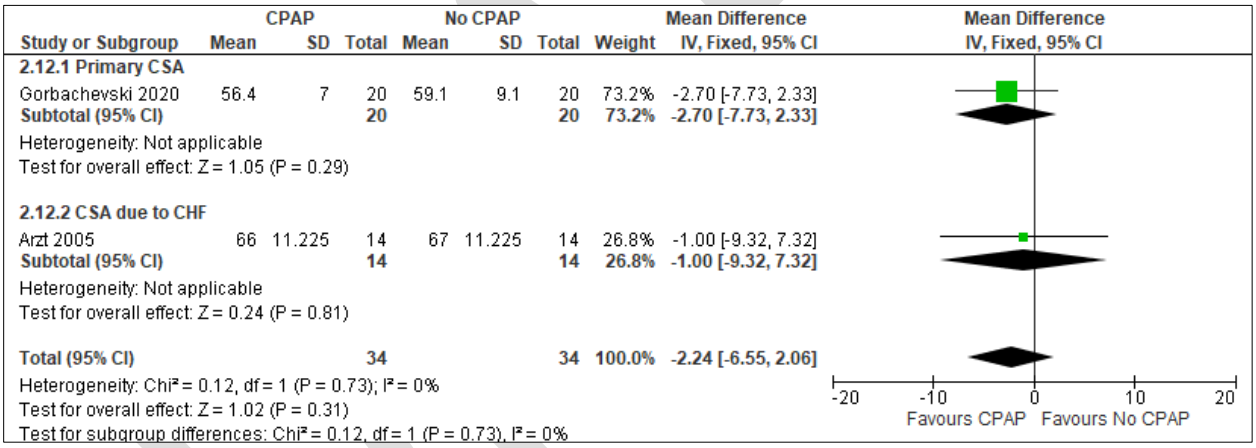
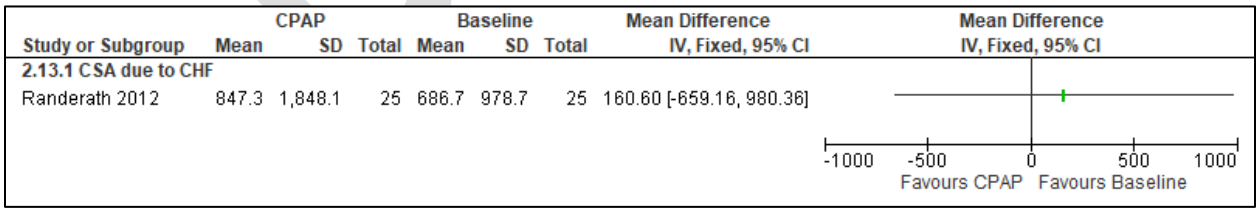
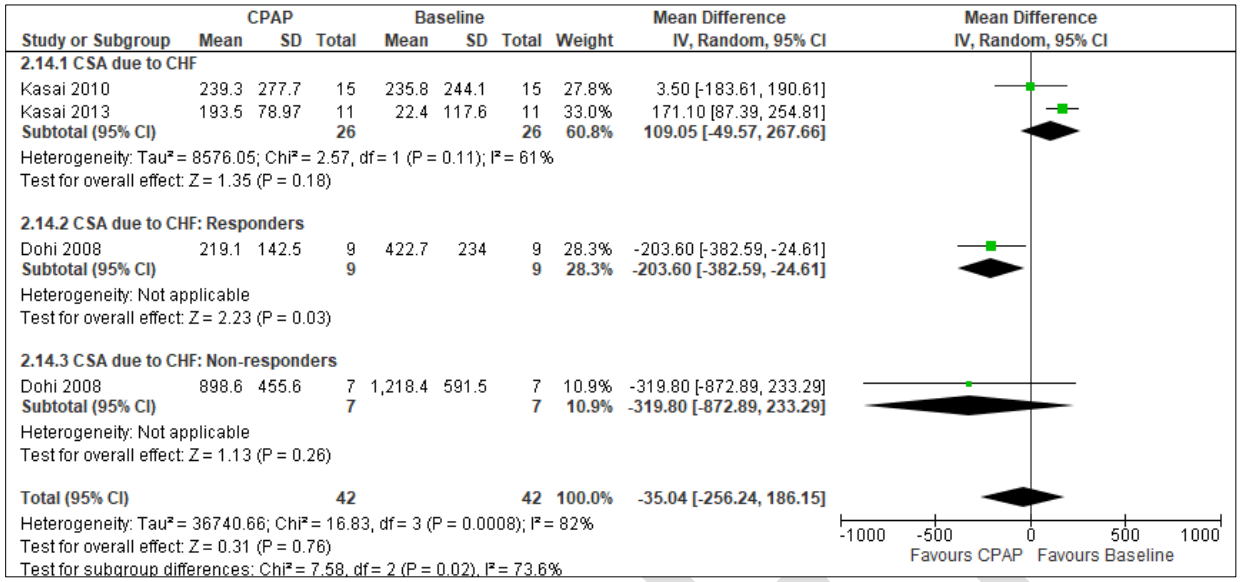


Figure S21. CPAP vs. Baseline (Cardiovascular disease, NT pro-BNP, ng/mL) [CST=50% reduction], RCTs (single-arm pre- posttreatment data) and observational studies



Randerath 2012 NT-pro BNP ng/ml

Figure S22. CPAP vs. Baseline (Cardiovascular disease, BNP pg/mL) [CST=50% reduction], RCTs (single-arm pre- posttreatment data) and observational studies



Kasai 2010 BNP pg/ml; Kasai 2013 reported BNP pg/ml median (IQR); figure 2 in Dohi 2008 BNP pg/ml

Important Outcomes

Figure S23. CPAP vs. Control (Fatigue subscale, Chronic Heart Failure Questionnaire) [CST= + 2 pts for fatigue], RCTs

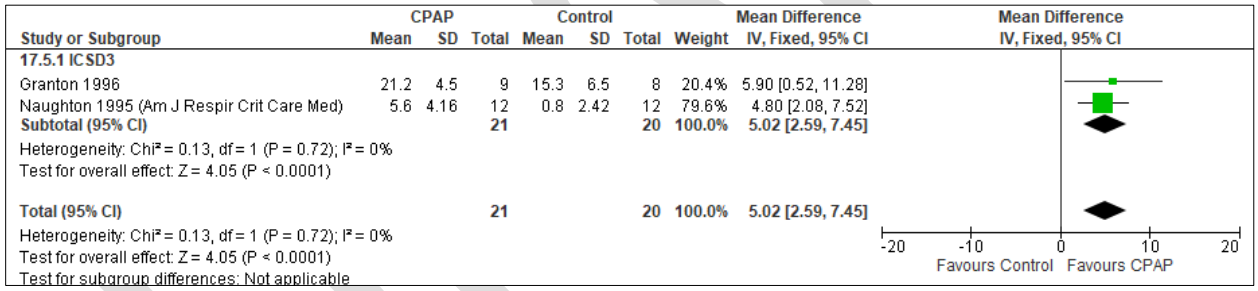


Figure S24 CPAP vs. Control (Sleep architecture (PSG), Sleep efficiency) [CST=10%], RCT

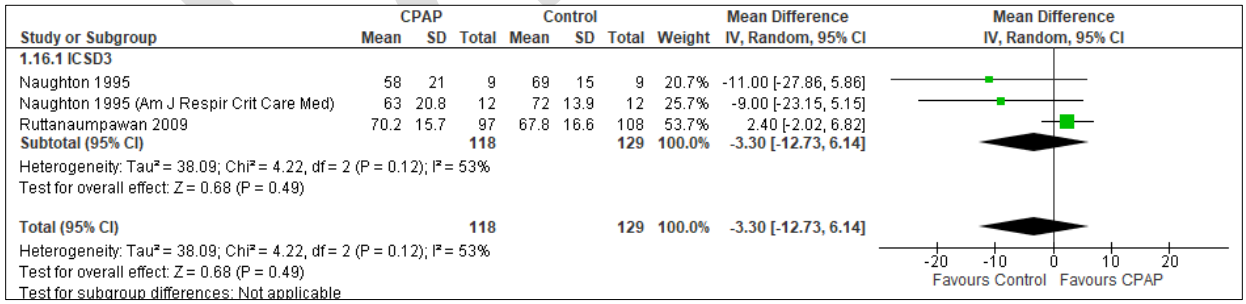
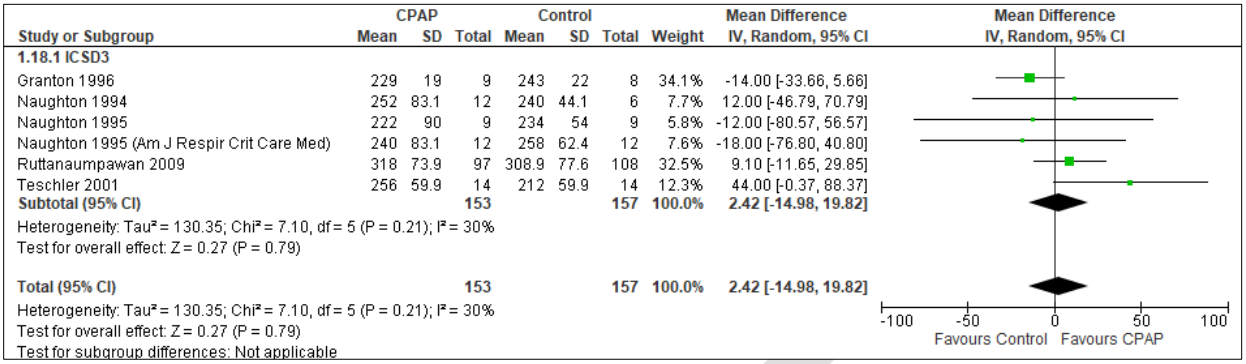
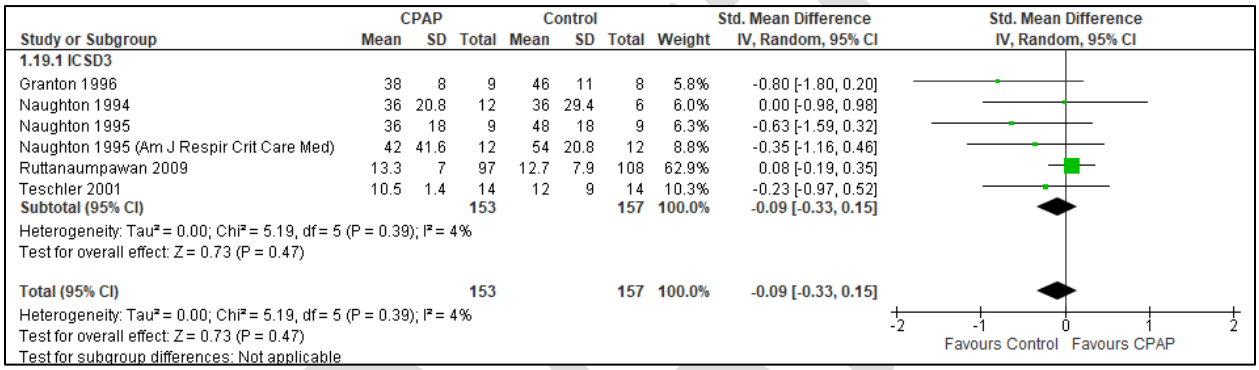


Figure S25. CPAP vs. Control (Sleep architecture (PSG), Total Sleep Time) [CST=15 min], RCT



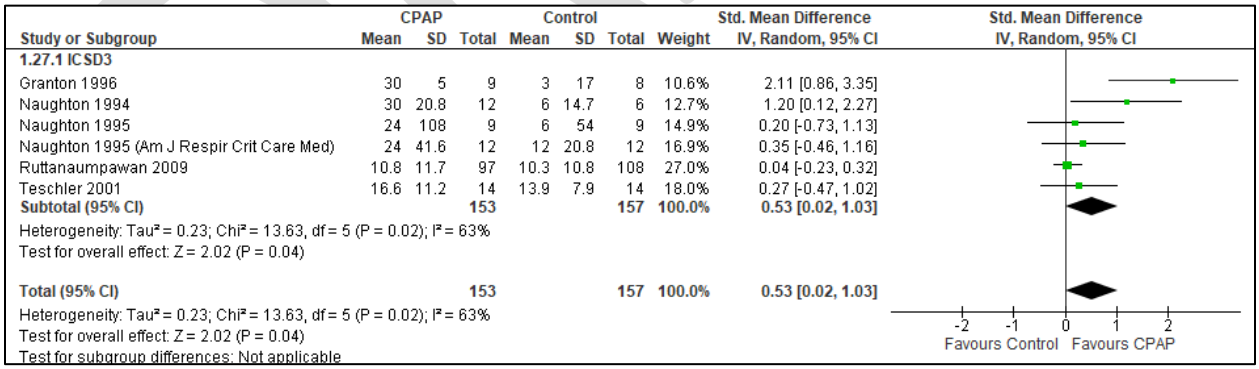
Naughton 1994, 1995, 1995 and Teschler 2001 SEM is converted to SD

Figure S26. CPAP vs. Control (Sleep architecture (PSG), REM%) [CST= +5% of TST], RCT



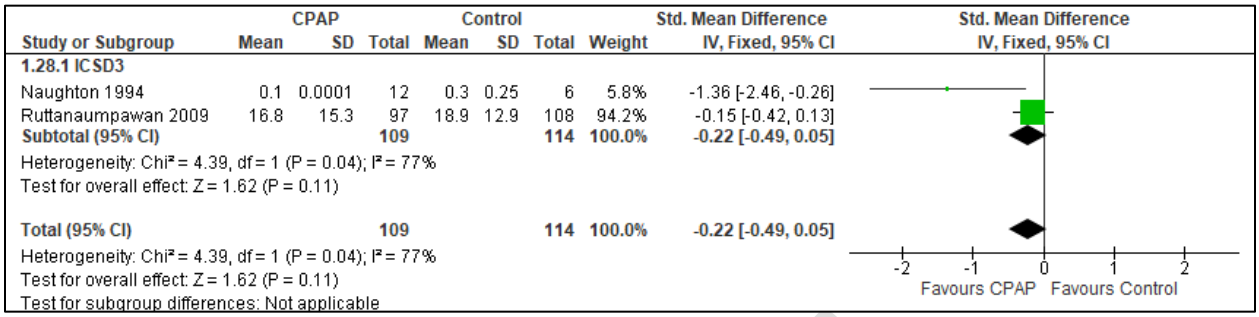
Naughton 1994, 1995, 1995 and Teschler 2001 SEM is converted to SD; Granton 1996 REM, minutes; Naughton 1994/1995/1995 (AJRCCM) REM hours -converted to minutes; Ruttanaumpawan 2009 REM%, Teschler 2001 REM%. The weighted average of the post intervention standard deviation of percent REM across Ruttanaumpawan and Teschler is 7.2. Re-expressed as percent REM, there was a mean decrease of -0.65% (95% CI -2.4, 1.08).

Figure S27. CPAP vs. Control (Sleep architecture (PSG), SWS%) [CST= +5% of TST], RCT



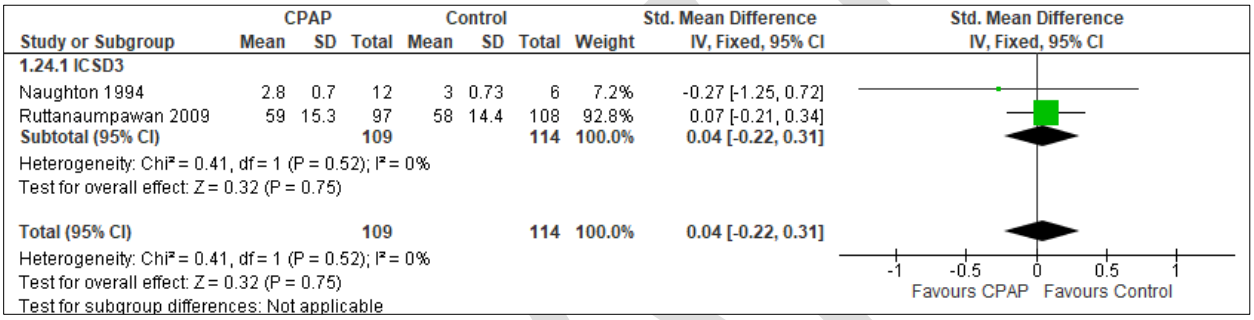
Naughton 1994, 1995, 1995 and Teschler 2001 SEM is converted to SD; Granton 1996 SWS, minutes; Naughton 1994/1995/1995 (AJRCCM) SWS hours -converted to minutes; Ruttanaumpawan 2009 SWS%, Teschler 2001 SWS%. The weighted average of the post intervention standard deviation of percent SWS across Ruttanaumpawan and Teschler is 11.04. Re-expressed as percent SWS, there was a mean increase of 5.9% (95% CI 0.22, 11.74).

Figure S28. CPAP vs. Control (Sleep architecture (PSG), Sleep stage N1%) [CST= -5% of TST], RCTs



Naughton 1994 S1 hours, SEM is converted to SD; Ruttanaumpawan 2009 N1%. The weighted average of the post intervention standard deviation of percent N1 for Ruttanaumpawan is 14.03. Re-expressed as percent N1, there was a mean decrease of -3.09% (95% CI -6.87, 0.7).

Figure S29. CPAP vs. Control (Sleep architecture (PSG), Sleep stage N2(%)) [CST= -5% of TST], RCTs



Naughton 1994 S2 hours, SEM is converted to SD; Ruttanaumpawan 2009 N2 %. The weighted average of the post intervention standard deviation of percent N2 for Ruttanaumpawan is 14.8. Re-expressed as percent N2, there was a mean increase of 0.6% (95% CI -3.26, 4.59).

Figure S30. CPAP vs. Control (Sleep architecture (PSG), Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], RCTs

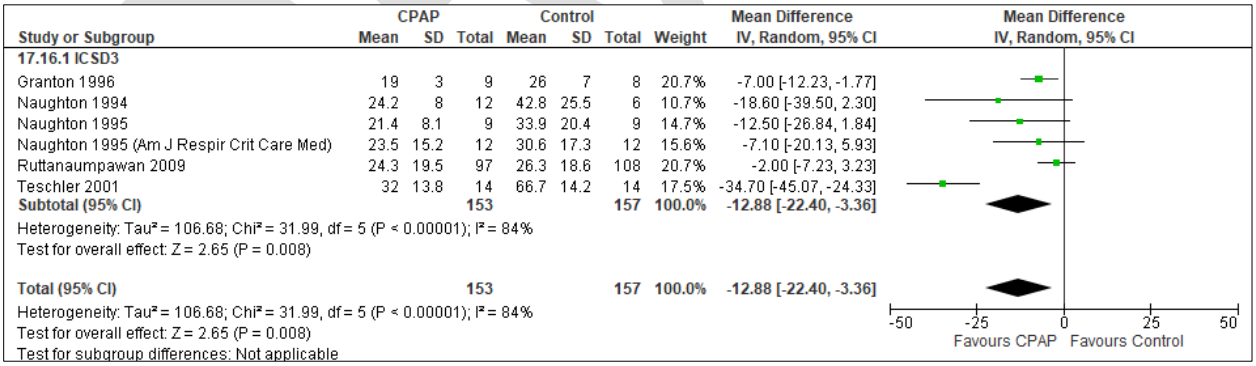
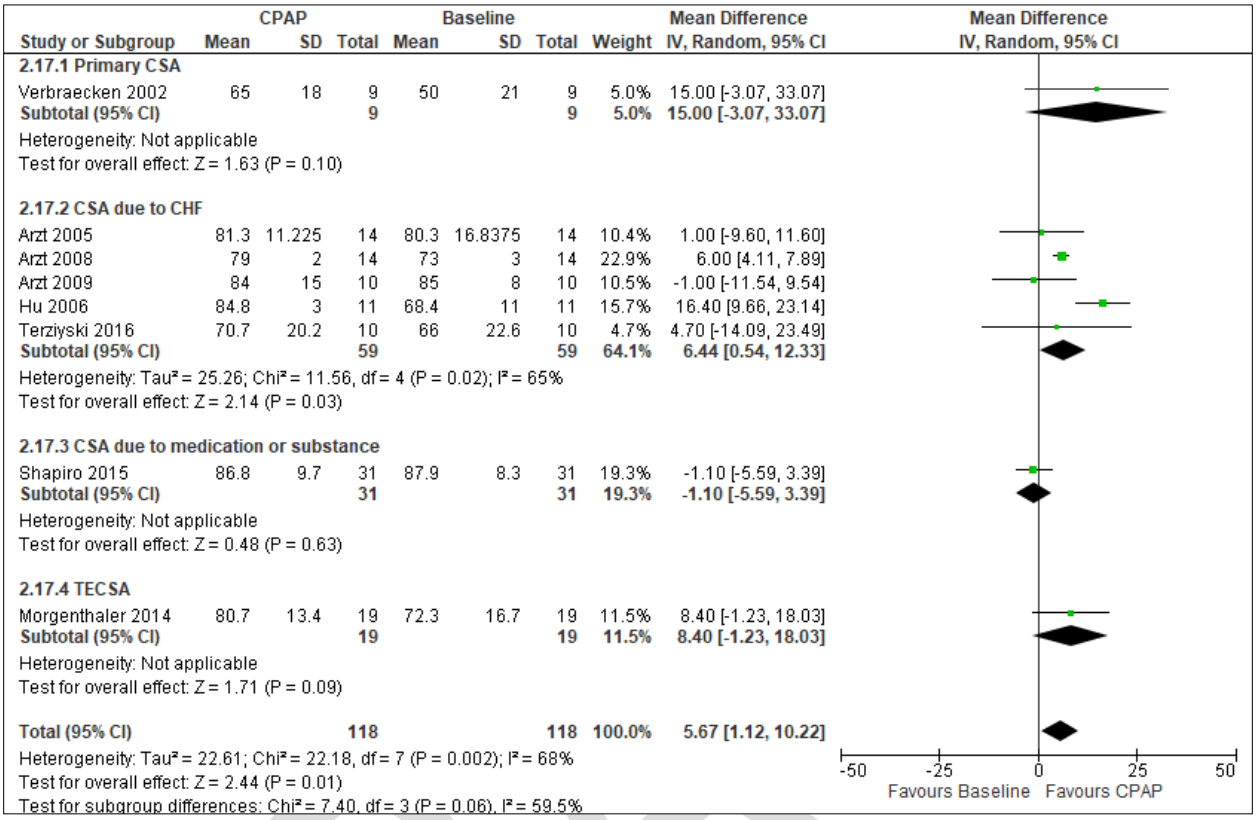


Figure S31. CPAP vs. Baseline (Sleep architecture (PSG), Sleep efficiency) [CST=10%], RCTs (single-arm pre- posttreatment data) and observational studies



Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S32. CPAP vs. Baseline (Sleep architecture (PSG), Total Sleep Time) [CST=15 min], RCTs (single-arm pre- posttreatment data) and observational studies

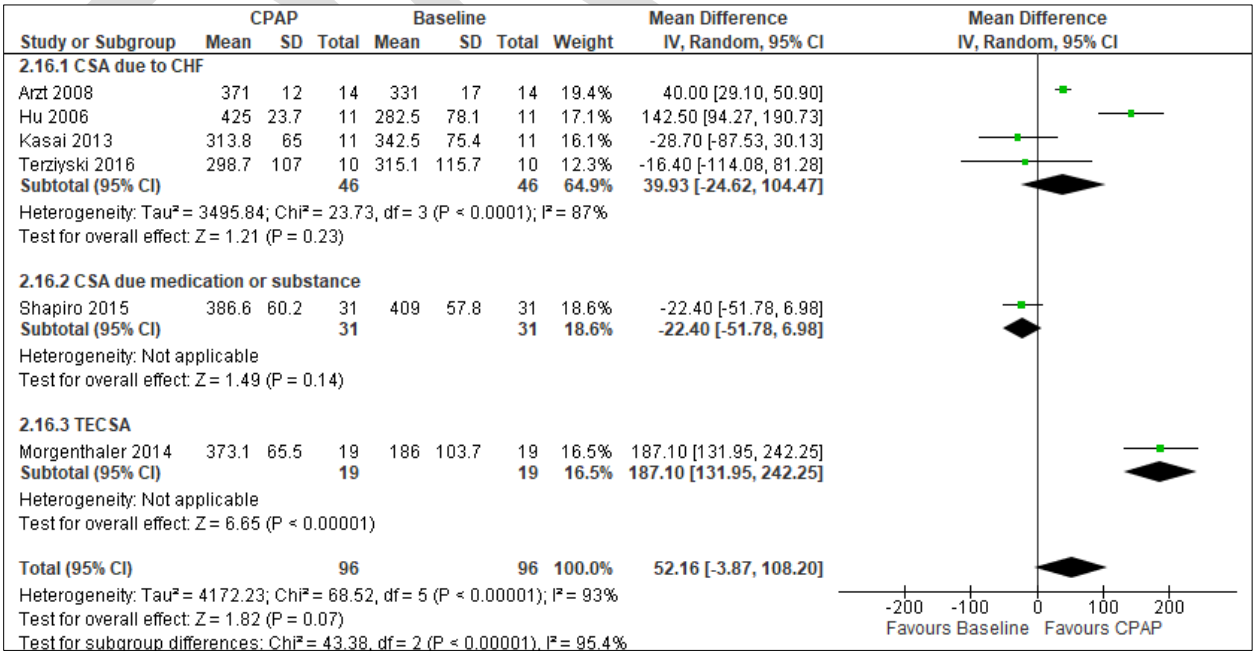


Figure S33. CPAP vs. Baseline (Sleep architecture, PSG, REM%) [CST=5% of TST], RCTs (single-arm pre-posttreatment data) and observational studies

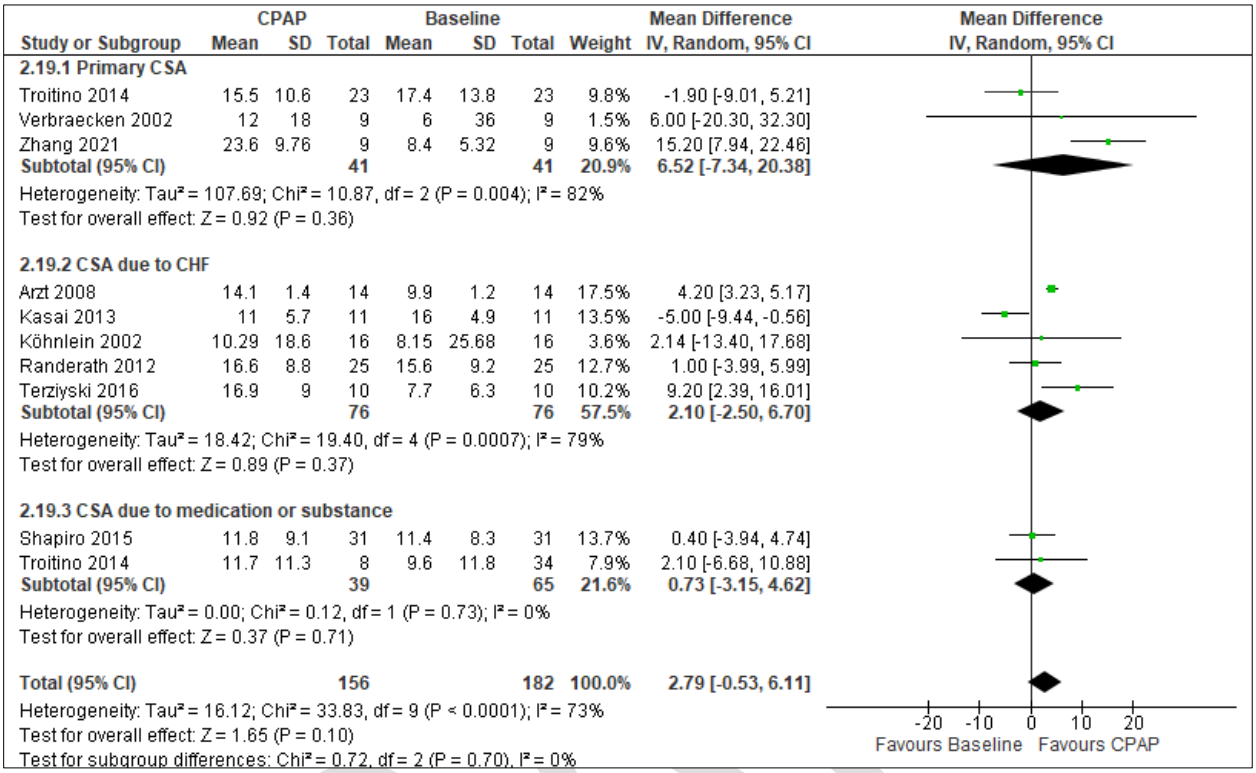


Figure S34. CPAP vs. Baseline (Sleep architecture, PSG Sleep Stage N1%), [CST=5% of TST], RCTs (single-arm pre- posttreatment data) and observational studies

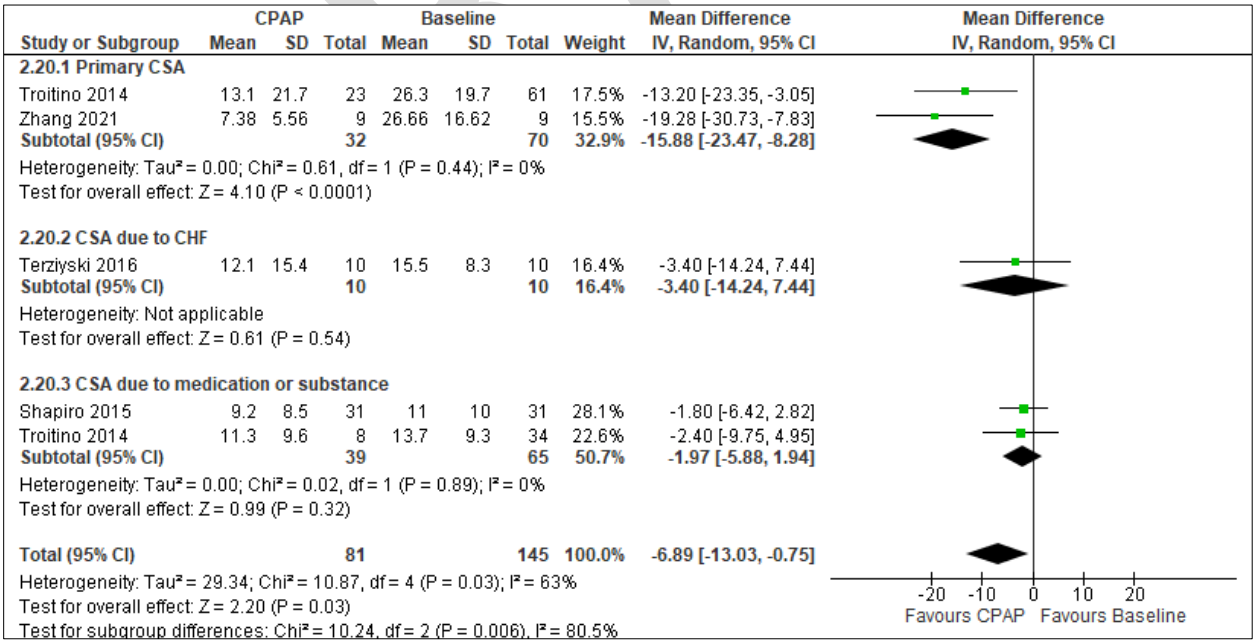


Figure S35. CPAP vs. Baseline (Sleep architecture, PSG Sleep Stage N2%), [CST=5% of TST], RCTs (single-arm pre- posttreatment data) and observational studies

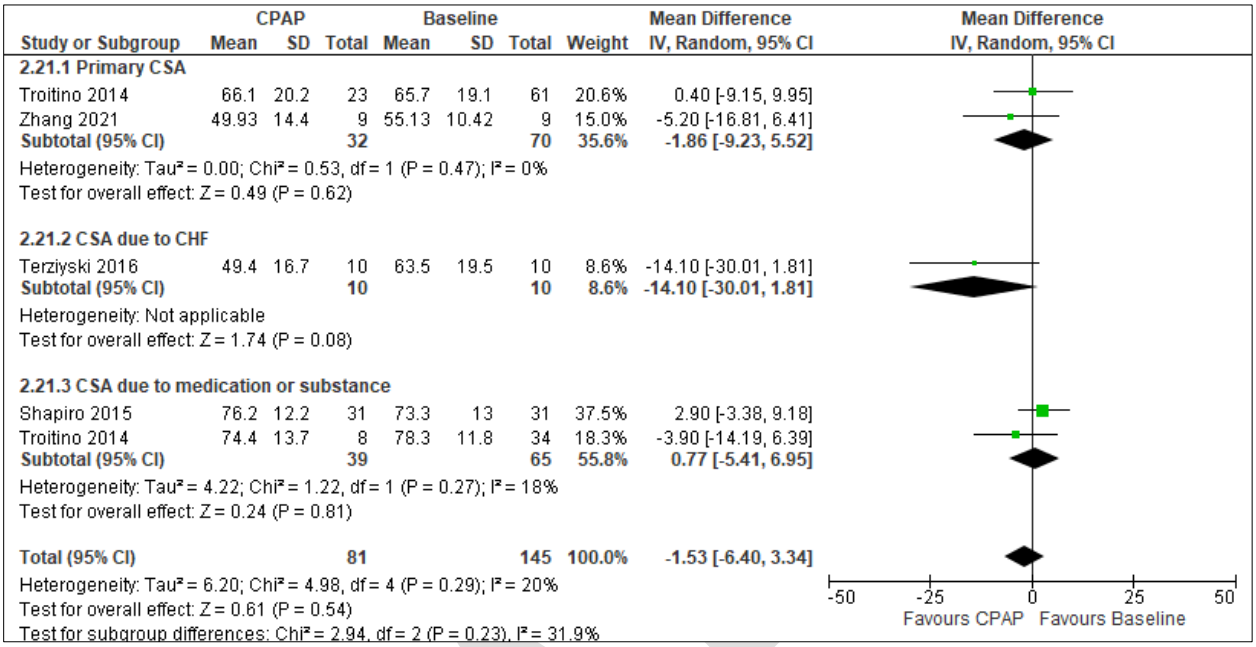


Figure S36. CPAP vs. Baseline (Sleep architecture, PSG, SWS%) [CST=5% of TST], RCTs (single-arm pre-posttreatment data) and observational studies

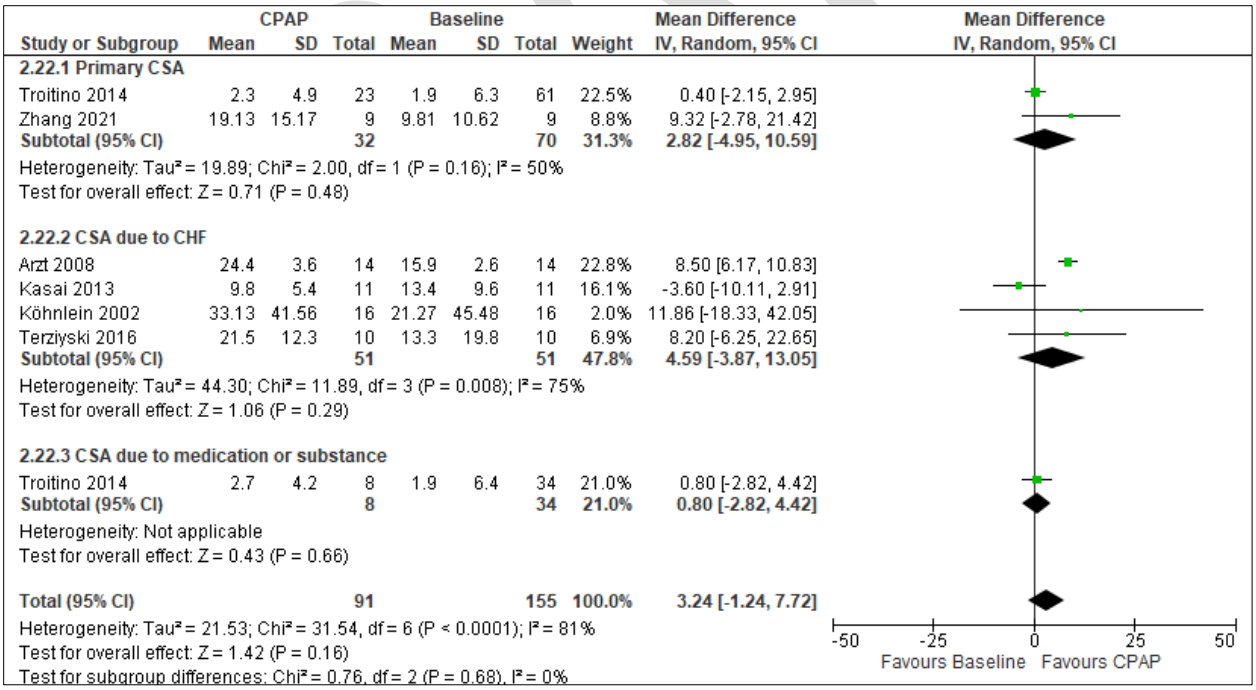
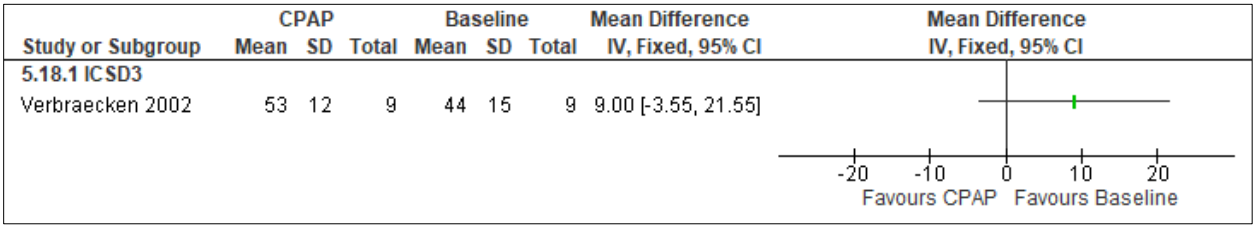
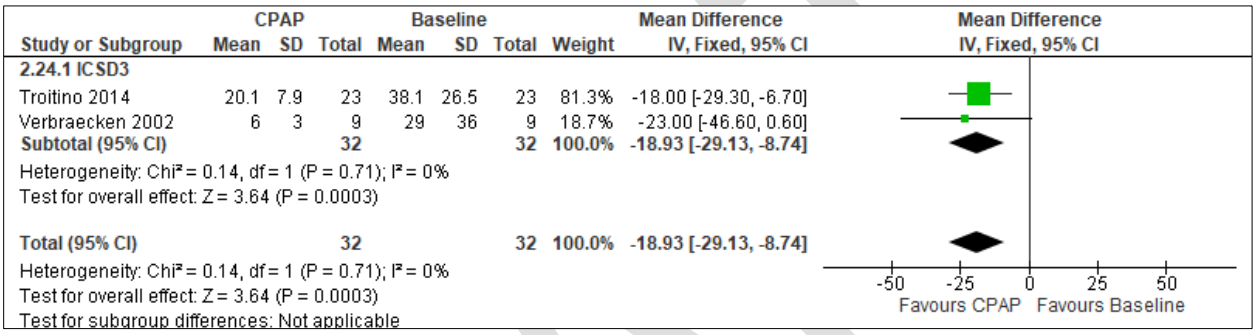


Figure S37. CPAP vs. Baseline (Sleep architecture, PSG, NREM%) [No CST], Non-randomized study



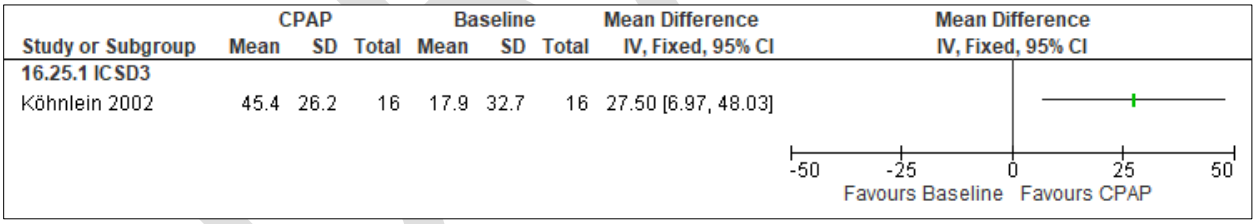
Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S38. CPAP vs. Baseline (Sleep architecture, PSG, Arousal Index (#/hr)) [CST=25% change from baseline or reduction to ≤12 events/hr], RCTs (single-arm pre- posttreatment data) and observational studies



Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S39. CPAP vs. Baseline (Daytime functioning, SF-36) [CST= 3 pts], RCT (single-arm pre-posttreatment data)



BPAP with a backup rate

Summary of Findings (GRADE)

Table S2 BPAP with a backup rate in adults with CSA

References: Cao 2014, Dellweg 2013, Dohi 2008, Fietze 2008, Hu 2006, Kasai 2005, Morgenthaler 2007, Teschler 2001, Troitino 2014

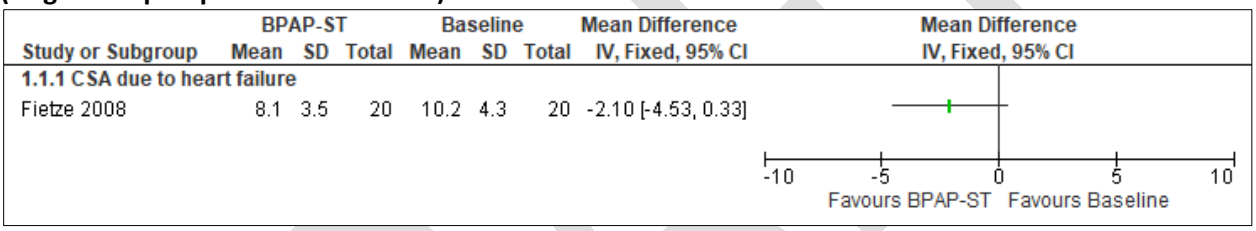
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference BPAP with a backup rate vs. baseline	No of Participants (studies)
Excessive sleepiness [ESS]	⊕◯◯◯ **VERY LOW**[a,b,c]	The mean difference in the BPAP with a backup rate group was **2.1 points lower (4.53 lower to 0.33 higher)** compared to baseline	20 (1 RCT)

Disease severity [AHI]	⊕◯◯◯ **VERY LOW**[a,b]	The mean difference in the BPAP with a backup rate group was **33.65 events/hour lower (41.44 lower to 25.86 lower)** compared to baseline	128 (9 studies)
Disease severity [CAI]	⊕◯◯◯ **VERY LOW**[a,b]	The mean difference in the BPAP with a backup rate group was **15.66 events/hour lower (25.12 lower to 6.2 lower)** compared to baseline	69 (5 studies)
Disease severity [CAHI]	⊕◯◯◯ **VERY LOW**[a,b]	The mean difference in the BPAP with a backup rate group was **15.5 events/hour lower (19.95 lower to 11.05 lower)** compared to baseline	11 (1 RCT)
Cardiovascular disease [LVEF]	⊕◯◯◯ **VERY LOW**[a,b]	The mean difference in the BPAP with a backup rate group was **7.83% higher (3.12 higher to 12.54 higher)** compared to baseline	34 (3 RCTs)

a. Downgraded quality of evidence due to data analyzed using pre- and posttreatment values
b. Imprecision due to small sample size (<200 participants)
c. Imprecision due to the 95% CI includes possibility for important benefit and no effect

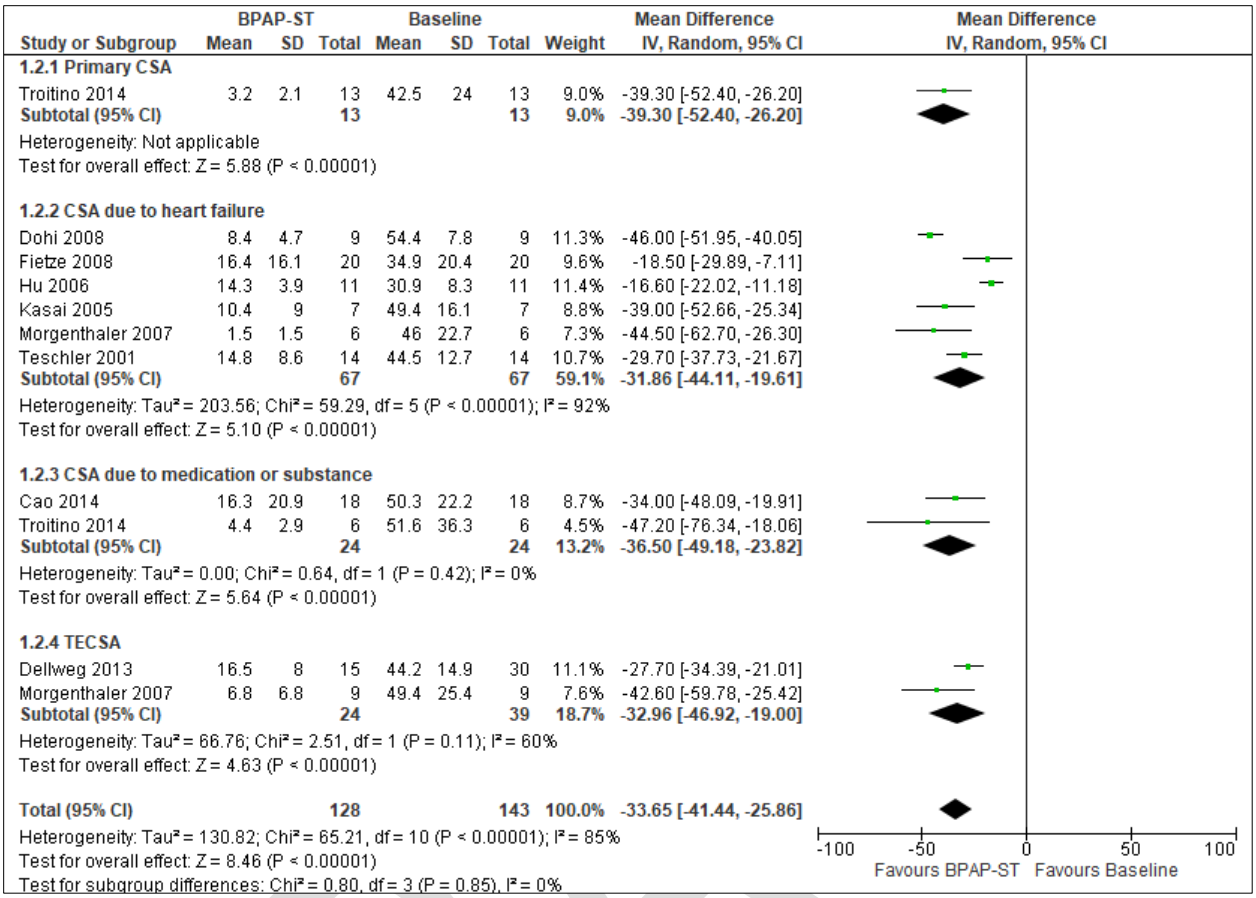
Critical Outcomes

Figure S40. BPAP with a backup rate vs. Baseline (Excessive sleepiness, ESS) [CST= - 2 points], RCT (single-arm pre- posttreatment data)



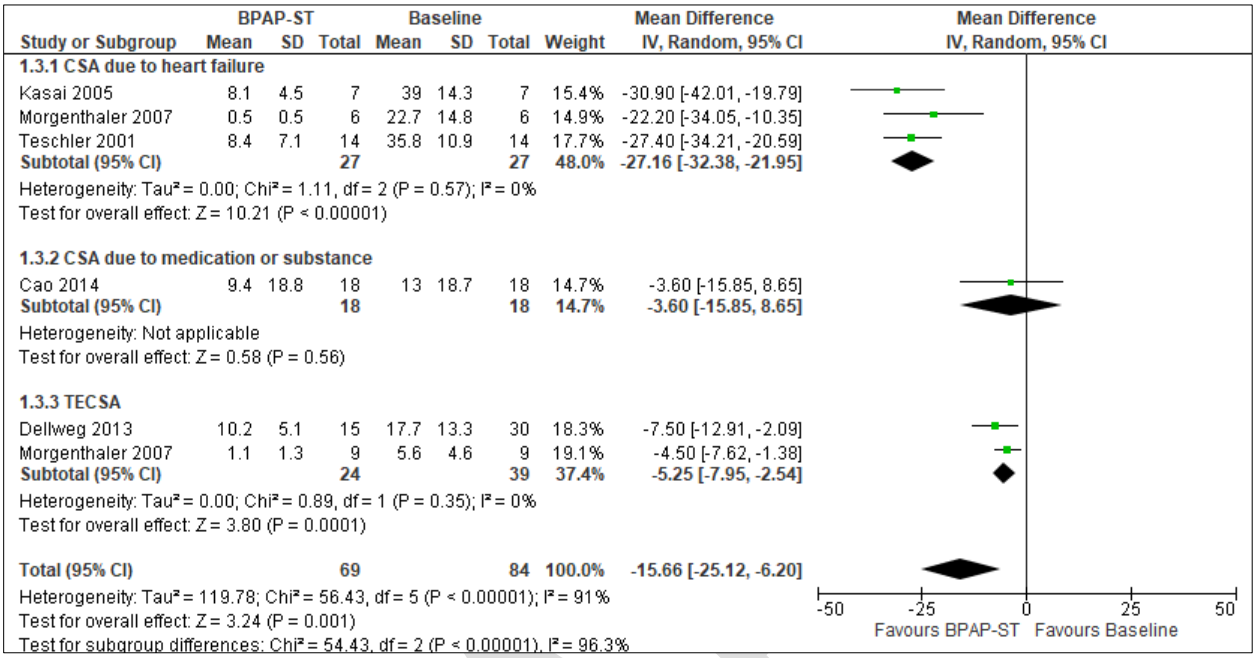
Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

Figure S41. BPAP-with a backup rate vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



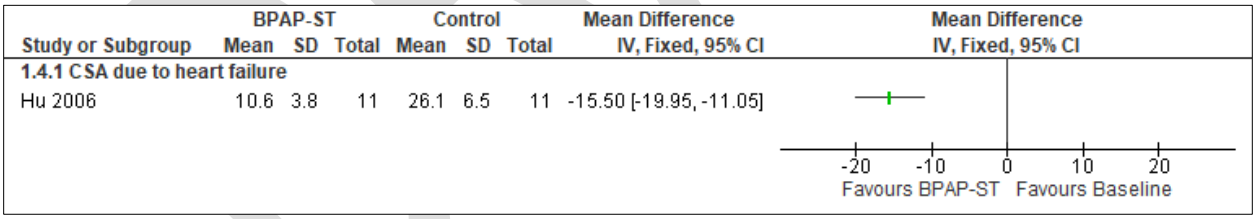
Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period ; Dohi 2008: baseline compared to BPAP-ST, 6-month follow-up; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, data reported as RDI; Morgenthaler 2007: diagnostic polysomnograms were done as a split night protocol, baseline compared to BPAP-ST, single night protocol; Dellweg 2013: baseline data included participants in both the ASV and the BPAP-ST groups, 6-week follow-up; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD; Cao 2014: pre-entry baseline PSG compared to BPAP-ST, the second overnight study was conducted within 2 weeks of the first assessment; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD; Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention night

Figure S42. BPAP-with a backup rate vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



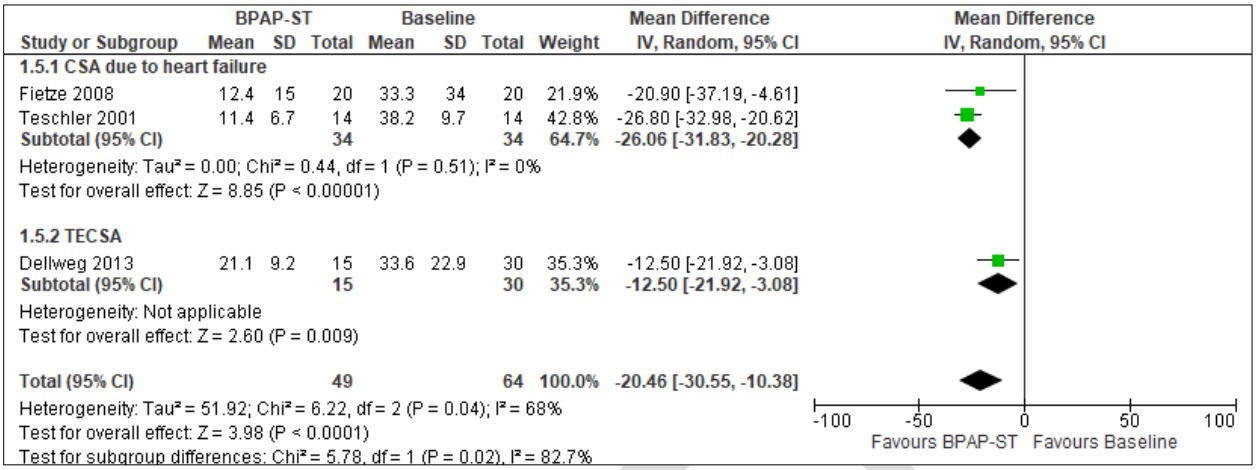
Morgenthaler 2007: diagnostic polysomnograms were done as a split night protocol, baseline compared to BPAP-ST, single night protocol; Dellweg 2013:baseline data included participants in both the ASV and the BPAP-ST groups , 6-week follow-up; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD ; Cao 2014:pre-entry baseline PSG compared to BPAP-ST, the second overnight study was conducted within 2 weeks of the first assessment; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Figure S43. BPAP-with a backup rate vs. Baseline (Disease Severity, CAHI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data)



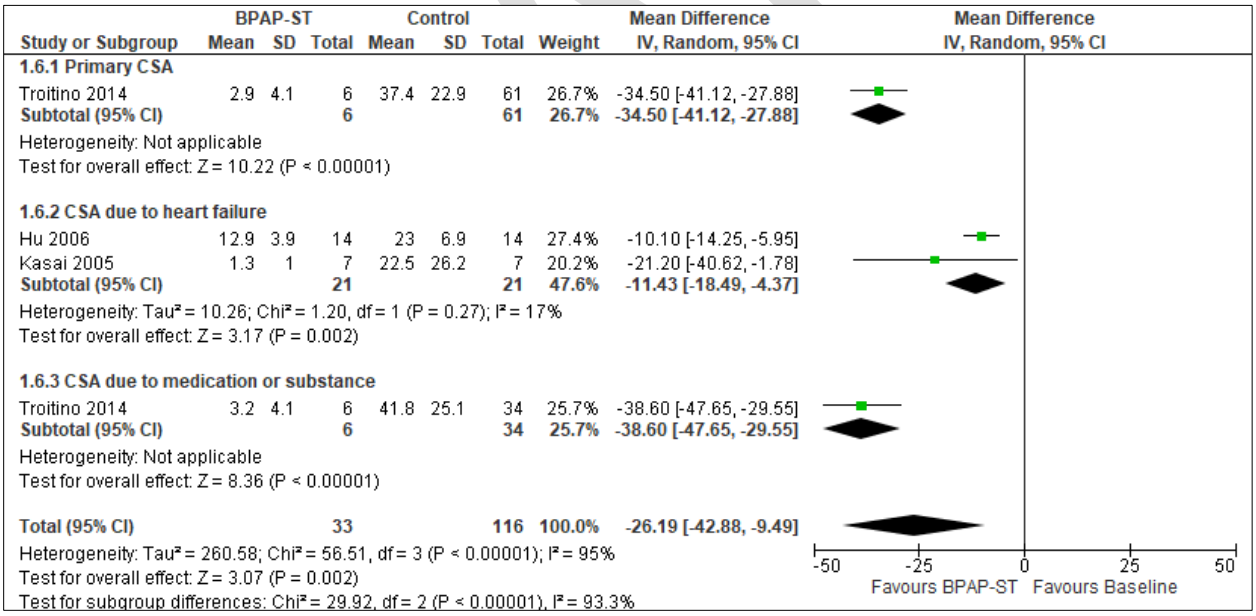
Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights.

Figure S44. BPAP-with a backup rate vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



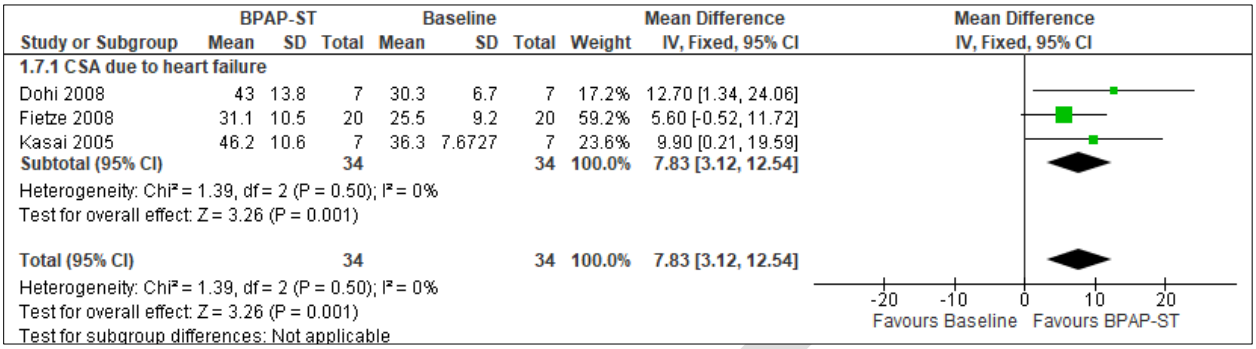
Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up; Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Figure S45. BPAP-with a backup rate vs. Baseline (Disease Severity, percentage sleep time with oxygen saturation <90 %) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



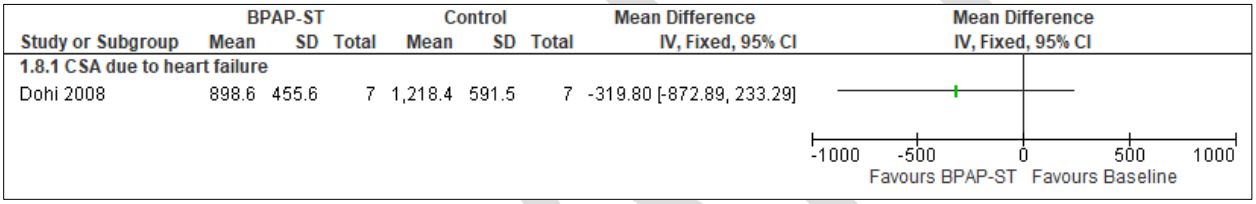
Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies -3 months later, data extracted from figure 1, SEM converted to SD; Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights

Figure S46. BPAP-with a backup rate vs. Baseline (Cardiovascular Disease, LVEF) [CST= + 5%], RCT (single-arm pre- posttreatment data) and observational studies



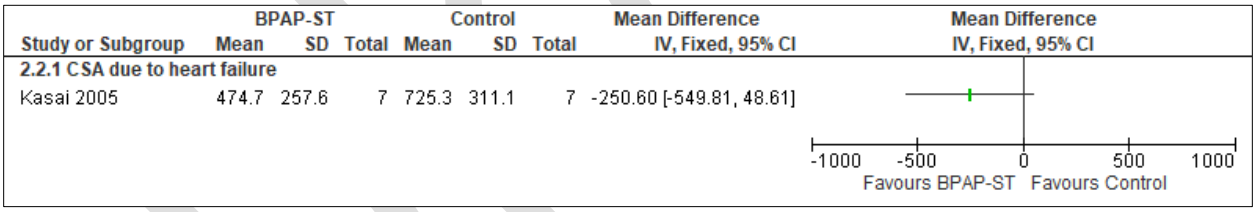
Dohi 2008: baseline compared to BPAP-ST, 6-month follow-up; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up; Kasai 2005: participants in control group refused BPAP-ST following diagnosis of CSA-CSR, 3-month follow-up, SEM converted to SD

Figure S47. BPAP-with a backup rate vs. Baseline (Cardiovascular Disease, BNP, pg/mL) [CST= - 50% reduction from baseline], Observational Study



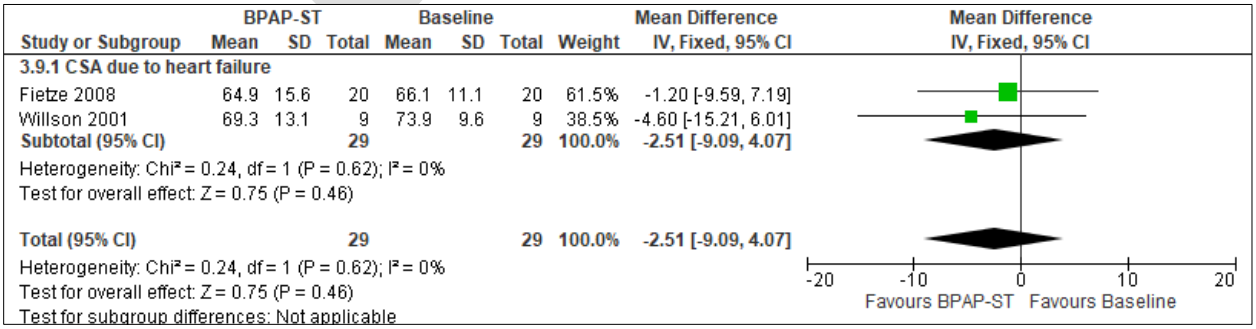
Data from figure 2 in Dohi 2008, BNP pg/ml: baseline compared to BPAP-ST, 6-month follow-up

Figure S48. BPAP-with a backup rate vs. Control (Cardiovascular Disease, BNP, pg/mL) [CST= - 50% reduction from baseline], Observational Study



Data from figure 5 in Kasai 2005: participants in control group refused BPAP-ST following diagnosis of CSA-CSR, 3-month follow-up, SEM converted to SD; BNP pg/ml. Baseline BPAP-ST 993.6 +/- 332

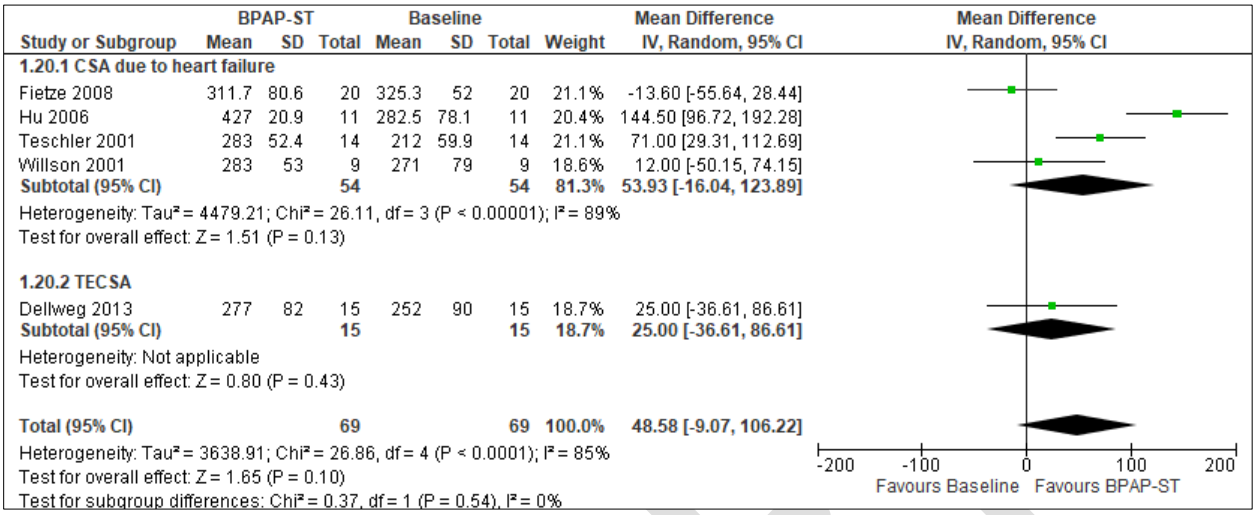
Figure S49. BPAP-with a backup rate vs. Baseline (Cardiovascular Disease, HR) [No CST], Observational Study



*Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up
Willson 2001: Follow-up duration unclear

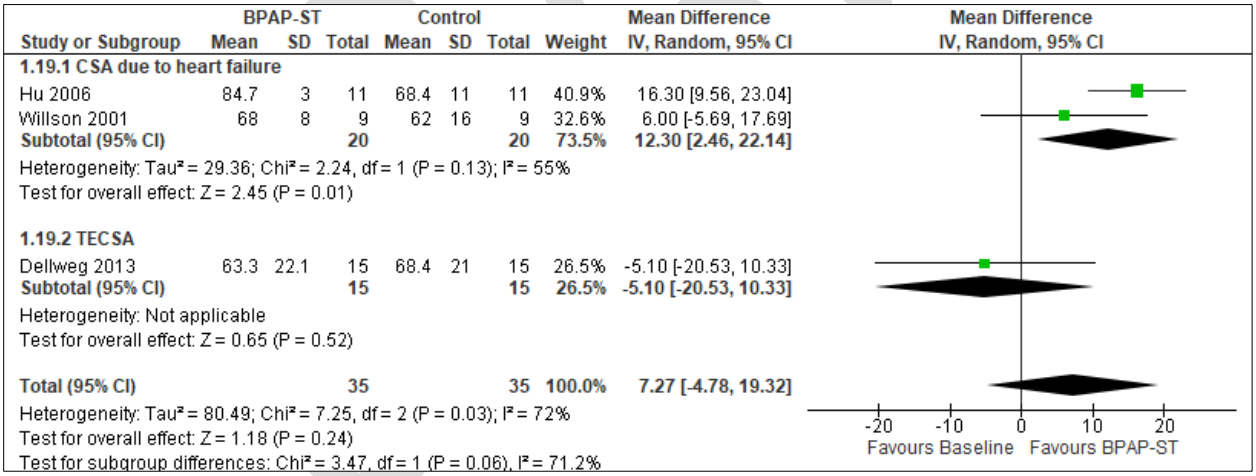
Important Outcomes

Figure S50. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST=+15 minutes], Observational Studies



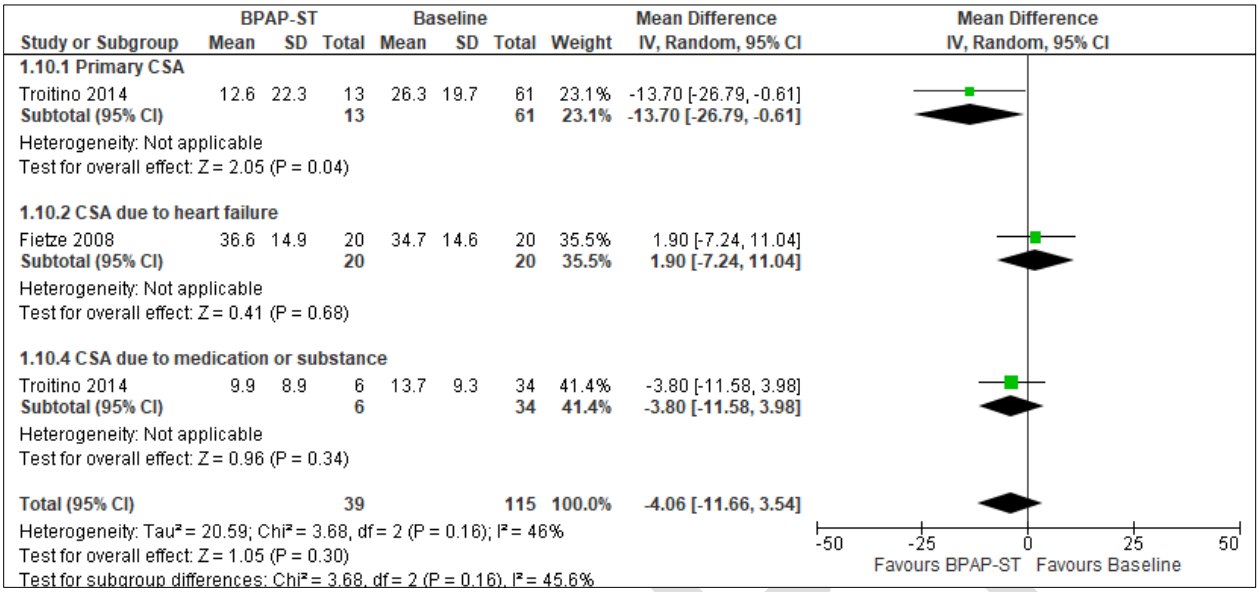
Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up; Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up; Willson 2001: Follow-up duration unclear; Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention

Figure S51. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep Efficiency) [CST=+10%], Observational Studies



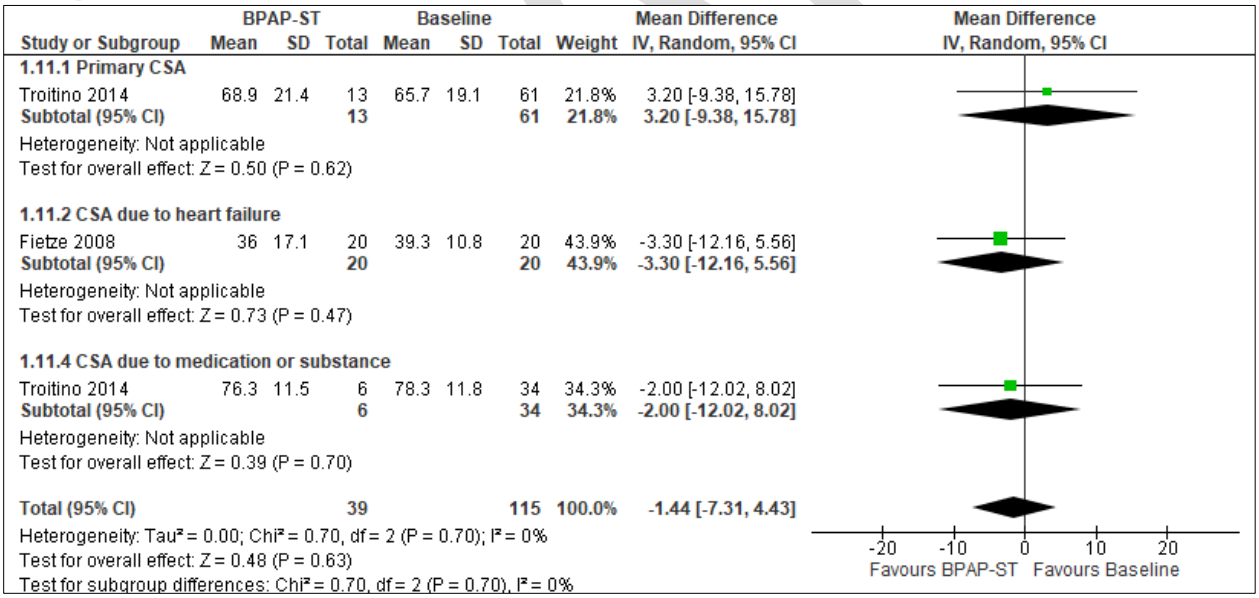
Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up
Willson 2001: Follow-up duration unclear
Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention

Figure S52. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep stage N1%) [CST=-5% of TST], Observational Studies



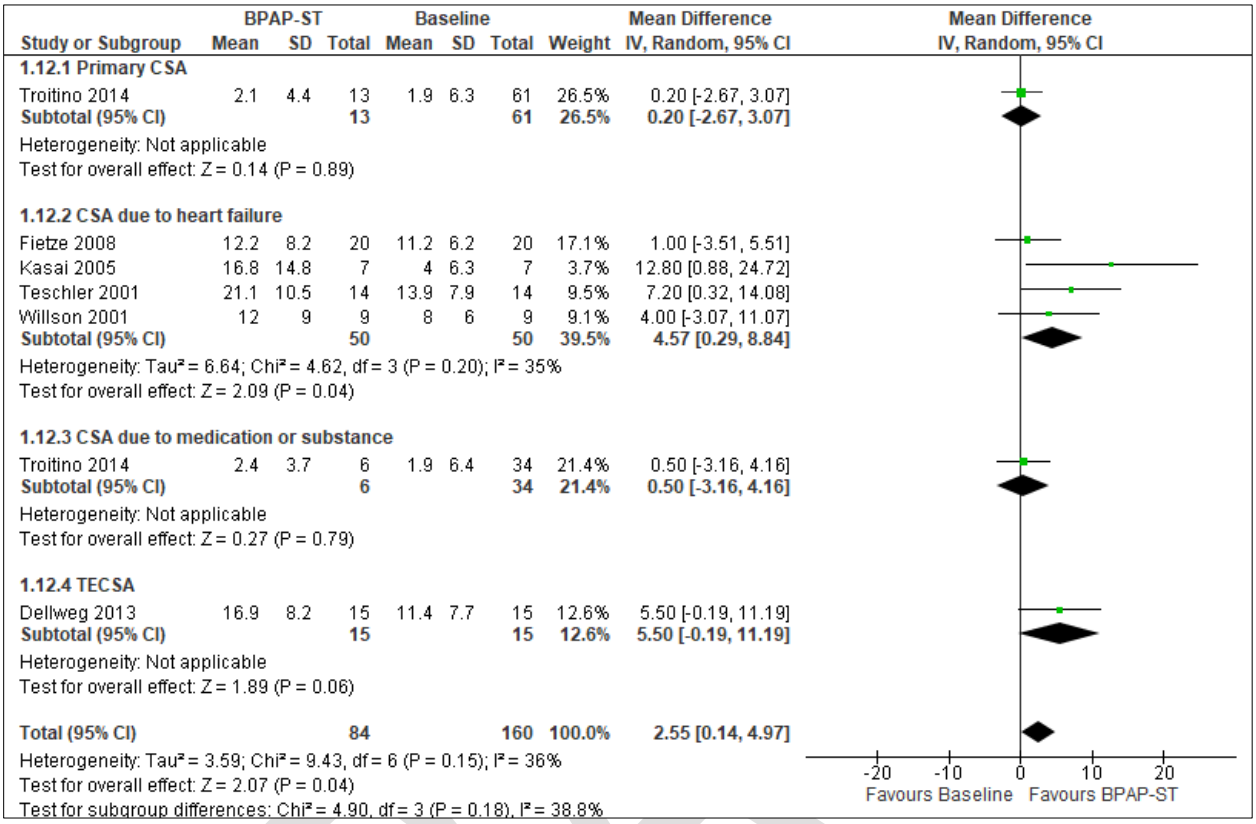
*Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period, N1 %; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, reported as N1%

Figure S53. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep stage N2%) [CST=-5% of TST], Observational Studies



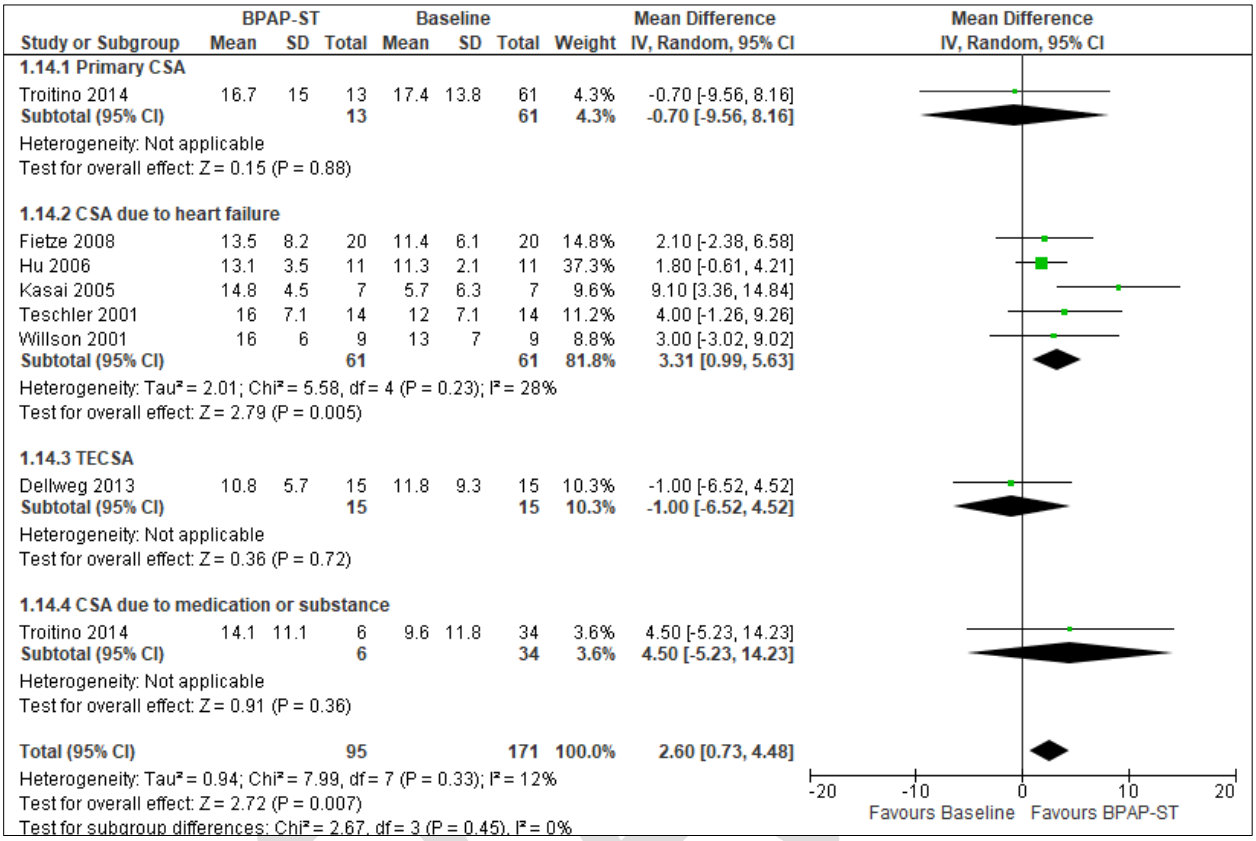
*Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period, N2 %; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, N2%

Figure S54. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep stage N3%) [CST=+5% of TST], Observational Studies



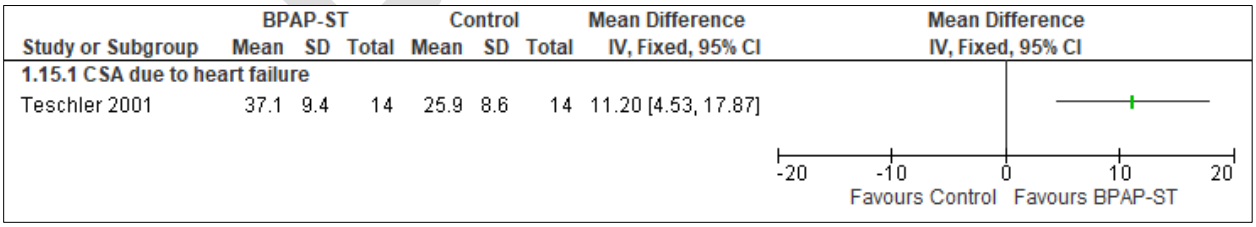
*Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period, N3% Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, N3% Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up, SWS%; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD, SWS%; Willson 2001: Follow-up duration unclear, SWS%; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD, SWS%

Figure S55. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, REM %) [CST=+5% of TST], Observational Studies



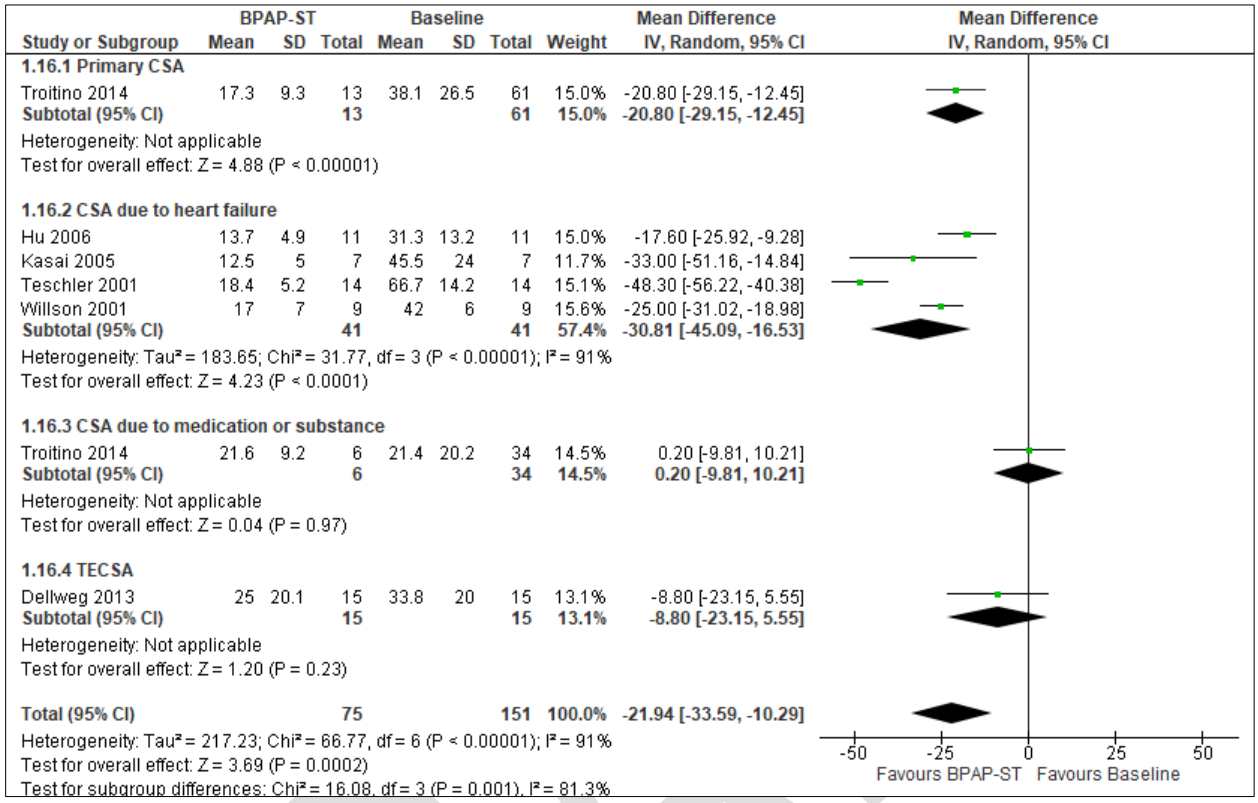
Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period
Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up
Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up
Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD
Willson 2001: Follow-up duration unclear
Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD
Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights

Figure S56. BPAP-with a backup rate vs. Control (Sleep architecture, PSG, SWS% and REM%) [No CST], RCTs



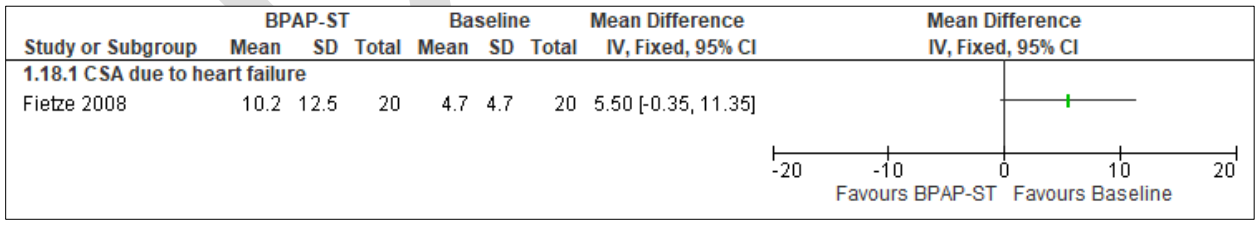
Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Figure S57. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Arousal Index) [CST=25% percent reduction from baseline or reduction to ≤12 events/hr], Observational Studies



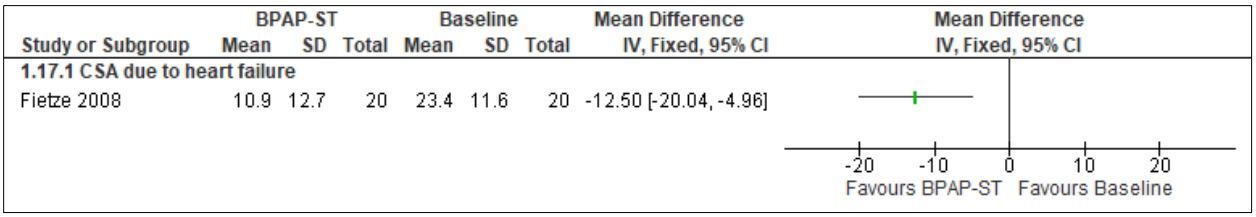
Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period
Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up
Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD
Willson 2001: Follow-up duration unclear
Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD
Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights

Figure S58. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Movement arousals) [CST=25% percent reduction from baseline], Observational Studies



Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

Figure 59. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Respiratory-related arousals) [CST=25% percent reduction from baseline], Observational Studies



Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

BPAP (without a backup rate)

Summary of Findings (GRADE)

Table S3 BPAP in adults with CSA

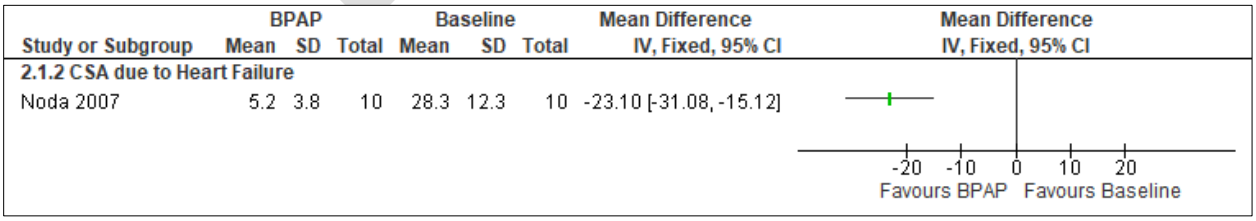
References: Noda 2007

Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **BPAP vs. baseline or control**	**No of Participants (studies)**
Disease severity [AHI]	⨁◯◯◯ **VERY LOW**[a,b,c]	The mean difference in the BPAP group was **23.1 events/hour lower (31.08 lower to 15.12 lower)** compared to baseline	10 (1 RCT)
Disease severity [CAI]	⨁◯◯◯ **VERY LOW**[a,b,c]	The mean difference in the BPAP group was **10.6 events/hour lower (11.13 lower to 10.07 lower)** compared to baseline	10 (1 RCT)
Cardiovascular disease [LVEF]	⨁◯◯◯ **VERY LOW** [b,c,d]	The mean difference in the BPAP group was **13% higher (3 higher to 23 higher)** compared to control	10 (1 RCT)
Cardiovascular disease [NYHA functional class score]*	⨁⨁◯◯ **LOW**[b,c]	The mean difference in the BPAP group was **0.7 lower (1.26 lower to 0.14 lower)** compared to control	10 (1 RCT)

a. Downgraded quality of evidence due to RCT data analyzed using pre- and posttreatment values
b. Imprecision due to small sample size (<200 participants)
c. Indirectness in the intervention
d. Imprecision due to the 95% CI includes possibility for important benefit and no effect
*CST not established by the task force

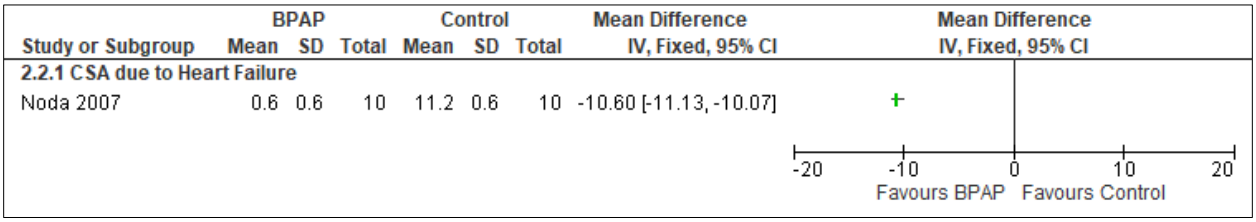
Critical Outcomes

Figure S60. BPAP vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline] RCT (single-arm pre- posttreatment data)



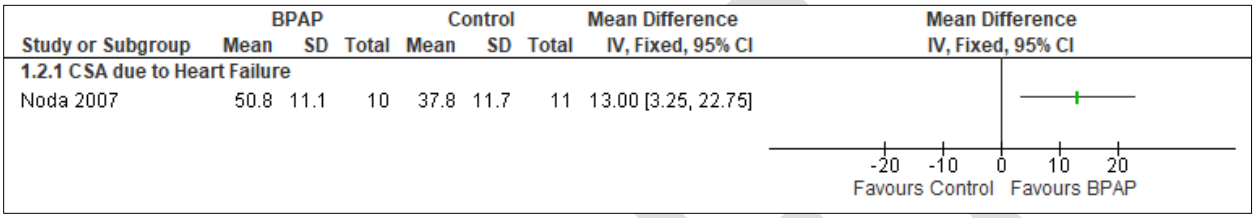
Noda 2007: SEM converted to SD, only baseline vs post-treatment data available for BPAP group. BPAP group had an 82% reduction in AHI from baseline.

Figure S61. BPAP vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCT (single-arm pre- posttreatment data)



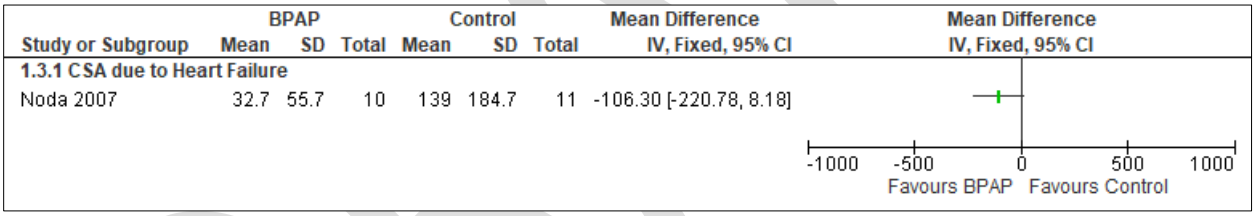
Noda 2007: SEM converted to SD, only baseline vs post-treatment data available for BPAP group. BPAP group had a 96% reduction in CAI from baseline.

Figure S62. BPAP vs. Control (Cardiovascular Disease, LVEF) [CST= +5%], RCT



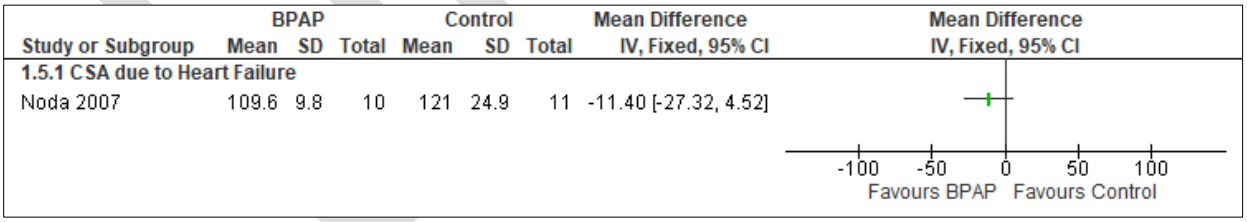
Noda 2007: SEM converted to SD

Figure S63. BPAP vs. Control (Cardiovascular Disease, BNP, pg/mL) [CST= -50% reduction from baseline], RCT



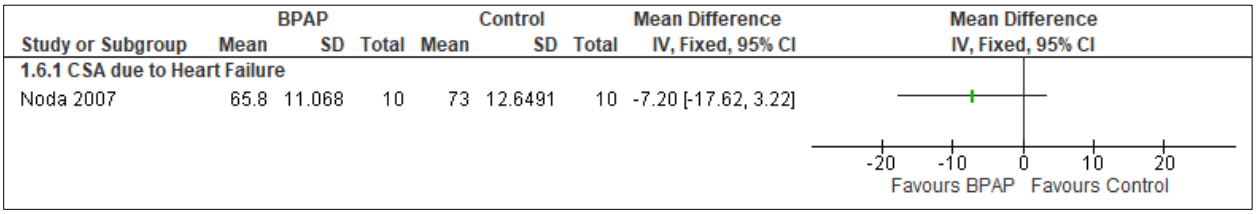
Noda 2007: SEM converted to SD; BNP pg/ml. Baseline BPAP BNP 162.8 +/- 44.5(SE)

Figure S64. BPAP vs. Control (Cardiovascular Disease, Systolic BP) [CST= - 2 mmHg], RCT



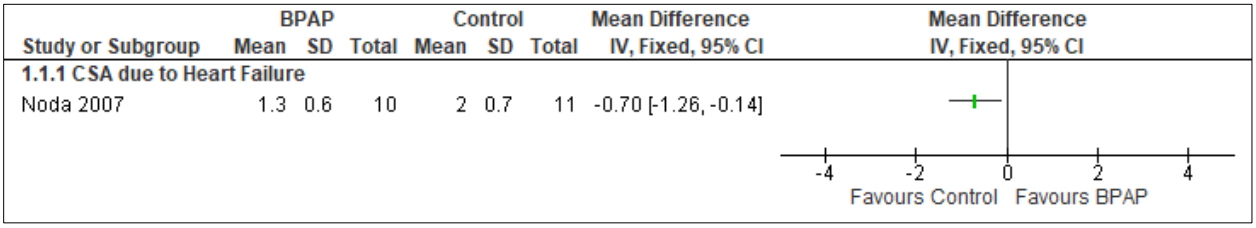
Noda 2007: SEM converted to SD

Figure S65. BPAP vs. Control (Cardiovascular Disease, Diastolic BP) [CST= - 1 mmHg], RCT



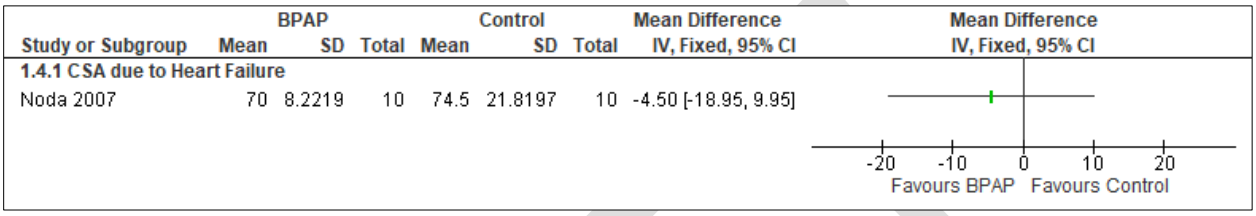
Noda 2007: SEM converted to SD

Figure S66. BPAP vs. Control (Cardiovascular Disease, NYHA functional class score) [No CST], RCT



Noda 2007: SEM converted to SD

Figure S67. BPAP vs. Control (Cardiovascular Disease, HR) [No CST], RCT



Noda 2007: SEM converted to SD

Important Outcomes

None

ASV

Summary of Findings (GRADE)

Table S4 ASV in adults with CSA

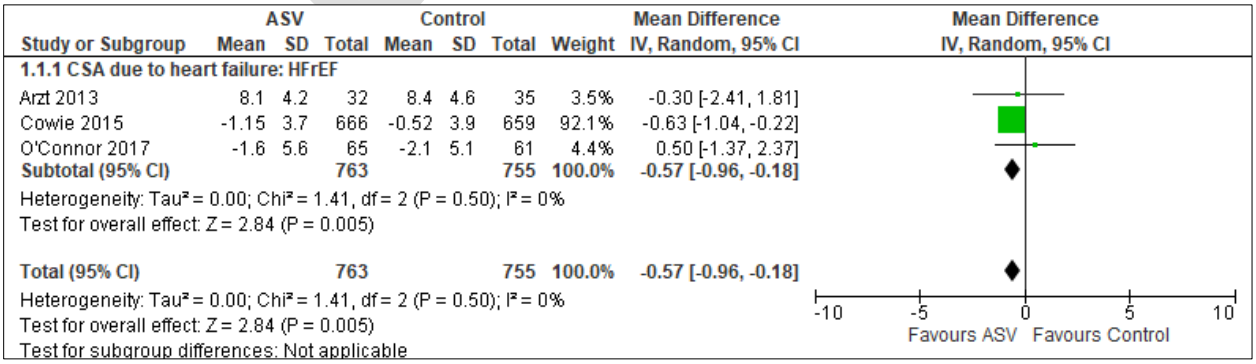
References: Arzt 2013, Bradley 2023, Cowie 2015, Daubert 2018, Hetzenecker 2016 (Sl Med), Ilious 2018, Miyata 2012, O'Connor 2017, Szollosi 2006, Tamisier 2022, Toyama 2017, Yoshihisa 2012 (EJHF)

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference ASV vs. control	No of Participants (studies)
Excessive sleepiness [ESS]	⊕⊕⊕◯ **MODERATE**[a]	The mean difference in the ASV group was **0.57 points lower (0.96 lower to 0.18 lower)** compared to control	1518 (3 RCTs)
Disease severity [AHI]	⊕⊕⊕◯ **MODERATE**[b]	The mean difference in the ASV group was **24.07 events/hour lower (30.22 lower to 17.92 lower)** compared to control	770 (10 RCTs)
Disease severity [CAI]	⊕⊕⊕◯ **MODERATE**[b]	The mean difference in the ASV group was **11.43 events/hour lower (15.42 lower to 7.44 lower)** compared to control	315 (4 RCTs)
Disease severity [CAHI]	⊕⊕⊕◯ **MODERATE**[c]	The mean difference in the ASV group was **15 events/hour lower (20.56 lower to 9.44 lower)** compared to control	63 (1 RCT)
Cardiovascular disease [6MWD]	⊕⊕⊕◯ **MODERATE**[d]	The mean difference in the ASV group was **10.68 meters lower (38.21 lower to 16.85 higher)** compared to control	1528 (3 RCTs)
Cardiovascular disease [NYHA classification score]*	⊕⊕⊕◯ **MODERATE**[c]	The mean difference in the ASV group was **0.5 lower (0.82 lower to 0.18 lower)** compared to control	30 (1 RCT)
Hospitalization [incidence (times/year)]	⊕⊕◯◯ **LOW**[e]	The risk ratio in the ASV group was **1.11 (0.86 to 1.43)** with an absolute risk of **44 more per 1,000 (56 fewer to 173 more**) compared to control	1649 (3 RCTs)
Mortality [reported deaths]	⊕⊕◯◯ **LOW**[e]	The risk ratio in the ASV group was **1.0 (0.71 to 1.41)** with an absolute risk of **0 fewer per 1,000 (80 fewer to 114 more)** compared to control	1716 (4 RCTs)

a. Risk of bias due to lack of blinding of the investigators and participants
b. Risk of bias due to overall loss to follow-up leading to concerns about generalizability
c. Imprecision due to small sample size (<200 participants)
d. Imprecision due to the 95% CI includes possibility for important harm and no effect
e. Imprecision due to the 95% CI includes possibility for important benefit and harm

Critical Outcomes

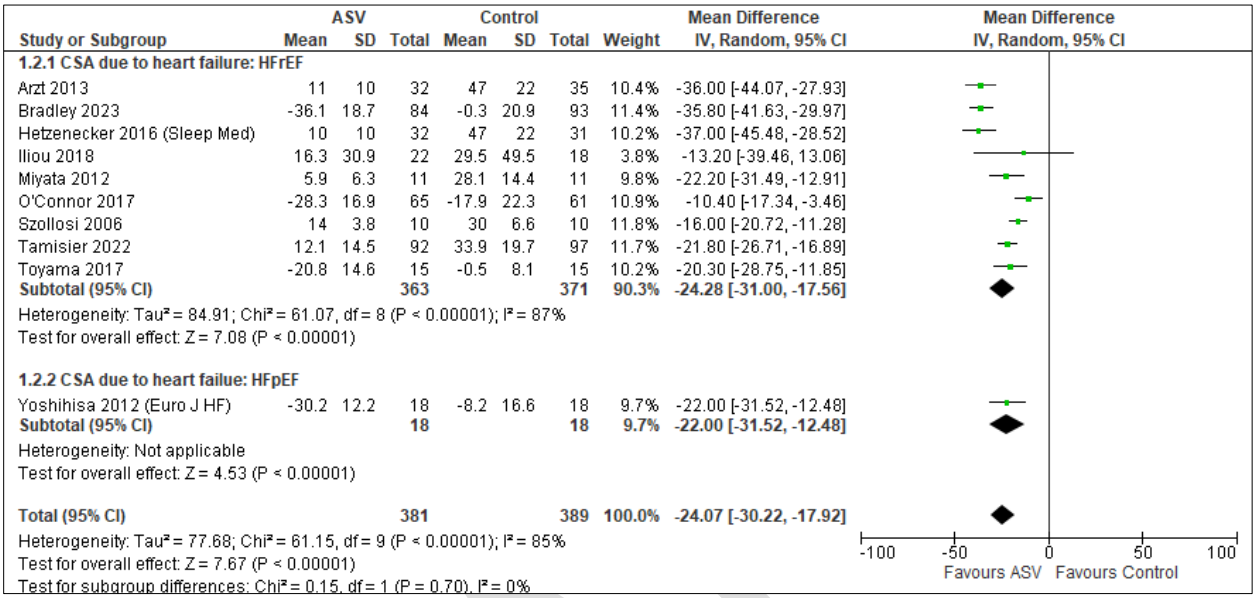
Figure S68. ASV vs. Control (Excessive sleepiness, ESS) [CST= -2 pts], RCTs



Cowie 2015: data was extracted from the graph. 12-month data was used, data reported as a change from baseline

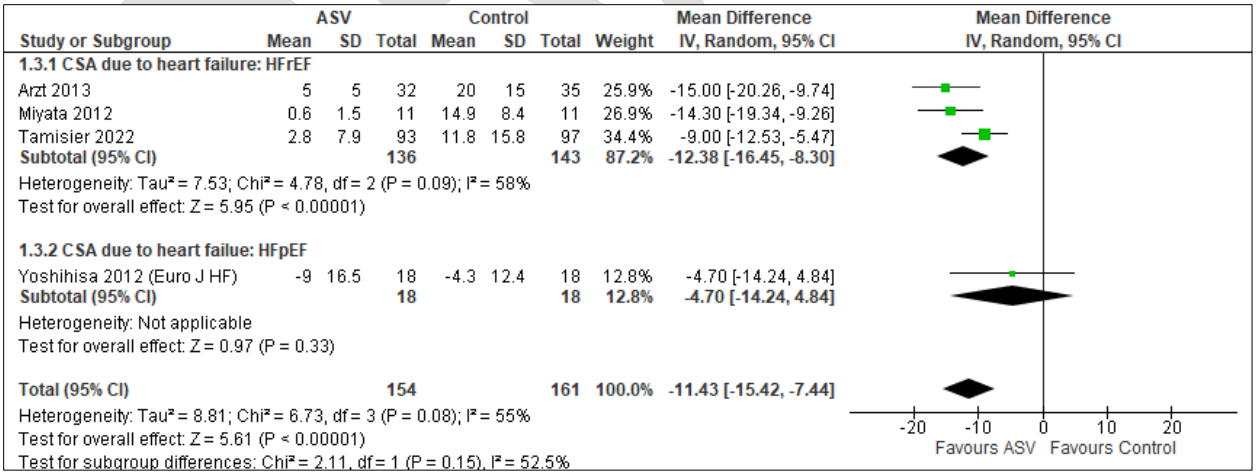
O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change from baseline

Figure S69. ASV vs. Control (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCTs



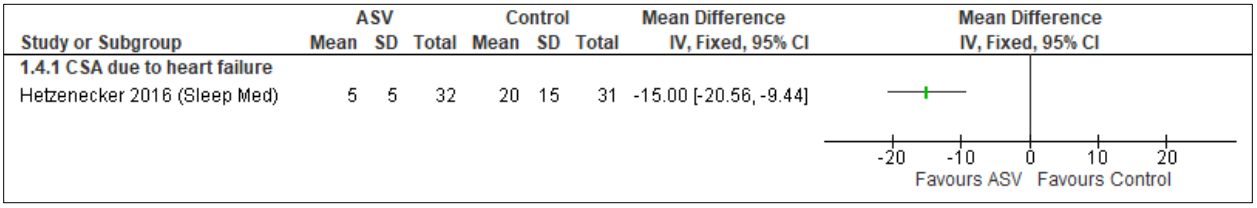
Arzt 2013: non-ICSD3, 12-week follow-up; Bradley 2023: 1-month data presented, data reported as a change from baseline; Hetzenecker 2016: optimal medical management or optimal medical management plus ASV therapy, 12-week study; Illiou 2018: nocturnal ventilation on top of exercise training (V + ET group) or to exercise training alone (ET group), median trial duration was 34 [28—48] days, SD calculated from median and IQR; Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, Control data received from author; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Szollosi 2006: single night study; Toyama 2017: 6-month study, data reported as a change score; Tamisier 2022: 12-month data reported, SERVE-HF sub-study; Arzt 2013: non-ICSD3, 12-week follow-up; AHI change from baseline was -74% reduction.

Figure S70. ASV vs. Control (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCT



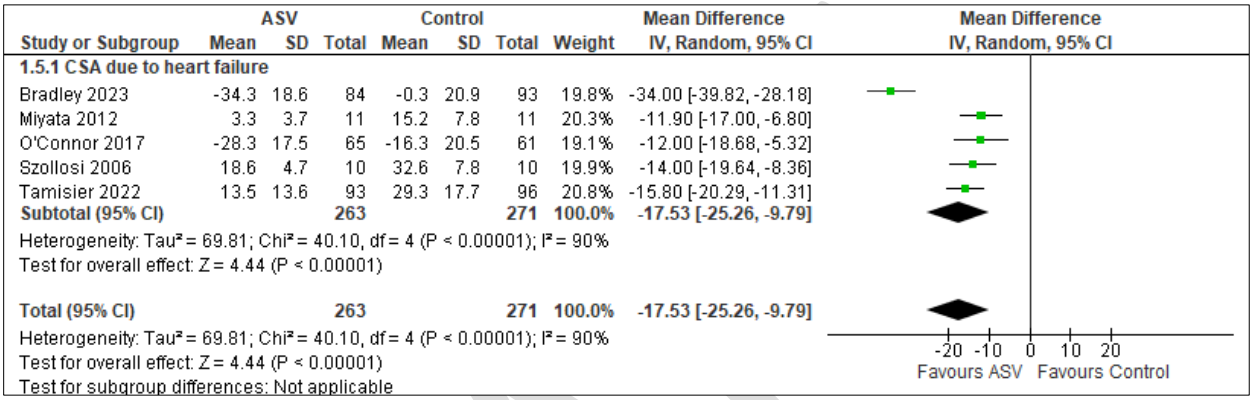
Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, data received from authors. CAI change from baseline was -83% reduction. ; Tamisier 2022: 12-month data reported, SERVE-HF sub-study; Arzt 2013: non-ICSD3, 12-week follow-up

Figure S71. ASV vs. Control (Disease Severity, CAHI) [CST= ≥ 50% reduction from baseline], RCT



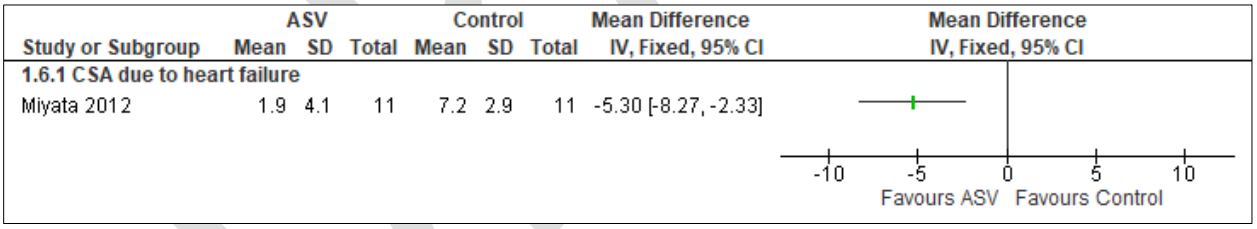
Hetzenecker 2016: optimal medical management or optimal medical management plus ASV therapy, 12-week study.

Figure S72. ASV vs Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT



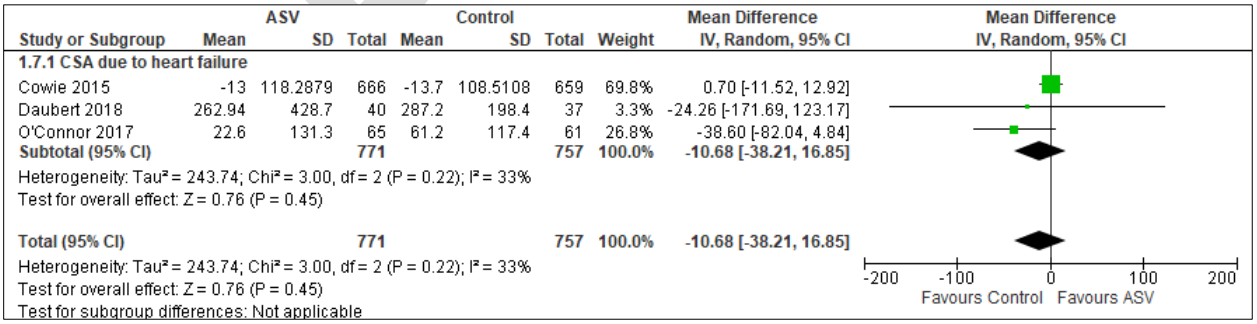
Bradley 2023: 1-month data presented, data reported as a change from baseline; Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, data received from authors'; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Szollosi 2006: single night study;; Tamisier 2022: 12-month data reported, SERVE-HF sub-study

Figure S73. ASV vs. Control (Disease Severity, % of TST with oxygen saturation <90%) [CST= ≥ 50% reduction from baseline], RCT



Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, data received from authors;

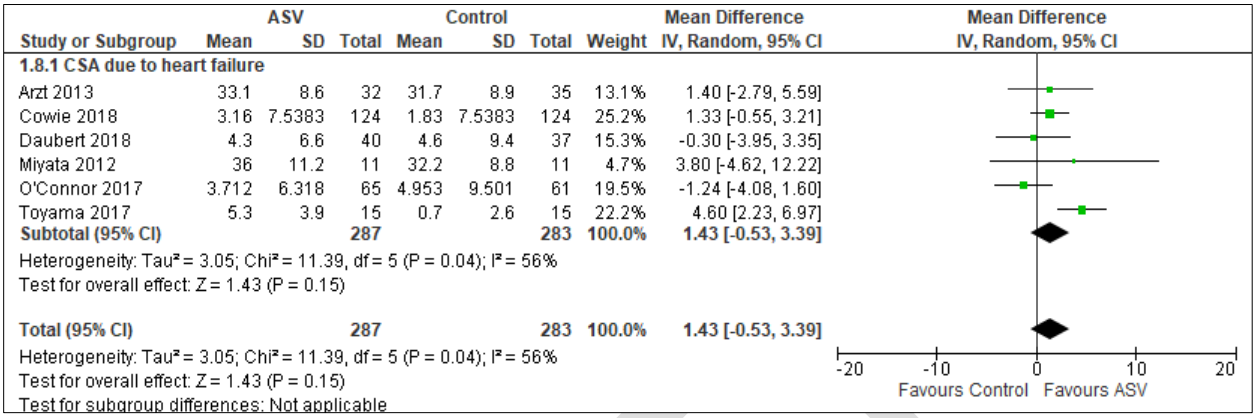
Figure S74. ASV vs. Control (Cardiovascular disease, 6MWD (change score)) [CST=+ 32 meters], RCTs



*O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Cowie 2015: 95% confidence intervals converted to SD, data is reported as a change from baseline, data extracted from

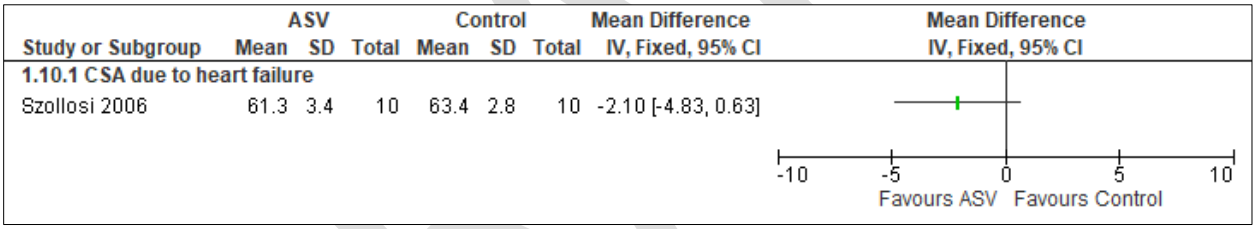
graph in supplemental document, 12-month study; Daubert 2018: IQR converted to SD, data extracted from graph, optimal medical therapy (OMT) or treatment with ASV and OMT, 6-month trial

Figure S75. ASV vs. control (Cardiovascular disease, LVEF (%)) [CST= +5%], RCTs



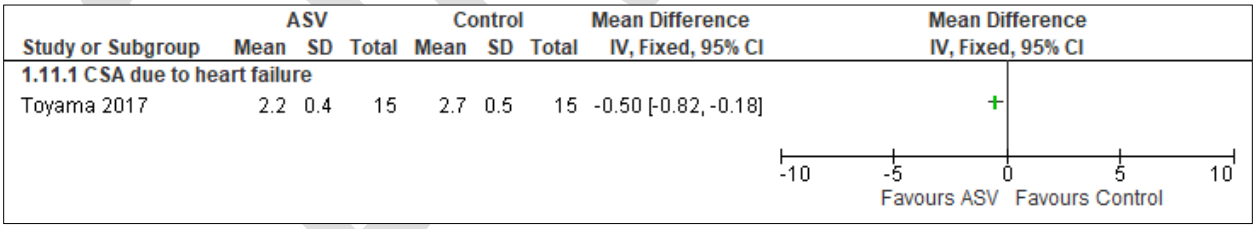
Cowie 2015: 95% confidence intervals converted to SD, data is reported as a change from baseline, data extracted from graph in supplemental document, 12-month study; Daubert 2018: IQR converted to SD, optimal medical therapy (OMT) or treatment with ASV and OMT, 6-month trial; Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, Control data received from author; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Toyama 2017: 6-month study, data reported as a change score

Figure S76. ASV vs. control (Cardiovascular disease, HR (beats/min)) [No CST], RCT



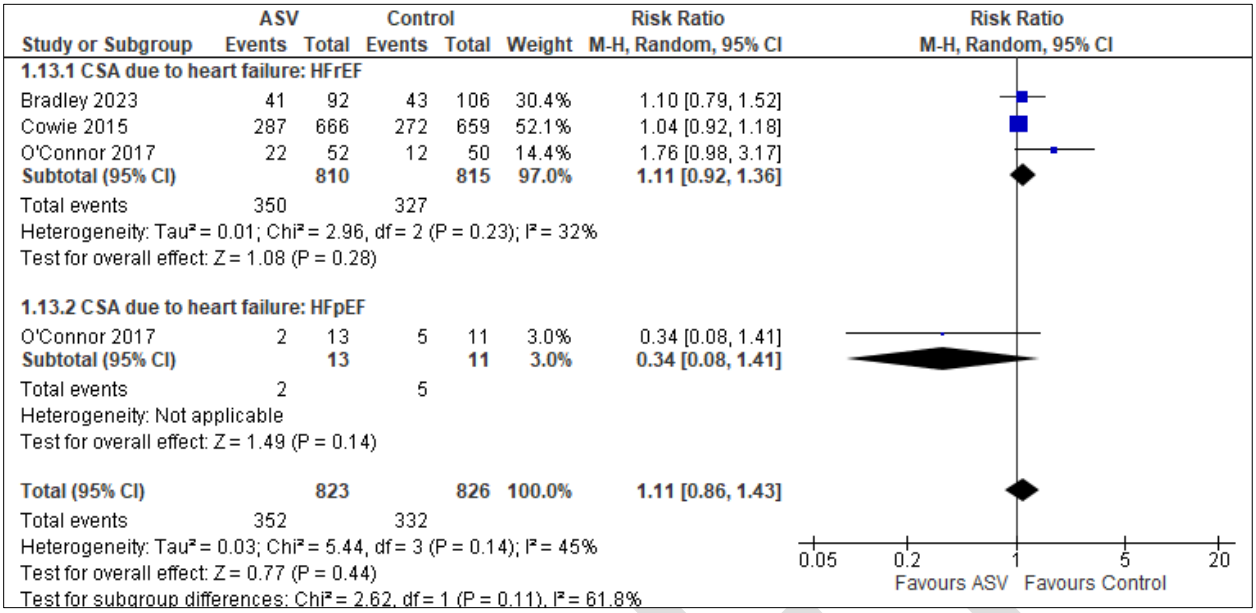
Szollosi 2006: single night study

Figure S77 . ASV vs. control (Cardiovascular disease, NYHA Class) [No CST], RCT



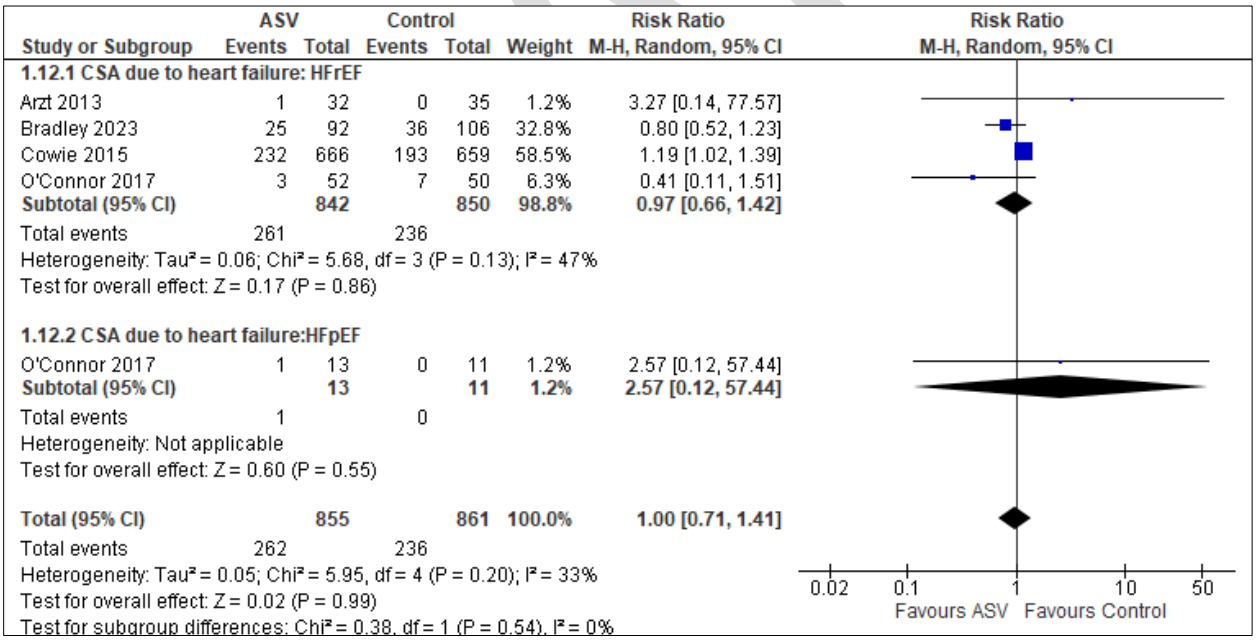
Toyama 2017: 6-month study

Figure S78. ASV vs. Control (Hospitalizations) [CST= 0.9], RCT



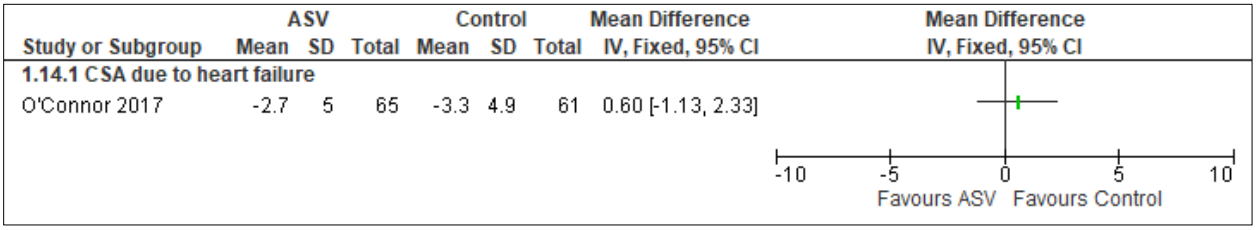
Bradley 2023: 1-month data presented; Cowie 2015: 12-month study; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial

Figure S79. ASV vs. Control (Mortality, All-cause mortality) [CST= 0.8], RCTs



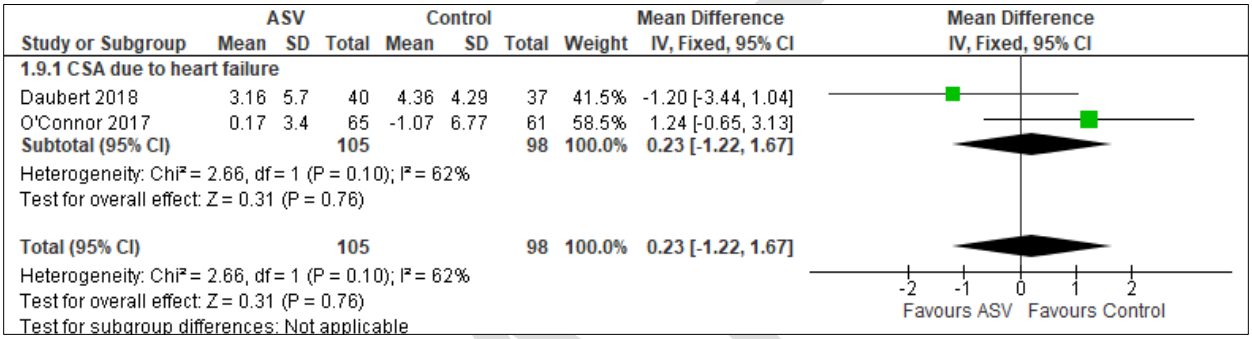
Bradley 2023: mean follow-up of 3.6 ± 1.6 years, all-cause mortality for CSA participants only; Cowie 2015: 60-month study, all cause deaths (data listed in Table 3); O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial; Arzt 2013: non-ICSD3 diagnostic criteria, 12-week follow-up

Figure S80. ASV vs. Control (Sleep Quality, PSQI) [CST= -3 points], RCT



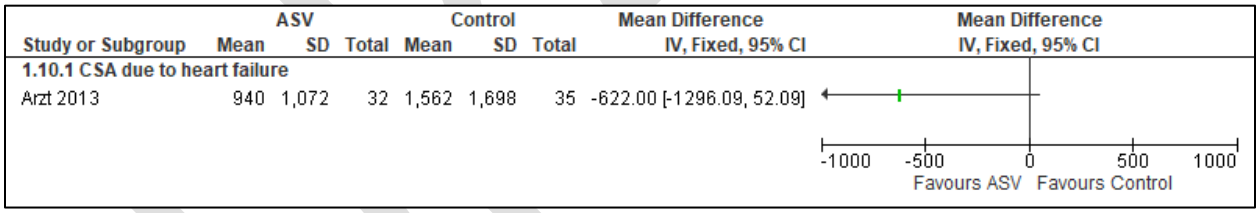
O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial

Figure S81. ASV vs. Control (Cardiovascular disease, NT pro-BNP, ng/mL) [CST= - 50% reduction from baseline], RCT



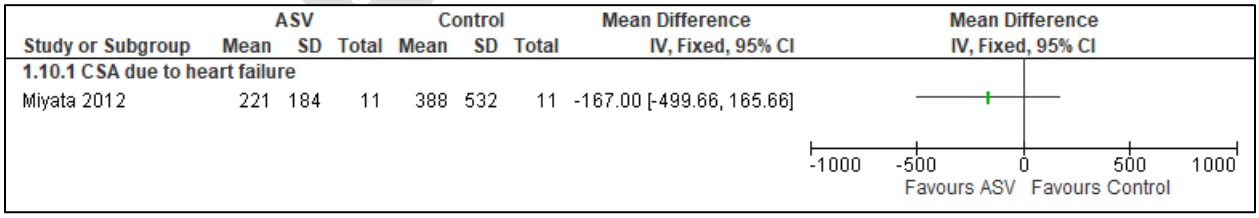
Daubert 2018: data from figure 2, IQR converted to SD, optimal medical therapy (OMT) or treatment with ASV and OMT, 6-month trial, NT-pro BNP pg/ml; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as change from baseline, NT-pro BNP pg/ml

Figure S82. ASV vs. Control (Cardiovascular disease, NT pro-BNP, ng/mL) [CST= - 50% reduction from baseline], RCT



Arzt 2013 NT-pro BNP ng/ml; separated from other NT pro-BNP analysis due to extreme variation in values. ASV baseline = 1039(1034) ng/mL

Figure S83. ASV vs. Control (Cardiovascular disease, BNP, pg/mL) [CST= - 50% reduction from baseline], RCT



Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, Control data received from author; median (IQR) BNP pg/ml

Figure S84. ASV vs. Baseline (Excessive sleepiness, ESS) [CST= -2 pts], Observational studies

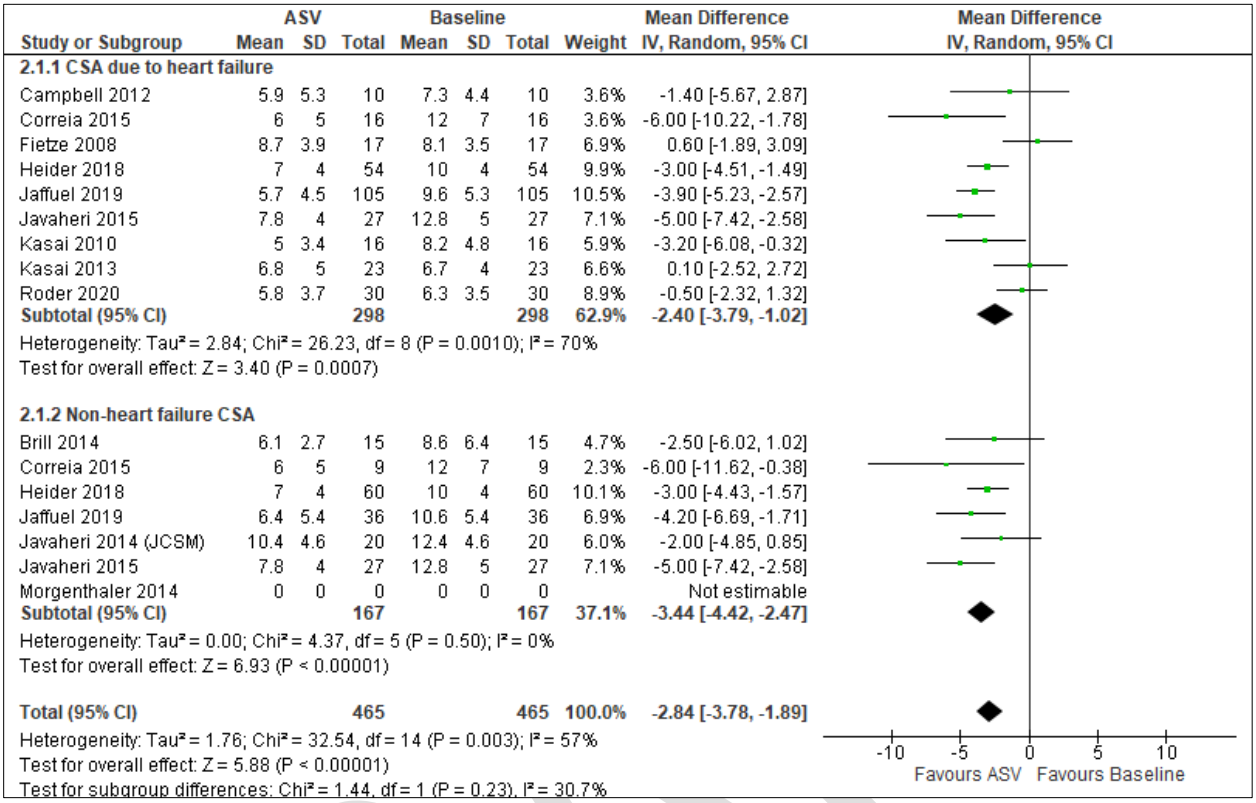


Figure S85. ASV vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], Observational Studies

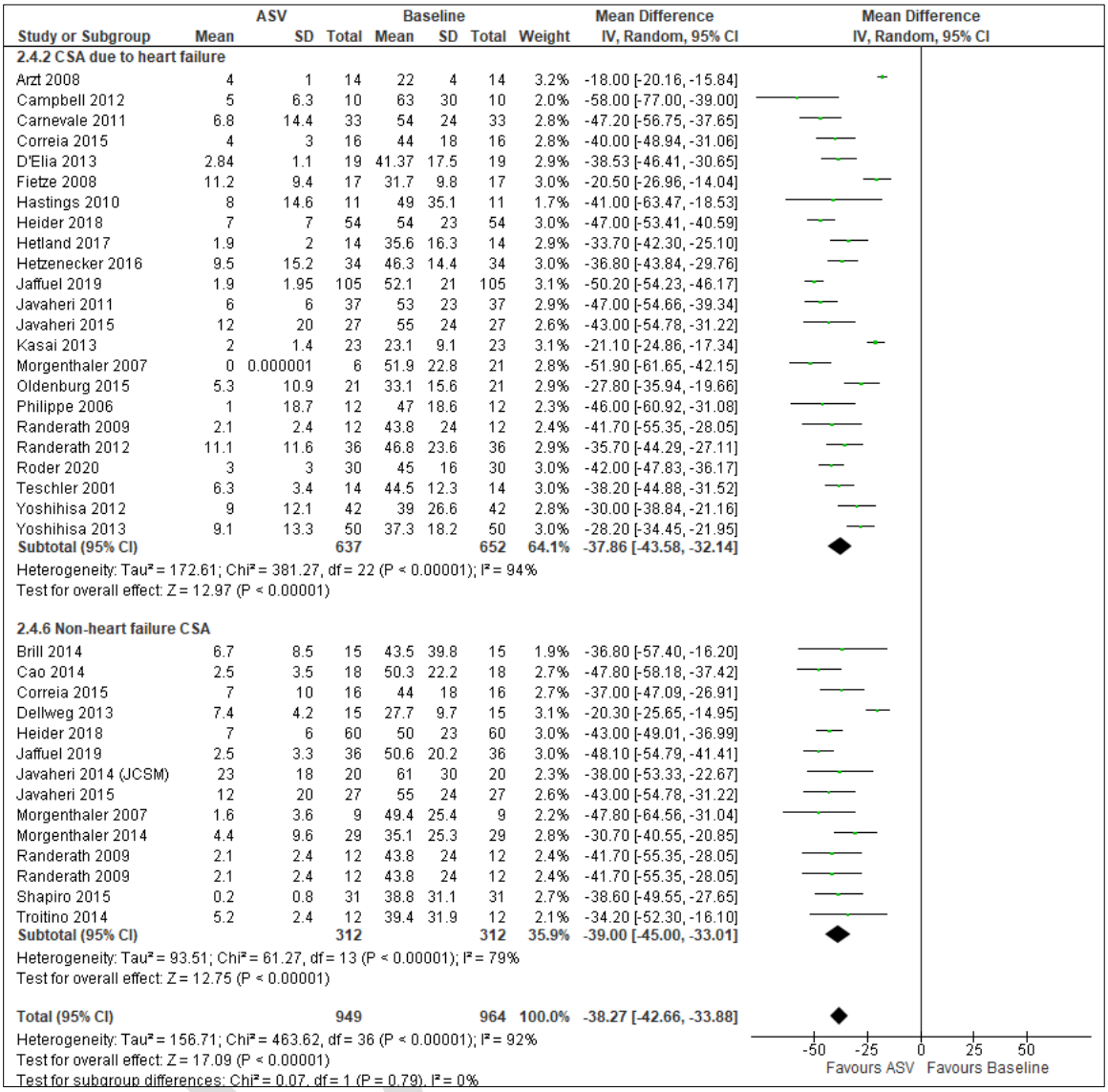


Figure S86. ASV vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], Observational Studies

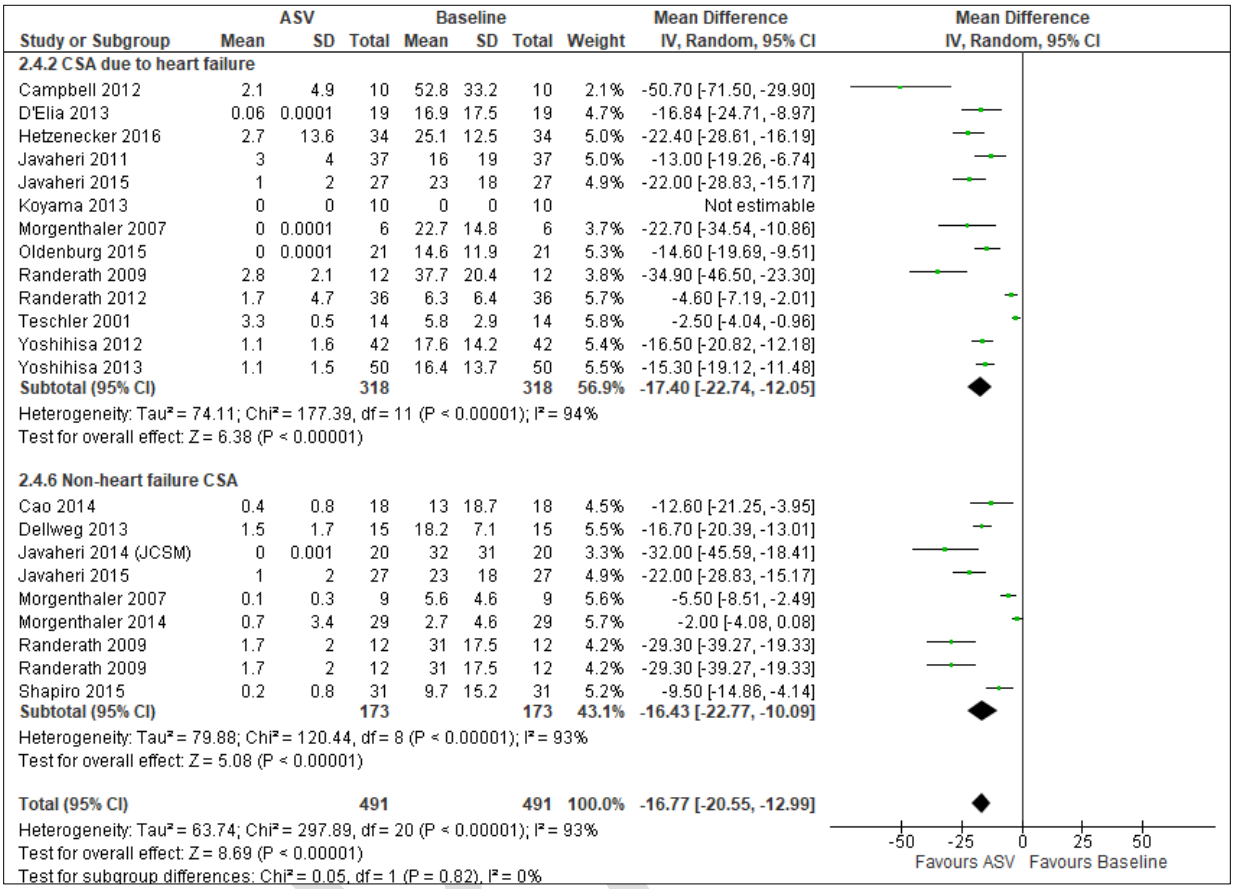


Figure S87. ASV vs Baseline (Disease Severity, CAHI) [CST= ≥ 50% reduction from baseline], Observational Studies

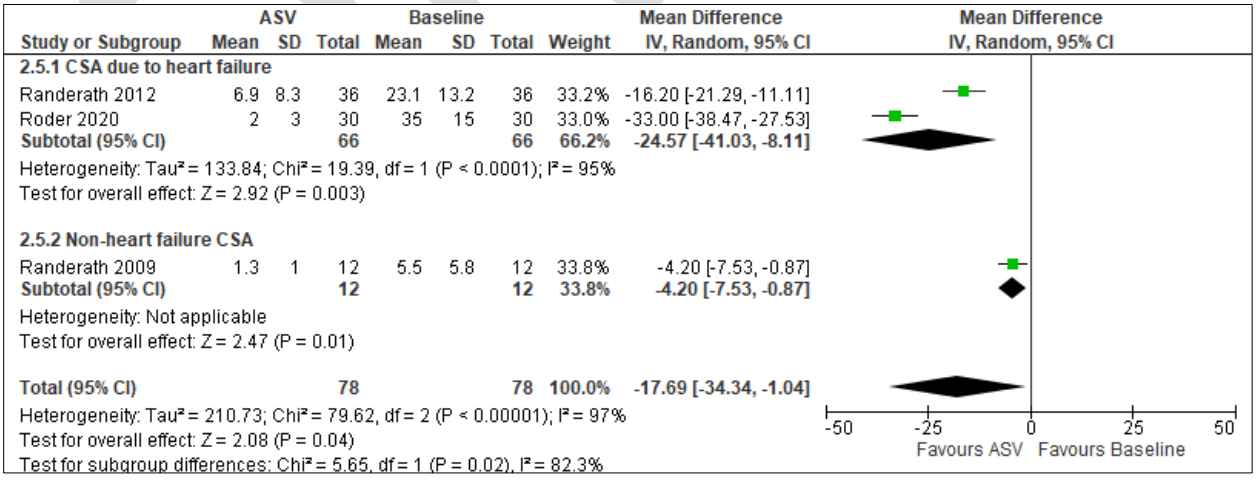


Figure S88. ASV vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], Observational study

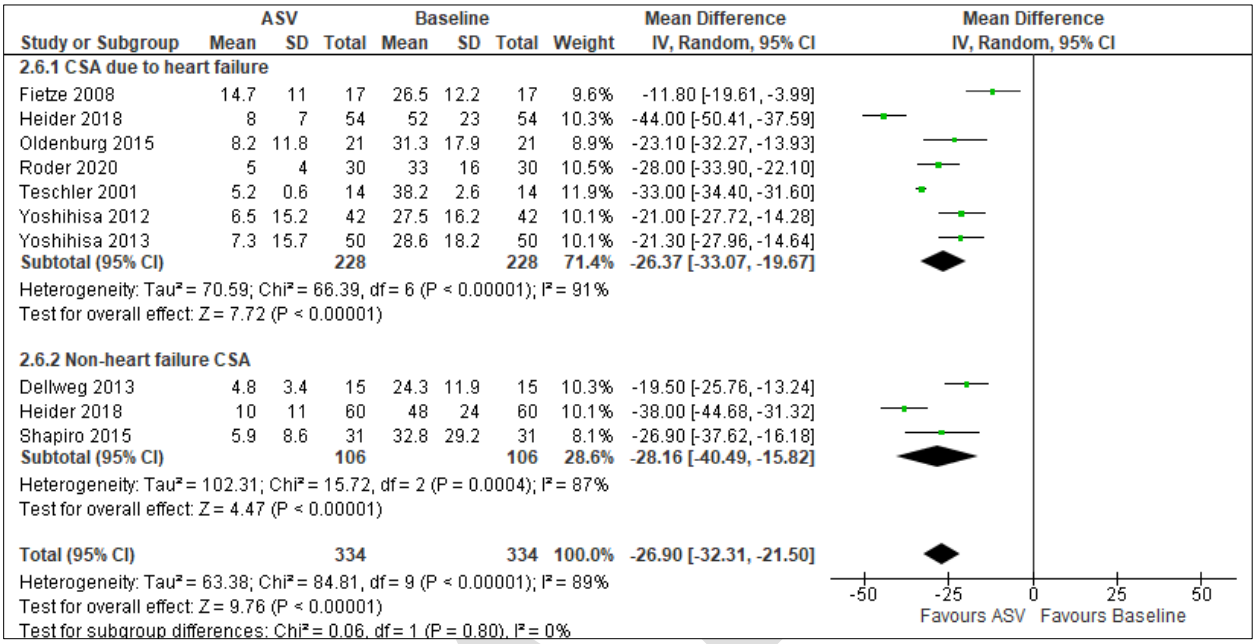


Figure S89. ASV vs. Baseline (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% reduction from baseline], Observational studies

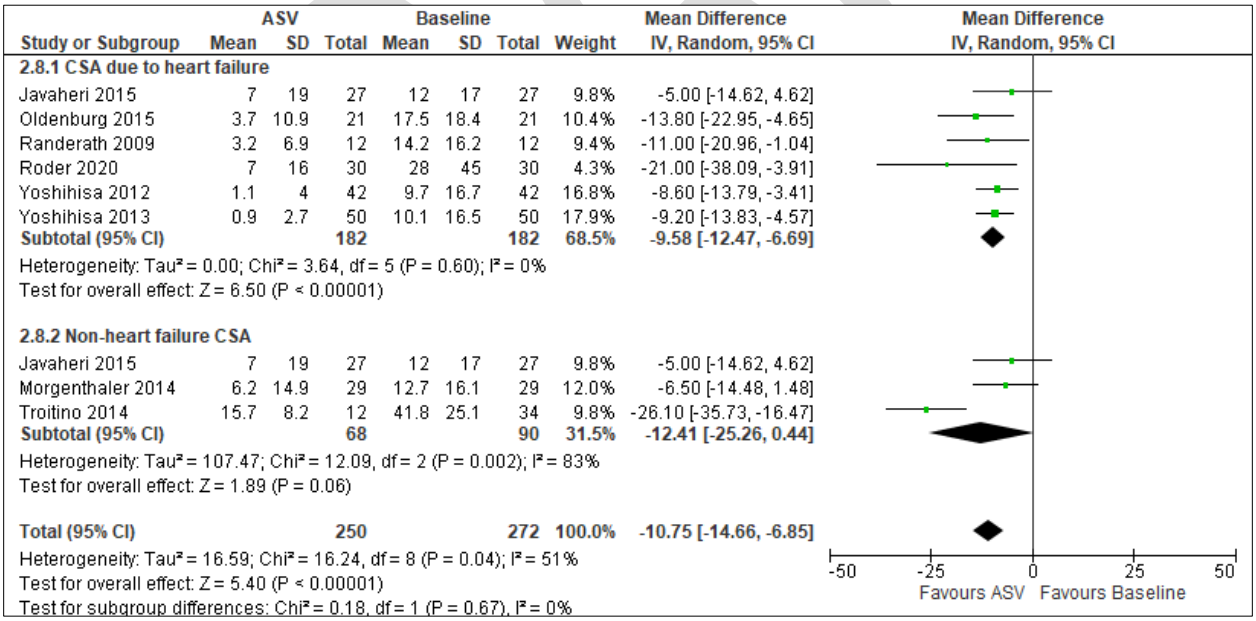


Figure S90. ASV vs. Baseline (Disease Severity, oxygen saturation >90% (%)) [CST= ≥ 50% increase from baseline], Observational studies

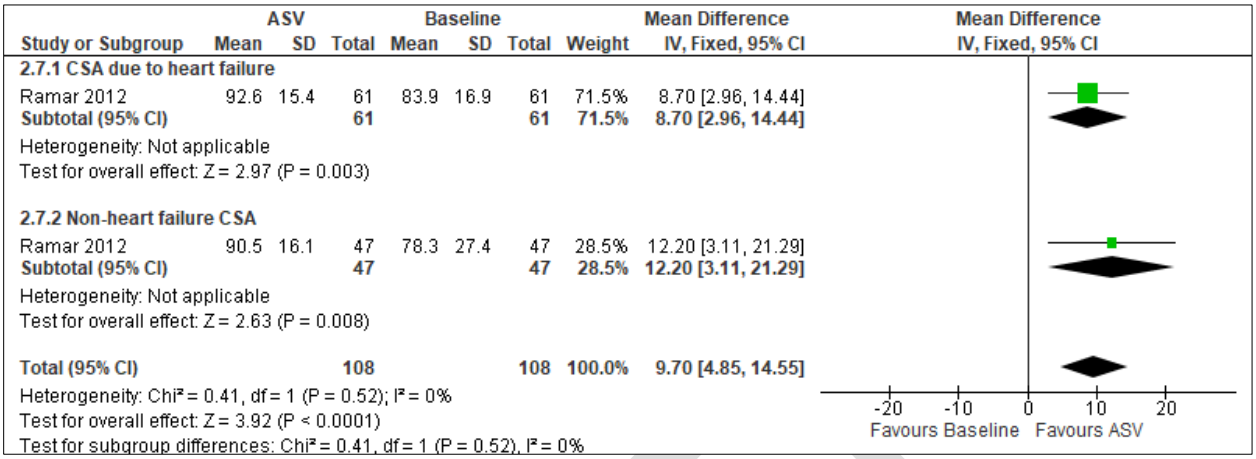
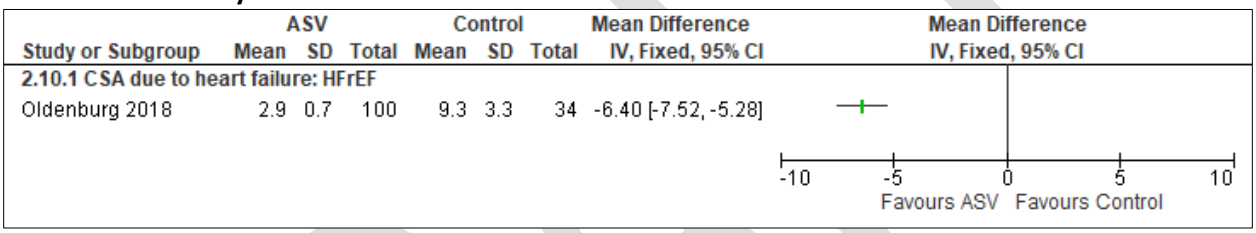
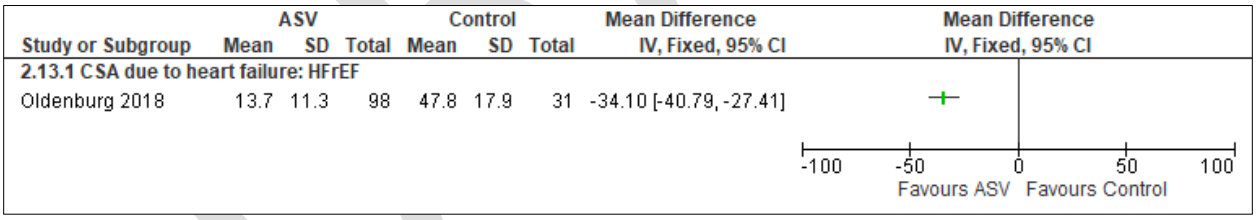


Figure S91. ASV vs. Control (Disease Severity, Apnea Index) [CST= ≥ 50% reduction from baseline], Observational Study



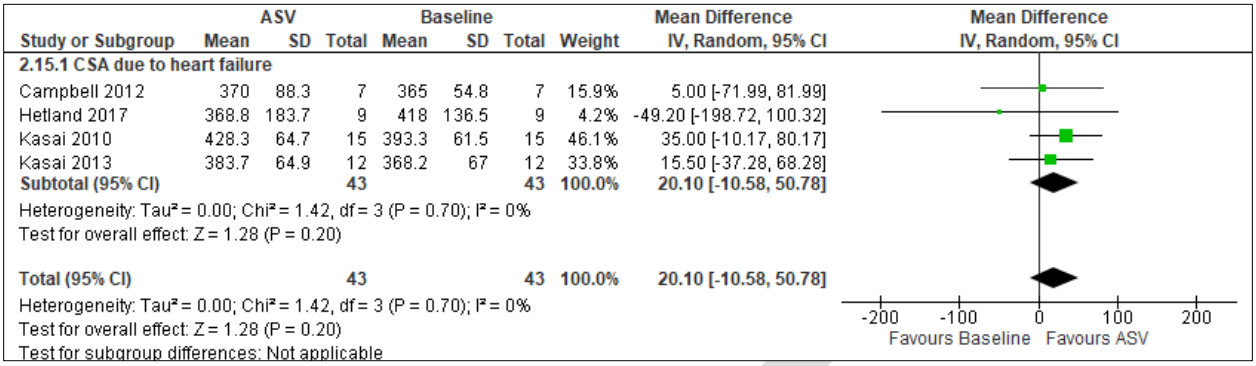
6-month data extracted from figure 1.

Figure S92. ASV vs. Control (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% reduction from baseline], Observational studies



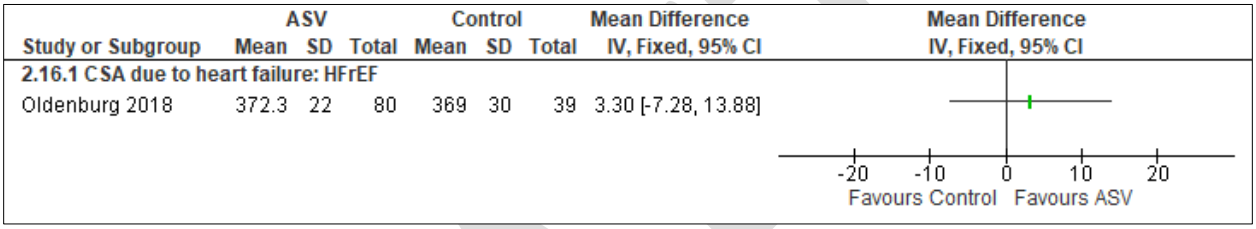
6-month data extracted from figure 1.

Figure S93. ASV vs. Baseline (Cardiovascular disease, 6MWD) [CST= +32 meters], Observational studies



Hetland 2017: median, IQR converted to mean and SD

Figure S94. ASV vs. Control (Cardiovascular disease, 6MWD) [CST= +32 meters], Observational studies



6-month data extracted from figure 1.

Figure S95. ASV vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= +5%], Observational studies

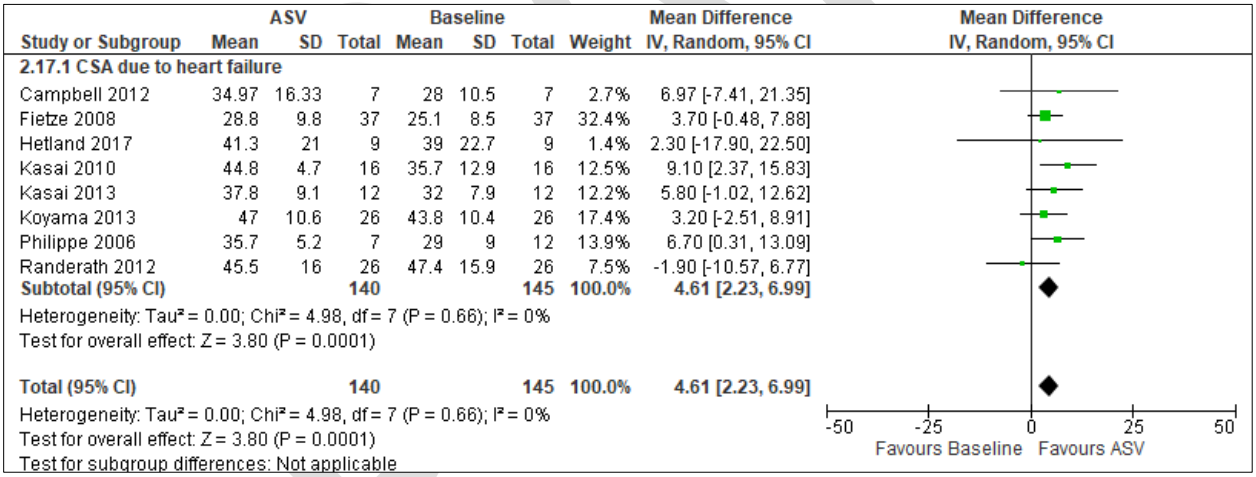
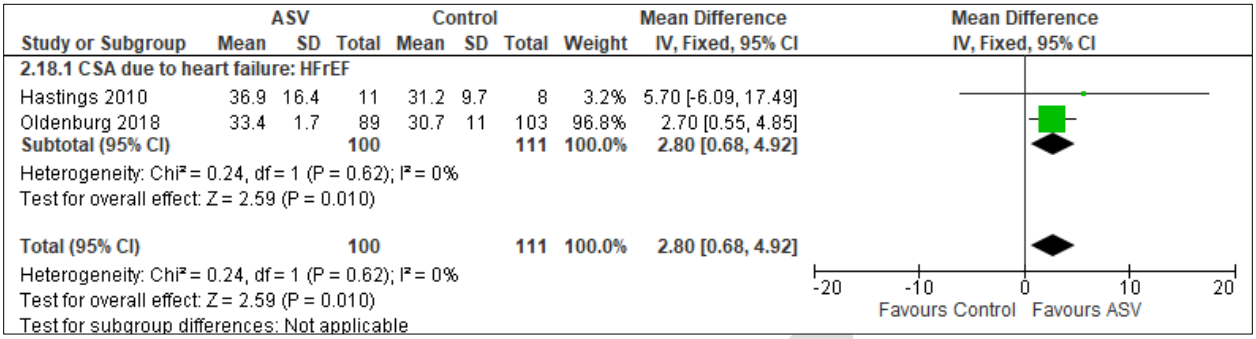


Figure S96. ASV vs. Control (Cardiovascular disease, LVEF (%)) [CST= +5%], Observational studies



Oldenburg 2018: data extracted from graph; 6-month data presented
Hastings 2010: 6-month data

Figure S97. ASV vs. Baseline (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], Observational studies

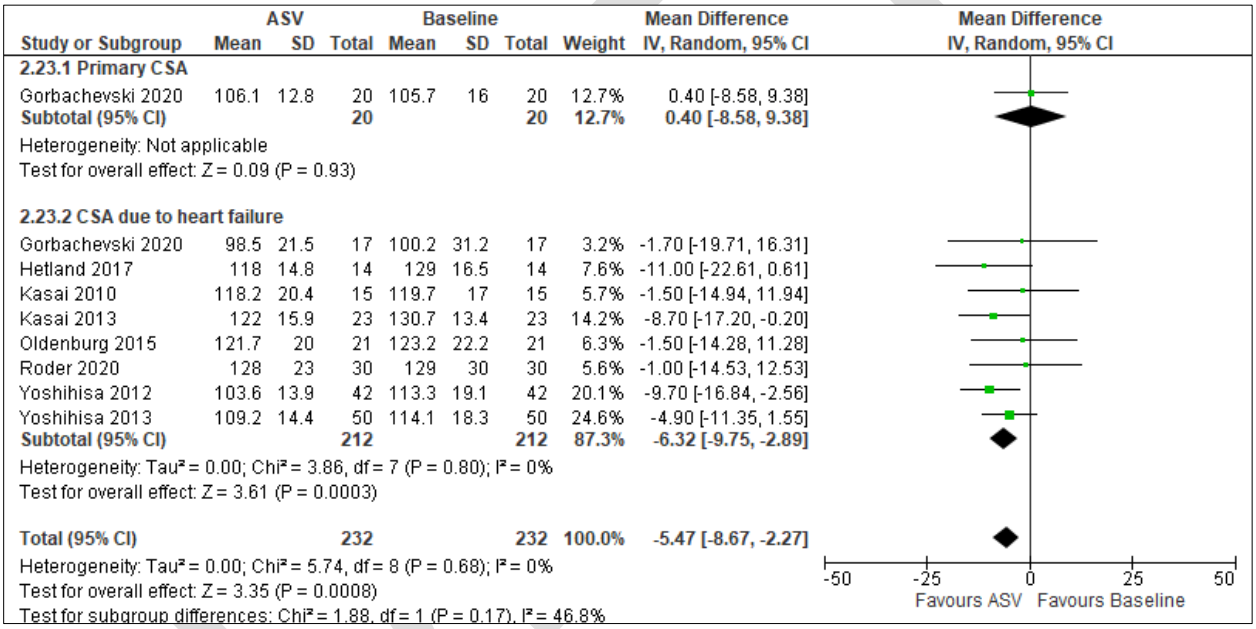


Figure S98. ASV vs. Control (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], Observational studies

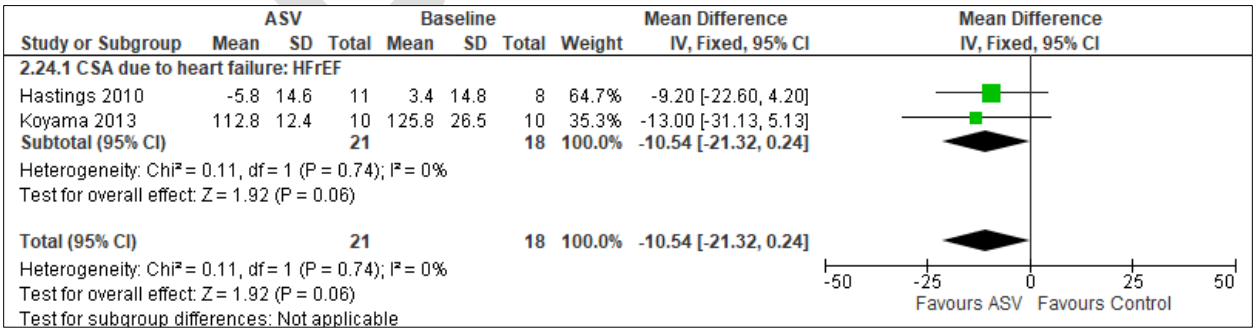


Figure S99. ASV vs. Baseline (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], Observational studies

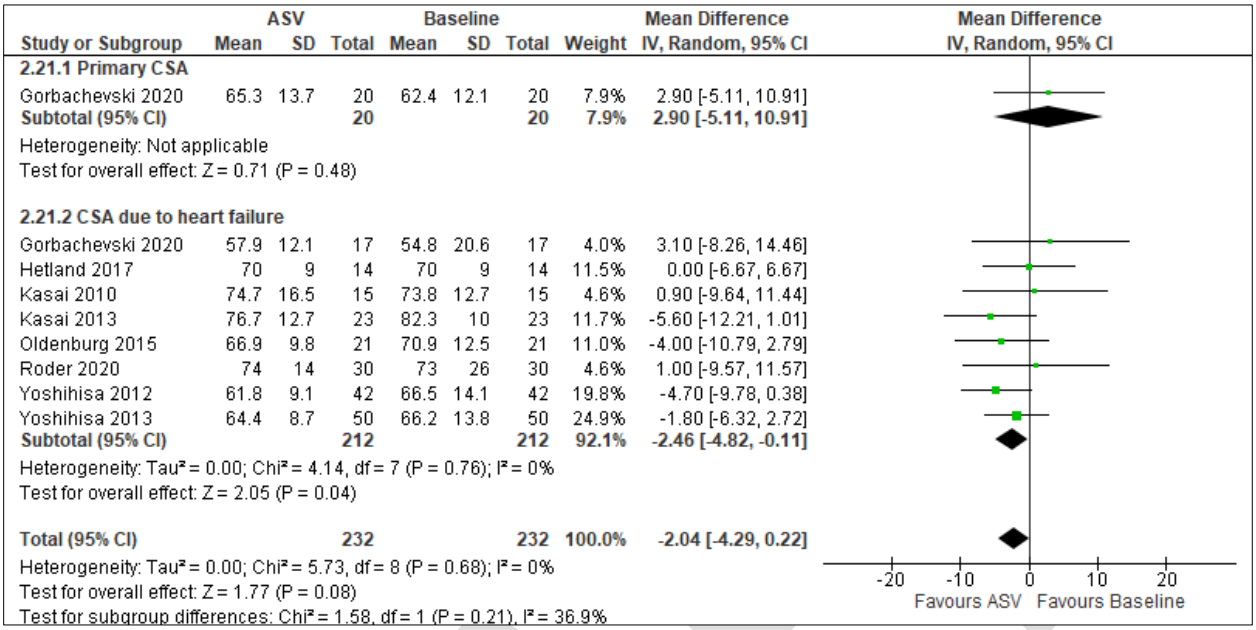


Figure S100. ASV vs. Control (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], Observational studies

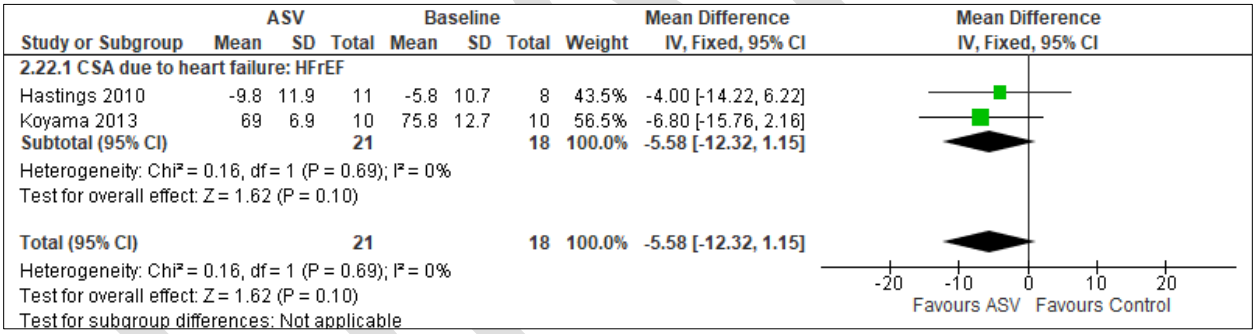


Figure S101. ASV vs. Baseline (Cardiovascular disease, HR (beats/min)) [No CST], Observational studies

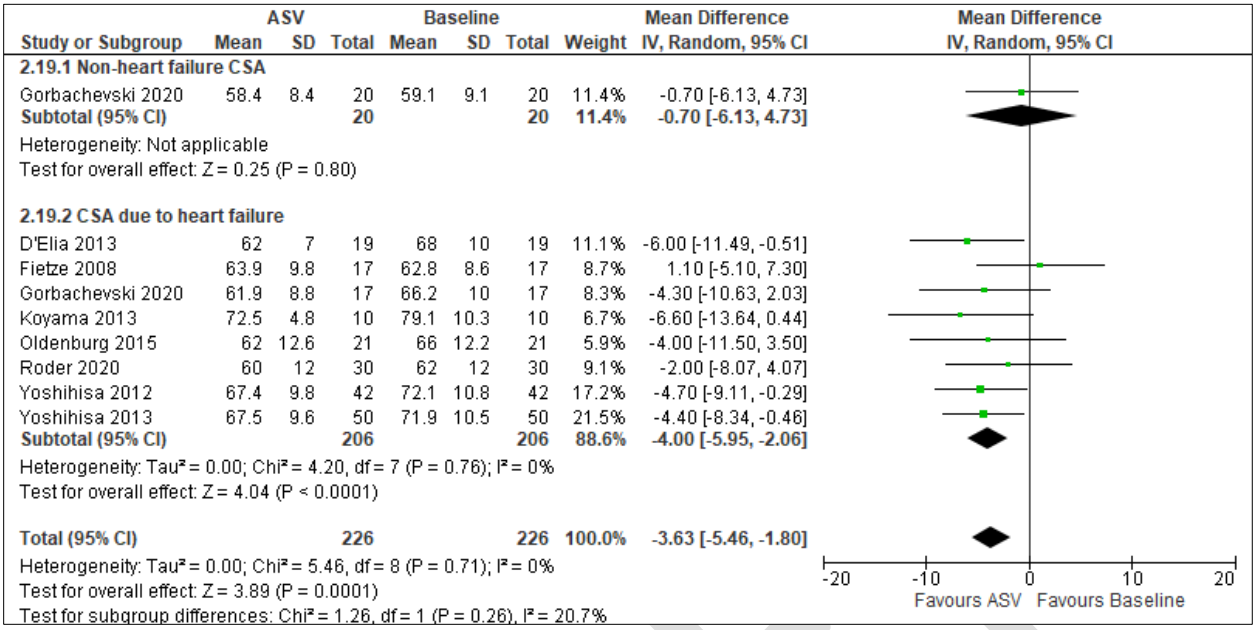


Figure S102. ASV vs. Control (Cardiovascular disease, HR (beats/min)) [No CST], Observational studies

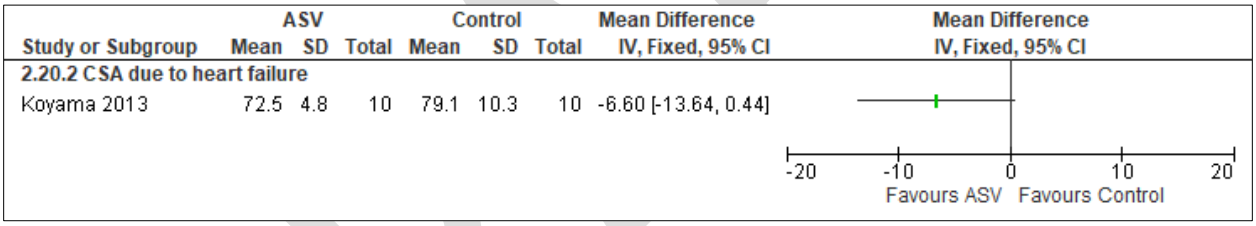
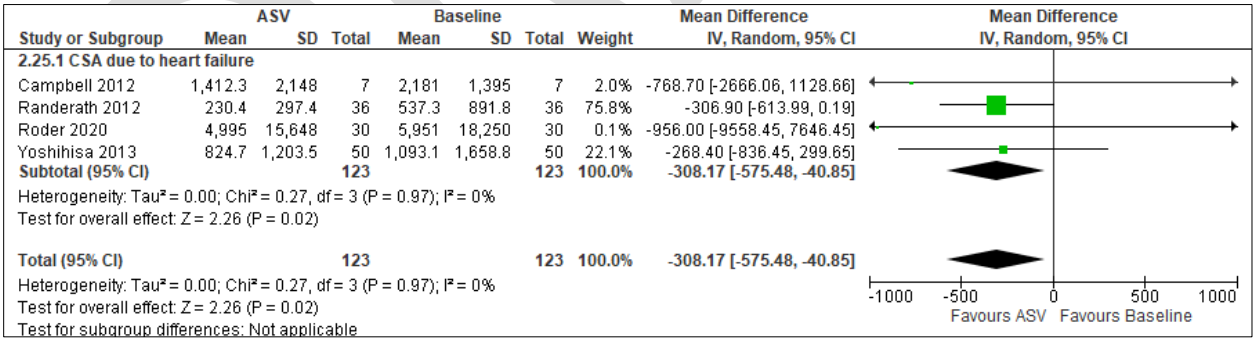
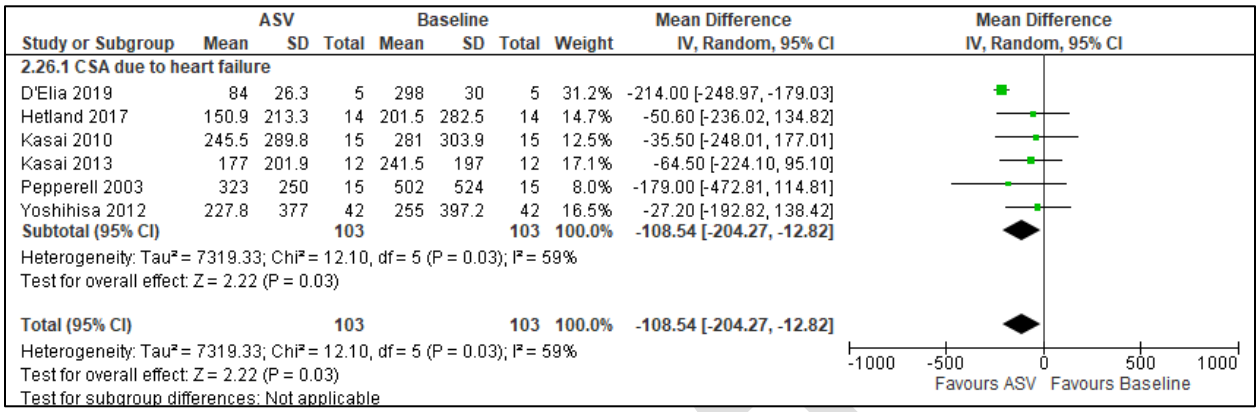


Figure S103. ASV vs. Baseline (Cardiovascular disease, NT pro-BNP, pg/mL) [CST= - 50% reduction from baseline], Observational studies



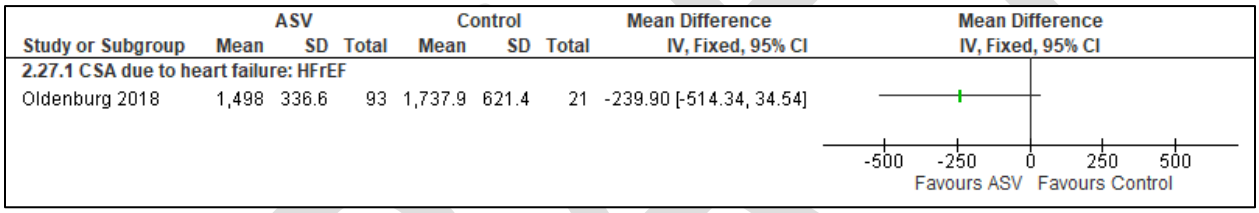
Campbell 2012: NT-BNP pmol/L, median IQR converted to m, SD converted to pg/mL; Randerath 2012: NT-proBNP (ng/L); Roder 2020: NT-proBNP (pg/mL); Yoshihisa 2013: NT-proBNP, pg/mL, median IQR converted to m, SD

Figure S104. ASV vs. Baseline (Cardiovascular disease, BNP pg/mL) [CST= - 50% reduction from baseline], Observational studies



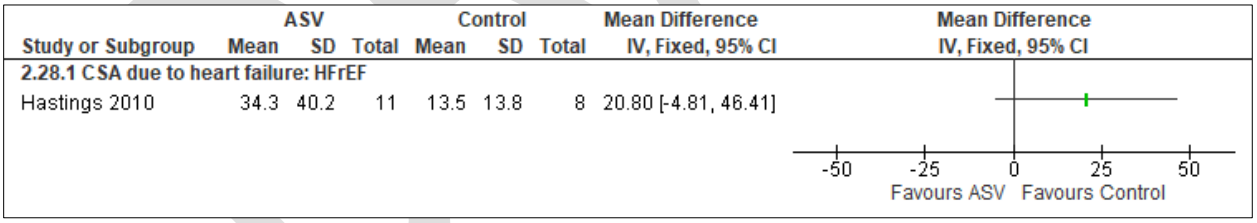
D'Elia 2019: BNP pg/mL; Hetland: median IQR converted to m, SD, BNP ng/L; Kasai 2010: BNP pg/mL; Kasai 2013: BNP pg/mL, median IQR converted to m, SD; Pepperell 2003: median and IQR converted to mean and SD, BNP (pg/ml); Yoshihisa 2012: BNP pg/mL, median IQR converted to m, SD

Figure S105. ASV vs. Control (Cardiovascular disease, NT pro-BNP, pg/mL) [CST=50% reduction from baseline], Observational studies



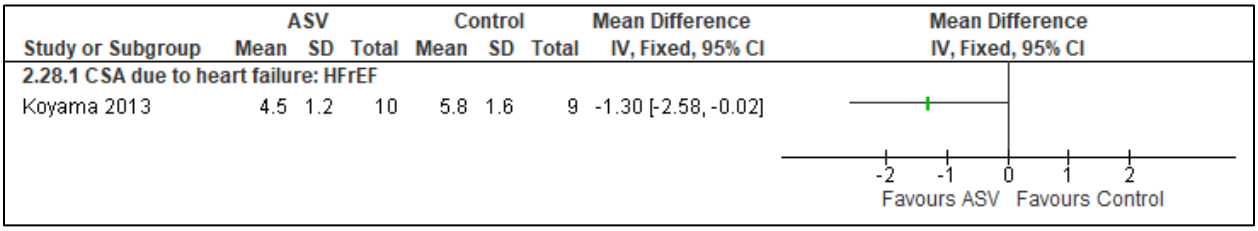
Oldenburg 2018: data extracted from graph, 6-month data presented NT pro- BNP (pg/ml)

Figure S106. ASV vs. Control (Cardiovascular disease, BNP, pmol/L) [CST=50% reduction from baseline], Observational studies



Hastings 2010: pmol/L

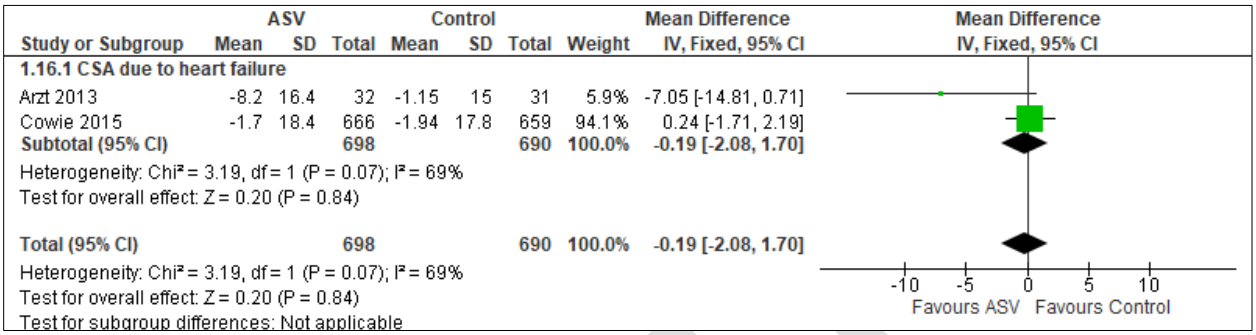
Figure S107. ASV vs. Control (Cardiovascular disease, BNP, ln BNP) [CST=50% reduction], Observational studies



Koyama 2013: ln BNP

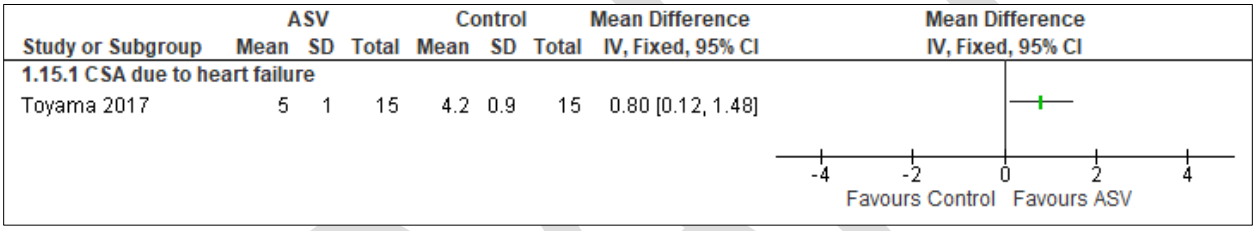
Important Outcomes

Figure S108. ASV vs. Control (Daytime Functioning, Minnesota Living with Heart Failure Questionnaire) [No CST] points], RCTs



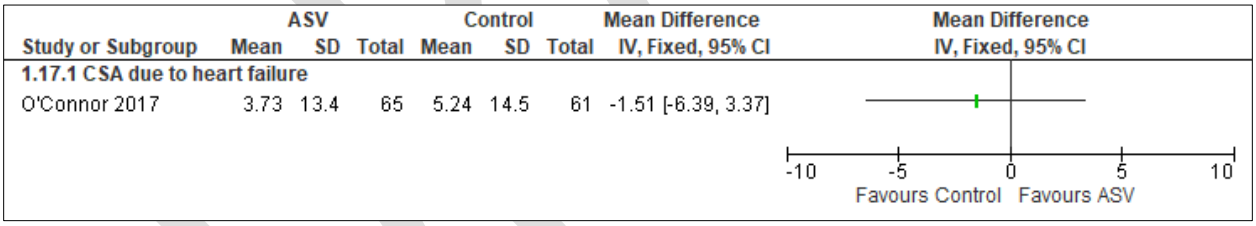
Cowie 2015: CI converted to SD, used 12-month timepoint, extracted from the graph, adjusted change score reported

Figure S109. ASV vs. Control (Daytime Functioning, Specific Activity Scale) [No CST], RCTs



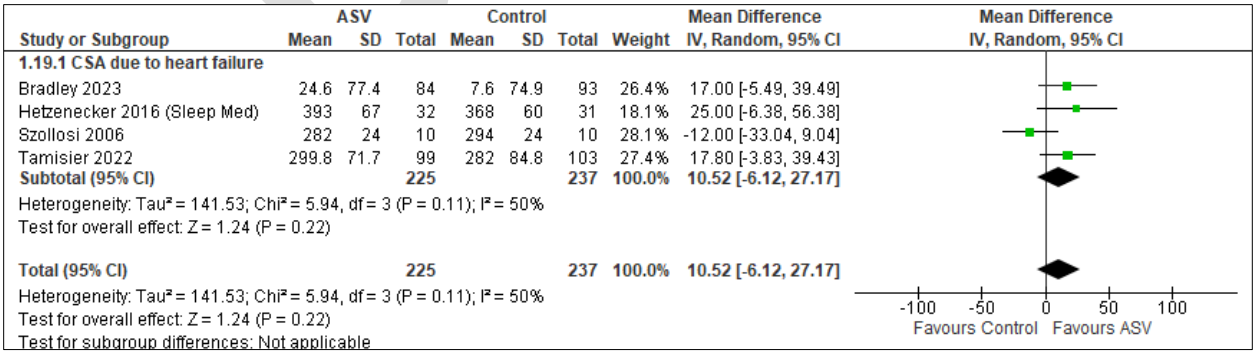
Toyama 2017: 6-month study

Figure S110. ASV vs. Control (Daytime Functioning, Duke Activity Status Index) [No CST], RCTs



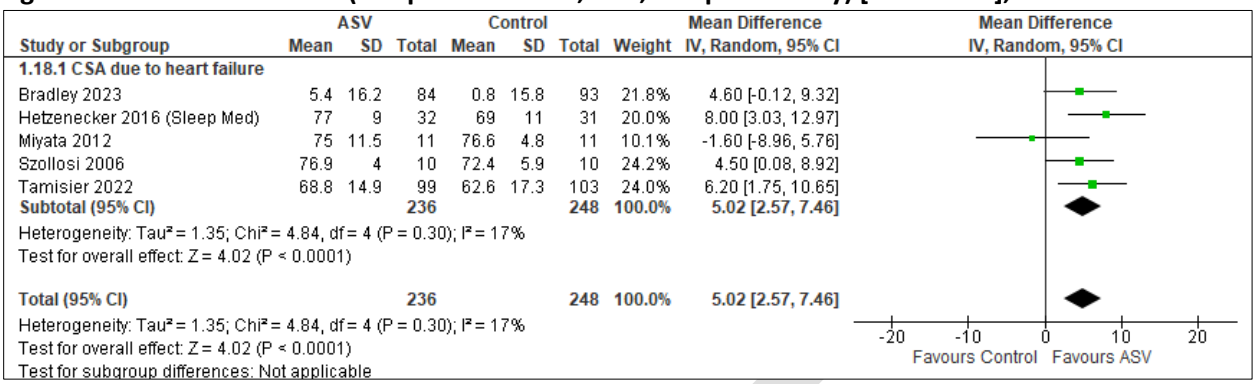
O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial

Figure S111. ASV vs. Control (Sleep architecture, PSG, Total Sleep Time) [CST=+15 min], RCTs



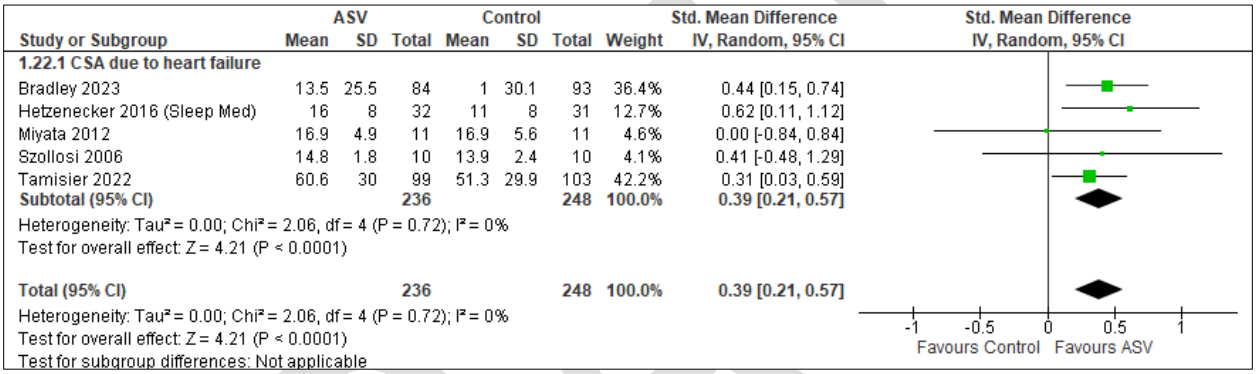
Bradley 2023 TST minutes (change score).

Figure S112. ASV vs. Control (Sleep architecture, PSG, Sleep efficiency) [CST=+10%], RCT



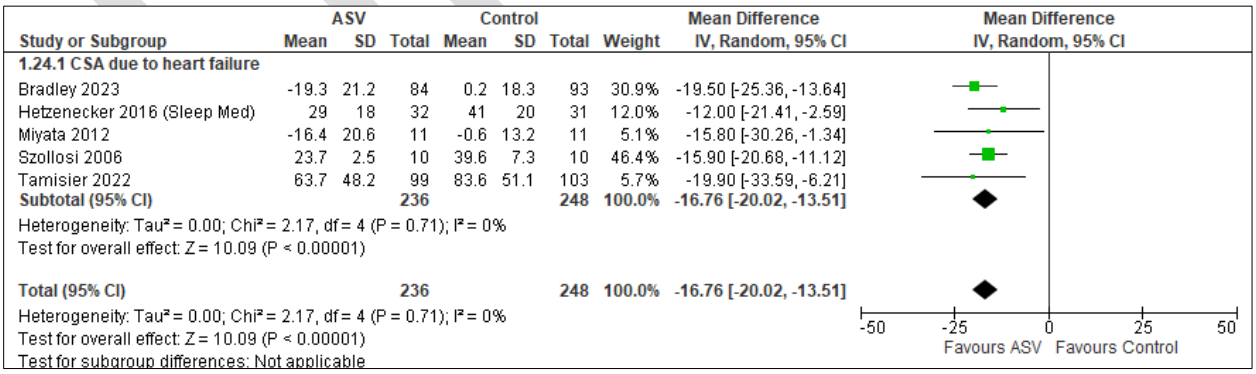
Bradley 2023 change score data at 1 month.

Figure S113. ASV vs. Control (Sleep architecture, PSG, REM%) [CST=+5% of TST], RCTs



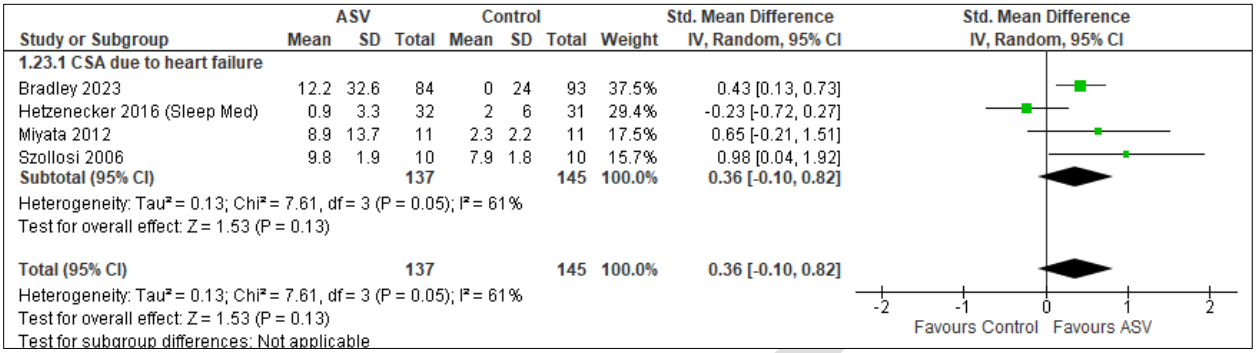
Bradley 2023 REM sleep, minutes (change score); Hetzenecker 2016 (SM) REM %; Miyata 2012 REM %* (control data received from authors); Szollosi 2006 REM %; Tamisier 2022 REM minutes. The weighted average of the post intervention standard deviation of percent REM across Hetzenecker, Miyata, and Szollosi is 6.3. Re-expressed as percent REM, there was a mean increase of 2.5% (95% CI 1.3, 3.6)

Figure S114. ASV vs. Control (Sleep architecture, PSG, Arousals) [CST=25% reduction from baseline or reduction to ≤12 events/hr], RCTs



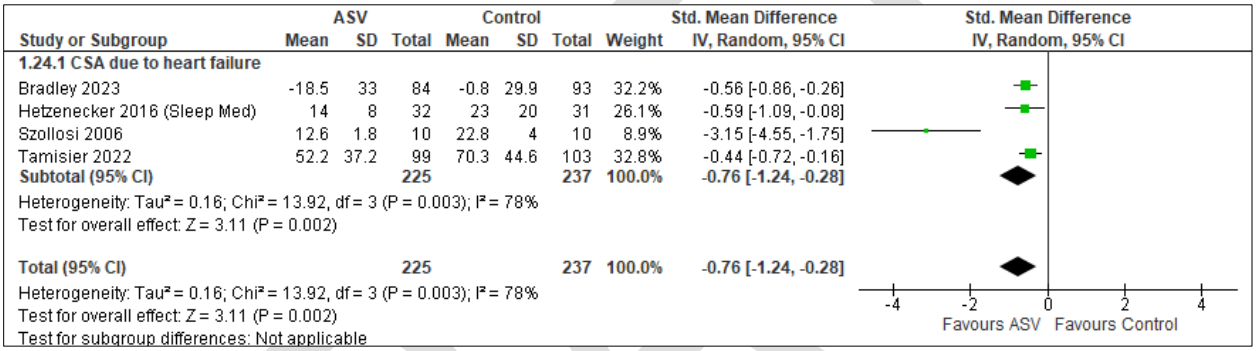
Miyata: control data received from authors; Hetzenecker 2016 (Sleep Med): change from baseline data; Tamisier 2022: data points reported at 3 and 12 months, 12-month data included in analysis

Figure S115. ASV vs. Control (Sleep architecture, PSG, SWS%) [CST=+5% of TST], RCT



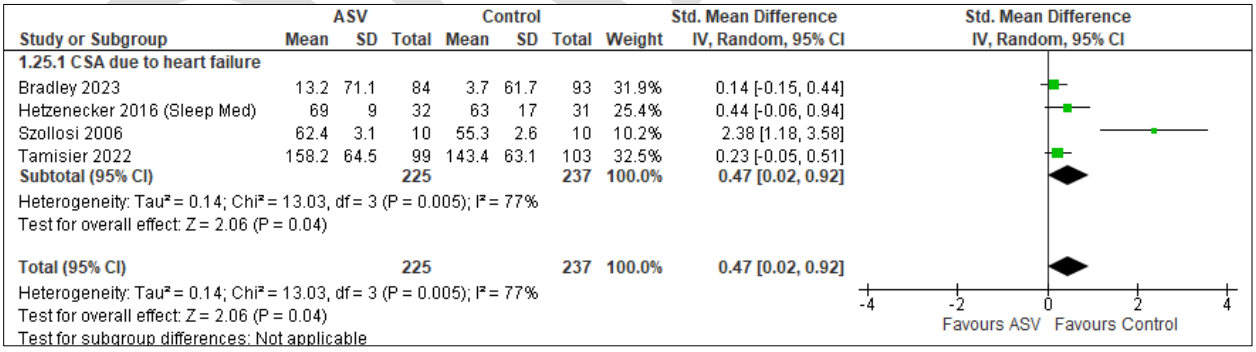
Bradely 2023 – SWS, minutes (change score); Hetzenecker 2016 (SM) SWS %; Miyata 2012 SWS % (control data received from authors); Szollosi 2006 SWS %. The weighted average of the post intervention standard deviation of percent SWS across Hetzenecker, Miyata, and Szollosi is 4.8. Re-expressed as percent REM, there was a mean increase of 1.6% (95% CI -0.48, 3.9)

Figure S116. ASV vs. Control (Sleep architecture, PSG, Sleep stage N1%) [CST=-5% of TST], RCTs



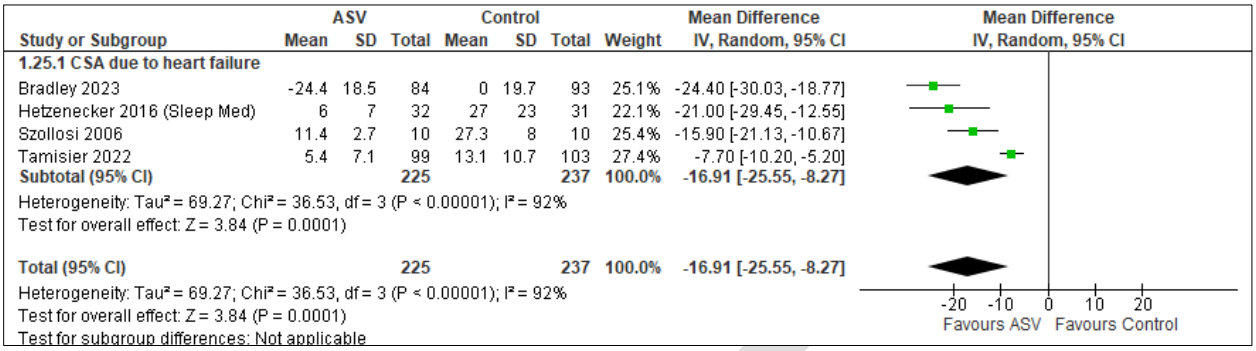
Bradley 2023 N1 minutes; Hetzenecker 2016 (SM) N1%; Szollosi 2006 N1%; Tamisier 2022 N1 minutes. The weighted average of the post intervention standard deviation of percent N1 across Hetzenecker and Szollosi is 11.4. Re-expressed as percent N1, there was a mean decrease of -8.7% (95% CI -14.1, -3.2).

Figure S117. ASV vs. Control (Sleep architecture, PSG, Sleep stage N2%) [CST=-5% of TST], RCTs



Bradley 2023 N2 minutes; Hetzenecker 2016 (SM) N2%; Szollosi 2006 N2%; Tamisier 2022 N2 minutes. The weighted average of the post intervention standard deviation of percent N2 across Hetzenecker and Szollosi is 10.6. Re-expressed as percent N2, there was a mean increase of 4.98% (95% CI 0.21, 9.75).

Figure S118. ASV vs. Control (Sleep architecture, PSG, Respiratory arousals) [CST=25% reduction from baseline], RCTs



Change from baseline: ASV=-49.92% (Note: baseline data for Szollosi was not available)

Figure S119. ASV vs. Baseline (Daytime functioning, Minnesota living with heart failure (MLHF)) [No CST], Observational Study

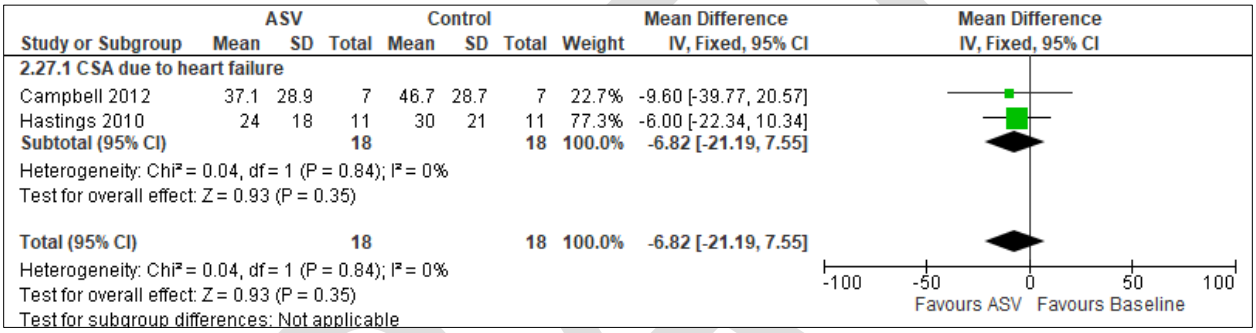


Figure S120. ASV vs. Control (Daytime functioning, SF-36) [No CST], Observational Study

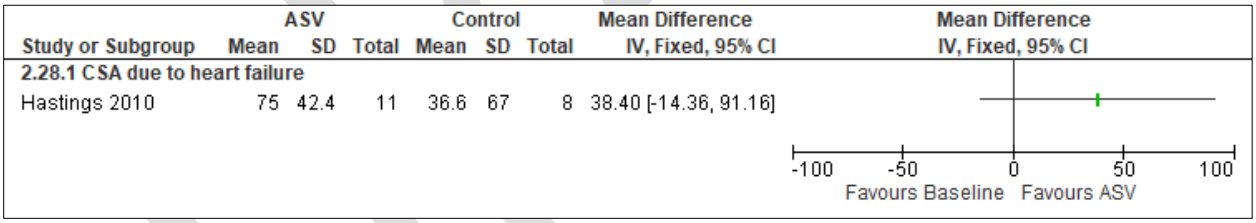


Figure S121. ASV vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST=+15 min], Observational studies

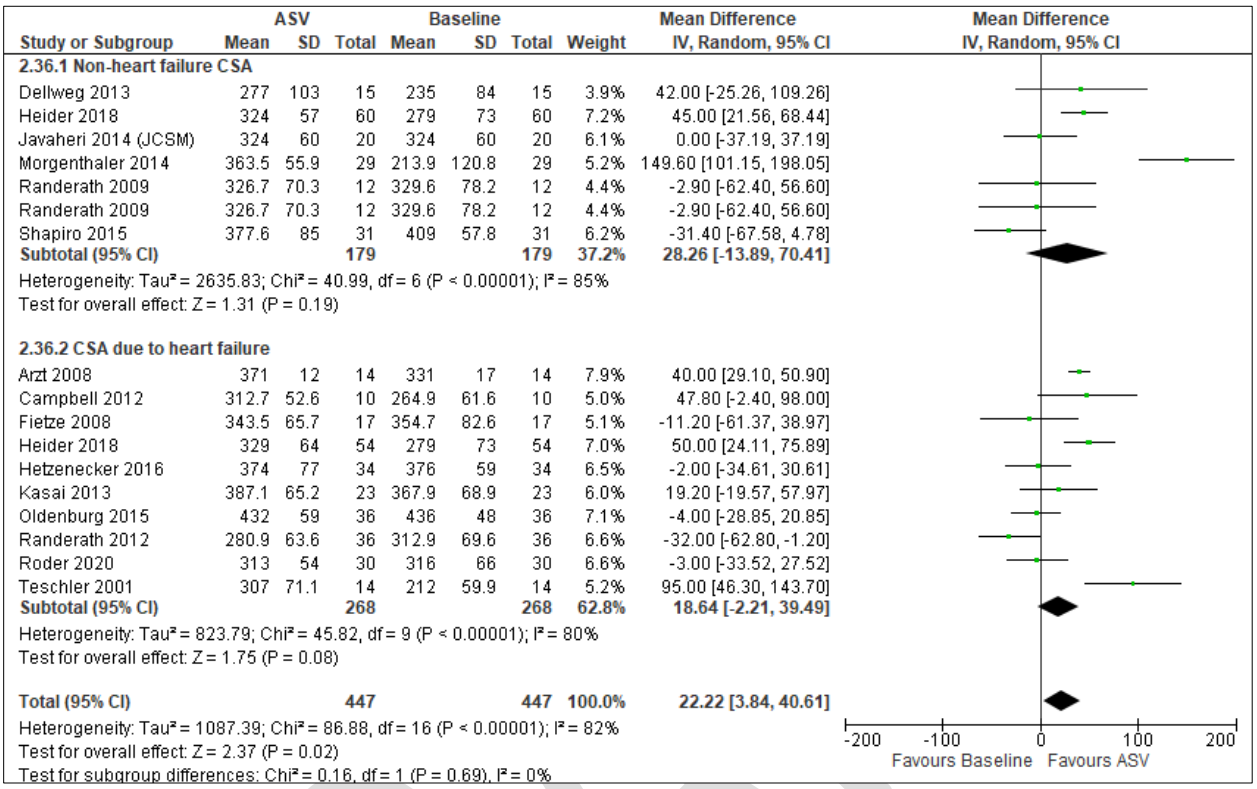


Figure S122. ASV vs. Control (Sleep architecture, PSG, Total Sleep Time) [CST=+15 min], Observational study

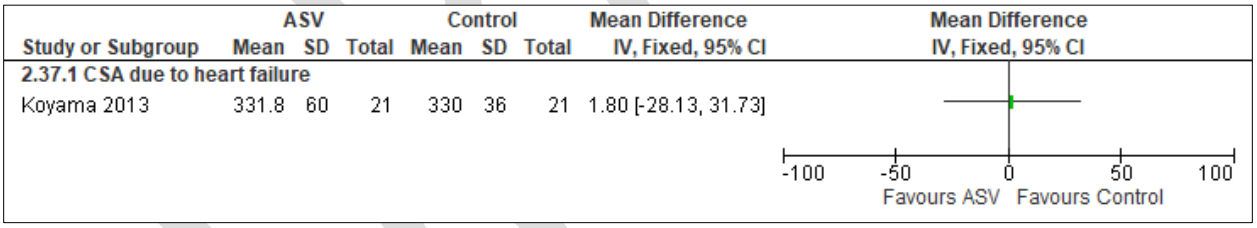


Figure S123. ASV vs. Baseline (Sleep architecture, PSG, Sleep efficiency) [CST=+10%], Observational studies

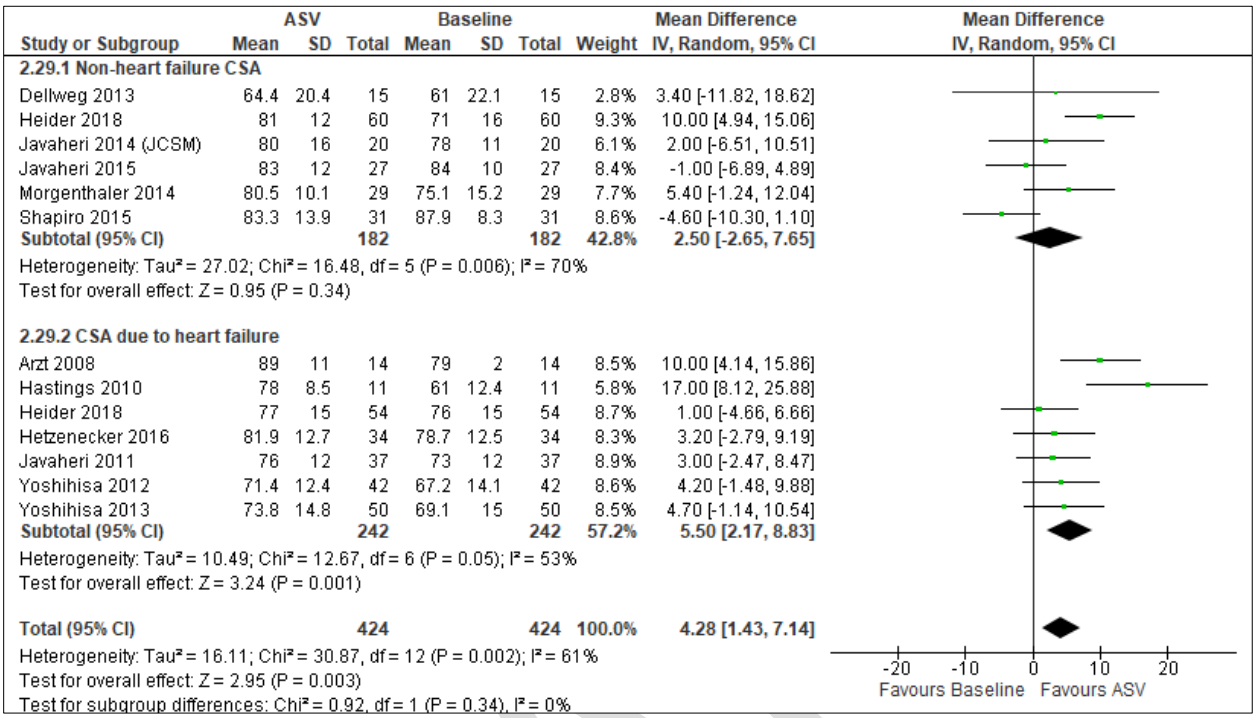


Figure S124. ASV vs. Baseline (Sleep architecture, PSG, REM (%)) [CST=+5% of TST], Observational studies

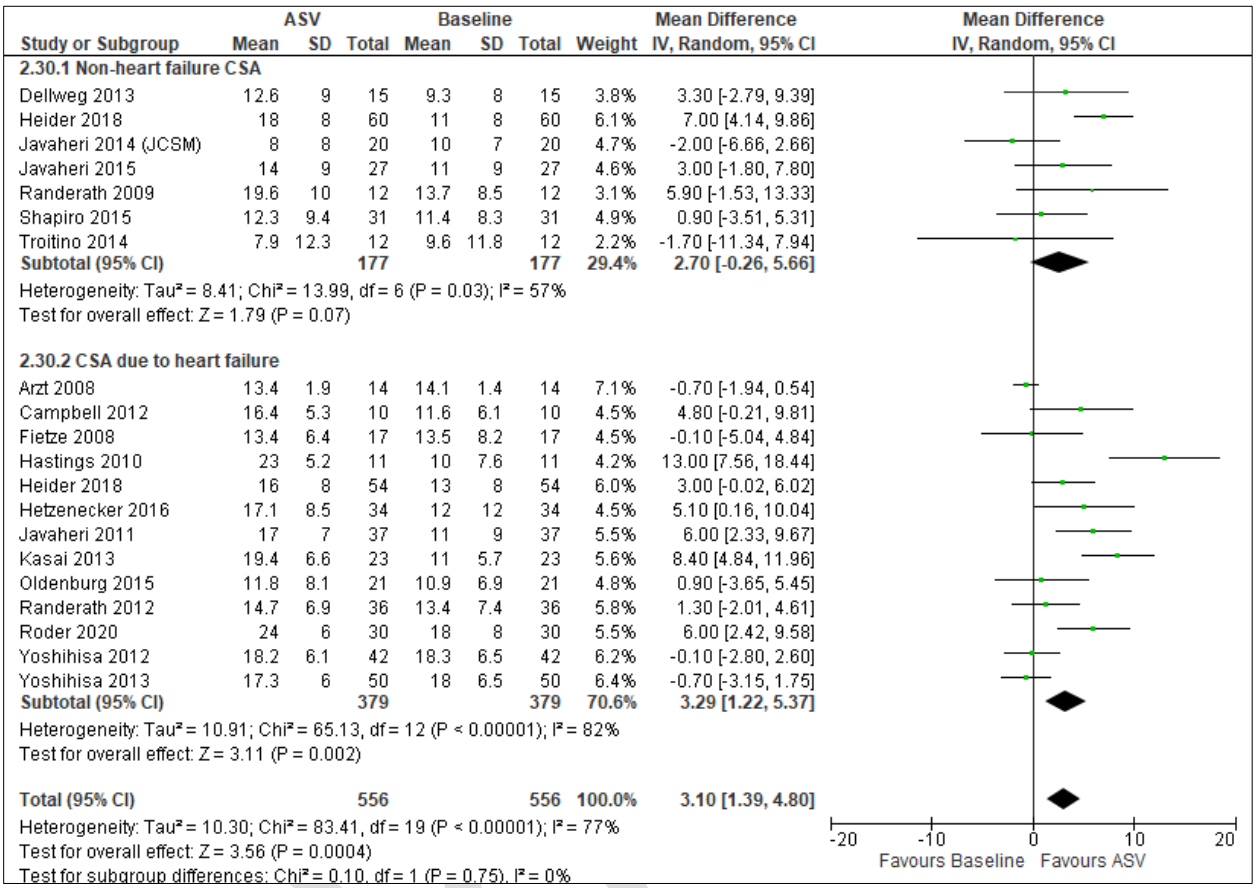


Figure S125. ASV vs. Baseline (Sleep architecture, PSG, SWS (%)) [CST=+5% of TST], Observational studies

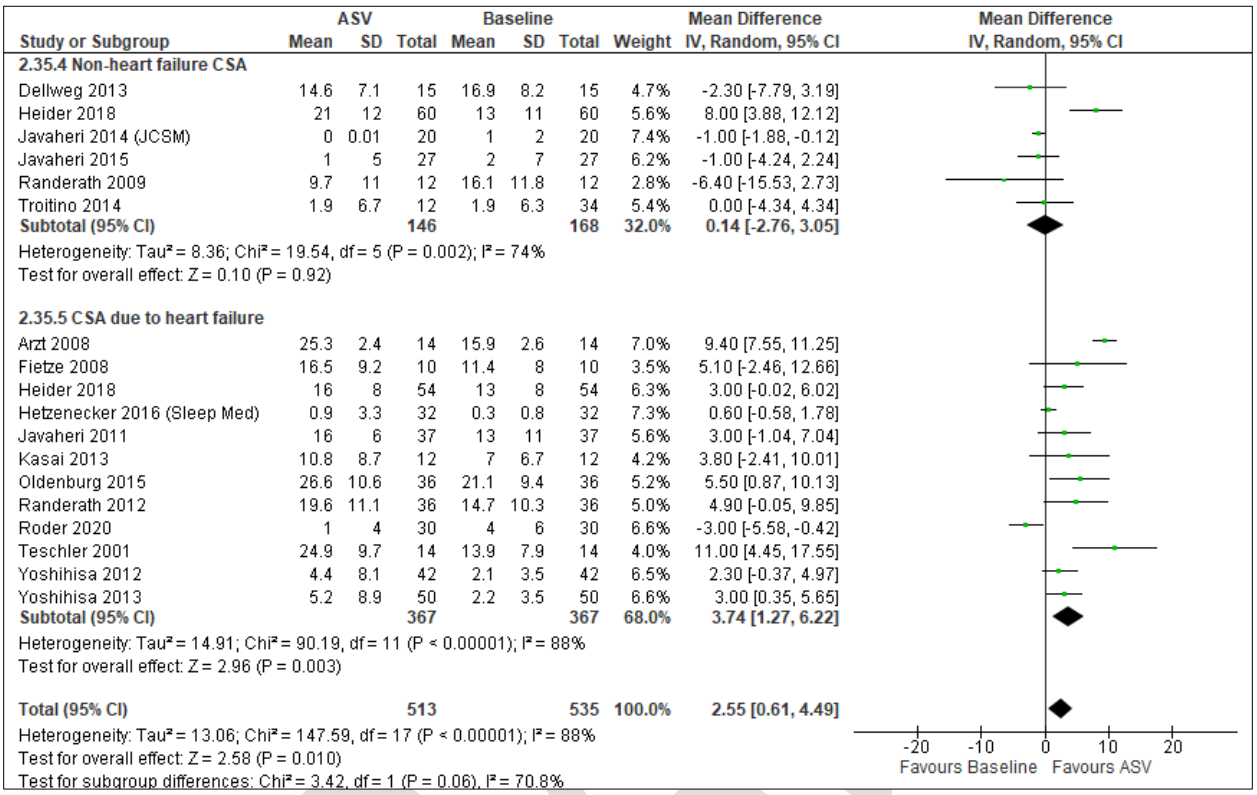


Figure S126. ASV vs. Baseline (Sleep architecture, PSG, Sleep Stage N1%) [CST=-5% of TST], Observational studies

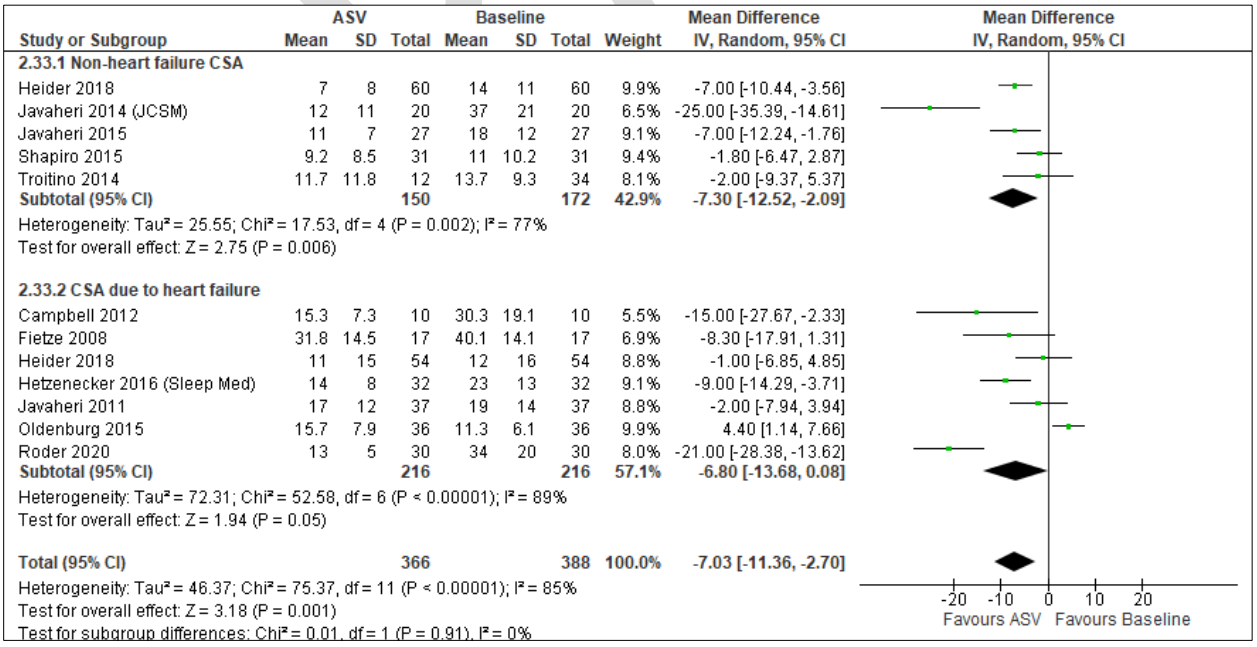


Figure S127. ASV vs. Baseline (Sleep architecture, PSG, Sleep Stage N2%) [CST=-5% of TST], Non-randomized studies

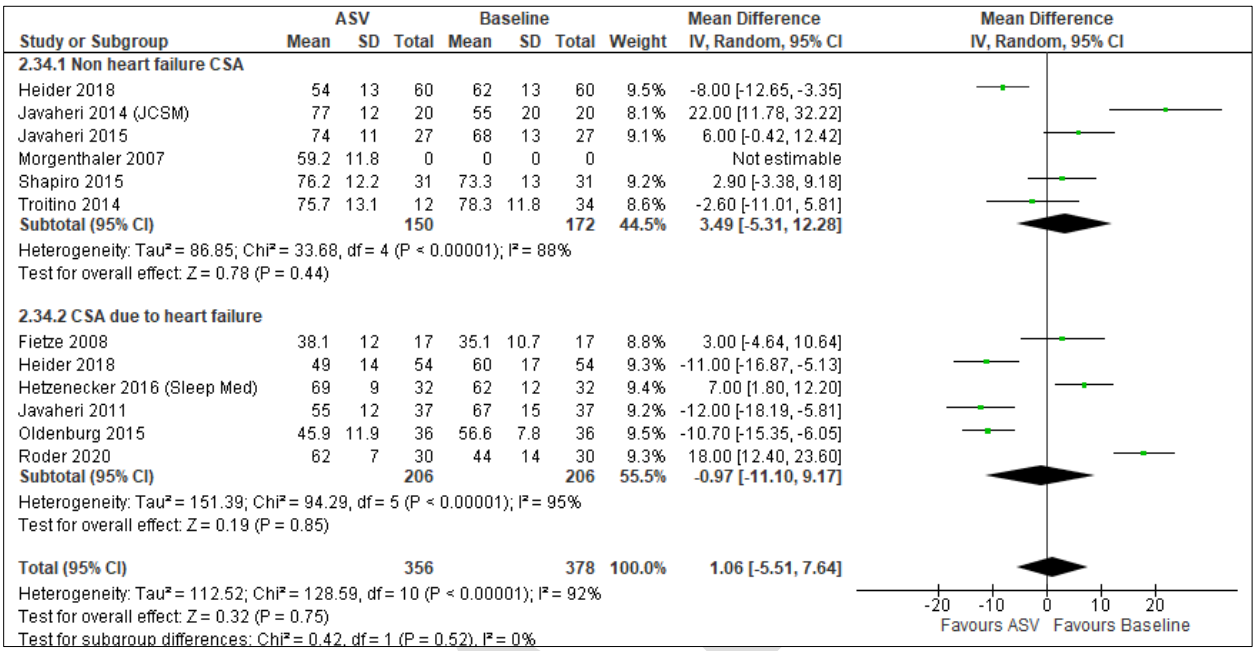


Figure S128. ASV vs. Baseline (Sleep architecture, PSG, Sleep Stage 1/2%) [No CST], Observational study

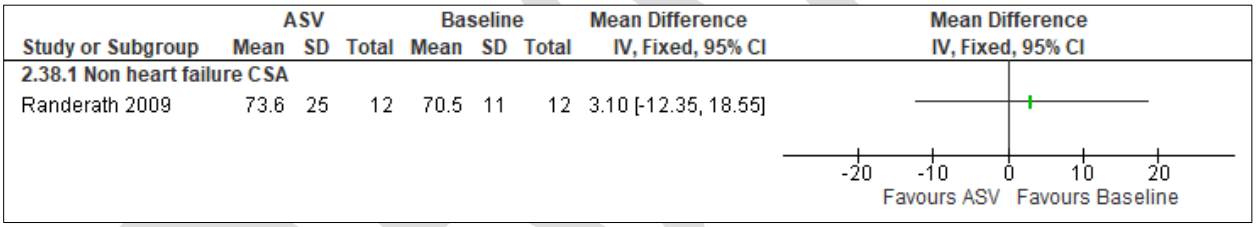
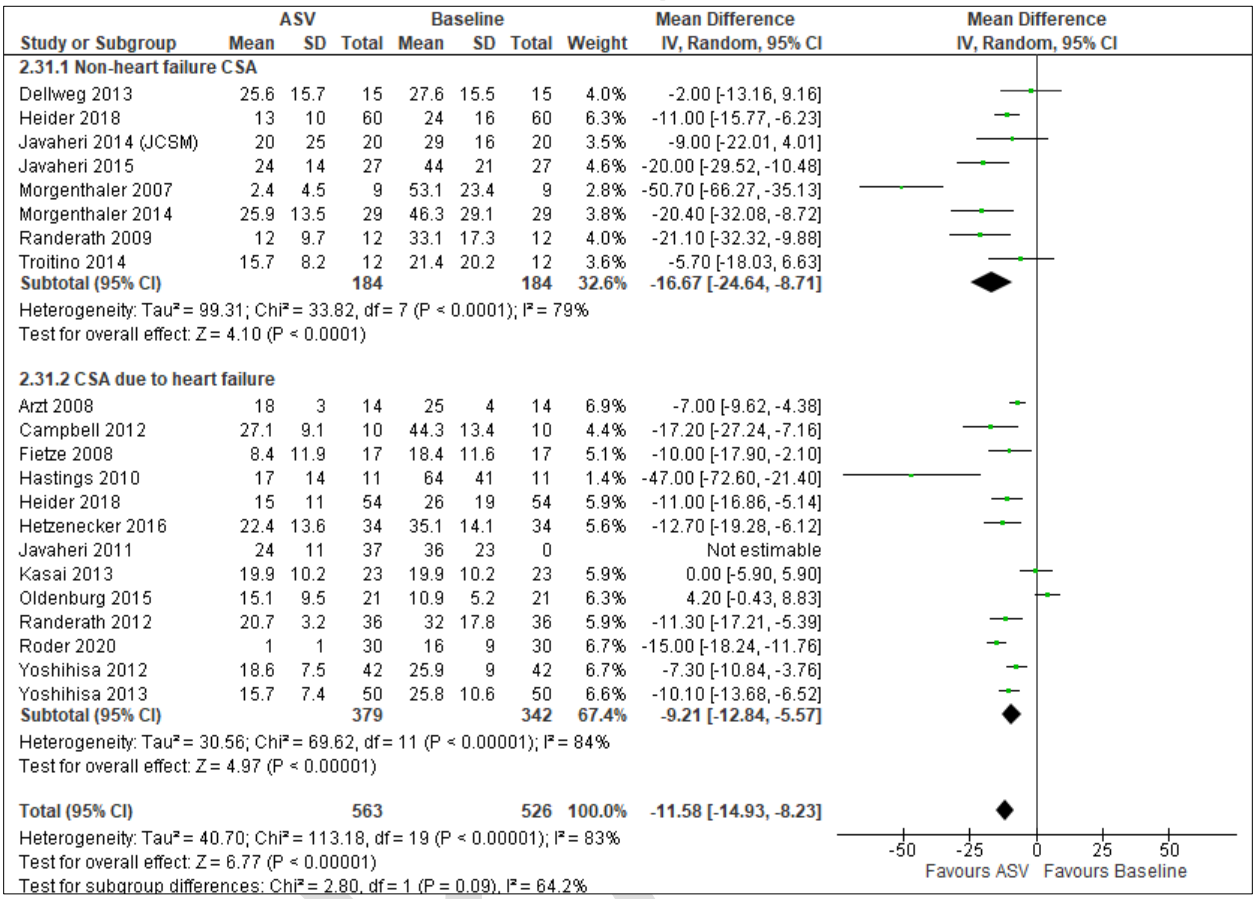
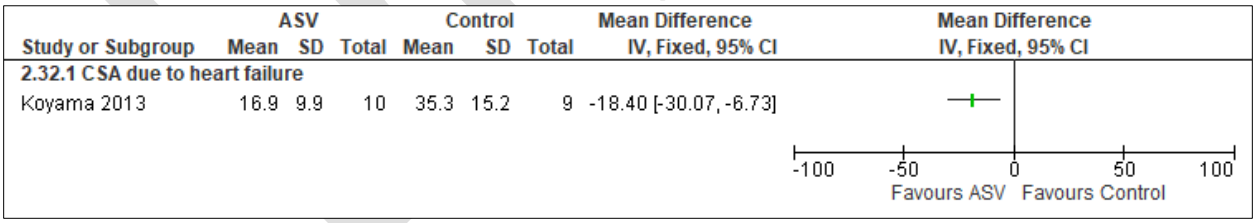


Figure S129. ASV vs. Baseline (Sleep architecture, PSG, Arousal Index (#/hr)) [CST=25% percent reduction from baseline or reduction to ≤12 events/hr], Observational studies



Roder 2020: respiratory arousals, percent change from baseline for the non-heart failure group=-44.94% and heart failure group=-33.29, total change from baseline from all CSA sub-groups=-40.86%

Figure S130. ASV vs. Control (Sleep architecture, PSG, Arousal Index (#/hr)) [CST=25% percent reduction from baseline or reduction to ≤12 events/hr], Observational studies



Low-flow Oxygen

Summary of Findings (GRADE)

Table S5 Low-flow oxygen in adults with CSA

References: Andreas 1996, Brostrom 2005, Campbell 2012, Hanly 1989, Nakao 2014, Sasayama 2006, Sasayama 2009, Seino 2007, Staniforth 1998, Toyama 2009

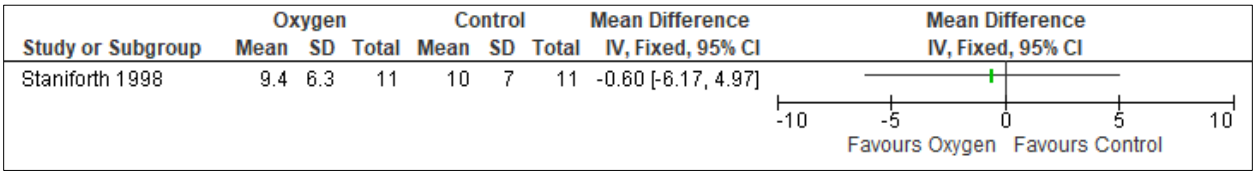
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference	No of Participants (studies)
		Low-flow oxygen vs. baseline or control	

Excessive sleepiness [ESS]	⊕⊕◯◯ **LOW**[a, b]	The mean difference in the low-flow oxygen group was **0.6 points lower (6.17 lower to 4.97 higher)** compared to control	22 (1 RCT)
Disease severity [AHI]	⊕⊕⊕⊕ **HIGH**	The mean difference in the low-flow oxygen group was **11.07 events/hour lower (13.71 lower to 8.43 lower)** compared to control	308 (7 RCTs)
Disease severity [CAI]	⊕⊕⊕⊕ **HIGH**	The mean difference in the low-flow oxygen group was **5.91 events/hour lower (8.87 lower to 2.95 lower)** compared to control	246 (5 RCTs)
Cardiovascular disease [LVEF]	⊕⊕⊕◯ **MODERATE**[c]	The mean difference in the low-flow oxygen group was **5.23 percent higher (2.02 lower to 8.44 higher)** compared to control	224 (4 RCTs)
Cardiovascular disease [6MWD]	⊕◯◯◯ **VERY LOW**[a, c, d]	The mean difference in the low-flow oxygen group was **13.73 m higher (29.73 lower to 57.2 higher)** compared to baseline	29 (2 non-RCTs)
Hospitalization [incidence (times/year)]	⊕◯◯◯ **VERY LOW**[a,d]	The mean difference in the low-flow oxygen group was **1.6 times/year lower (2.09 lower to 1.11 lower)** compared to baseline	53 (1 non-RCT)
Hospitalization [incidence of outpatient visits]	⊕◯◯◯ **VERY LOW**[a,d]	The mean difference in the low-flow oxygen group was **5.2 visits/year lower (8.35 lower to 2.05 lower)** compared to baseline	53 (1 non-RCT)
Hospitalization [emergency visits (time/year)]	⊕◯◯◯ **VERY LOW**[a,d]	The mean difference in the low-flow oxygen group was **1.7 times/year lower (2.58 lower to 0.82 lower)** compared to baseline	53 (1 non-RCT)
Hospitalization [Length of stay (days)]	⊕◯◯◯ **VERY LOW**[a,d]	The mean difference in the low-flow oxygen group was **4.1 days fewer (22.59 fewer to 14.39 more)** compared to baseline	53 (1 non-RCT)
Adverse events	⊕⊕◯◯ **LOW**[a]	**Campbell 2012:** 1 out 10 participants died ("heart attack") and 1 out of 10 participants required a hospital admission to CCU **Sasayama 2009:** 1 out of 51 patients died suddenly from arrhythmia and 7 out of 51 patients were hospitalized for worsening, HF in both groups. **Andreas 1996:** Three patients (out of 27) in the room air group and two patients (out of 27) in the oxygen group withdrew from the study because of the inconvenience of the nasal prongs, data from these patients not included in final analysis	116 (3 RCTs)

a. Imprecision due to small sample size (<200 participants)
b. Imprecision due to the 95% CI includes possibility for important benefit and harm
c. Imprecision due to the 95% CI includes possibility for important benefit and no effect
d. Downgraded quality of evidence due to data analyzed using pre- and posttreatment values

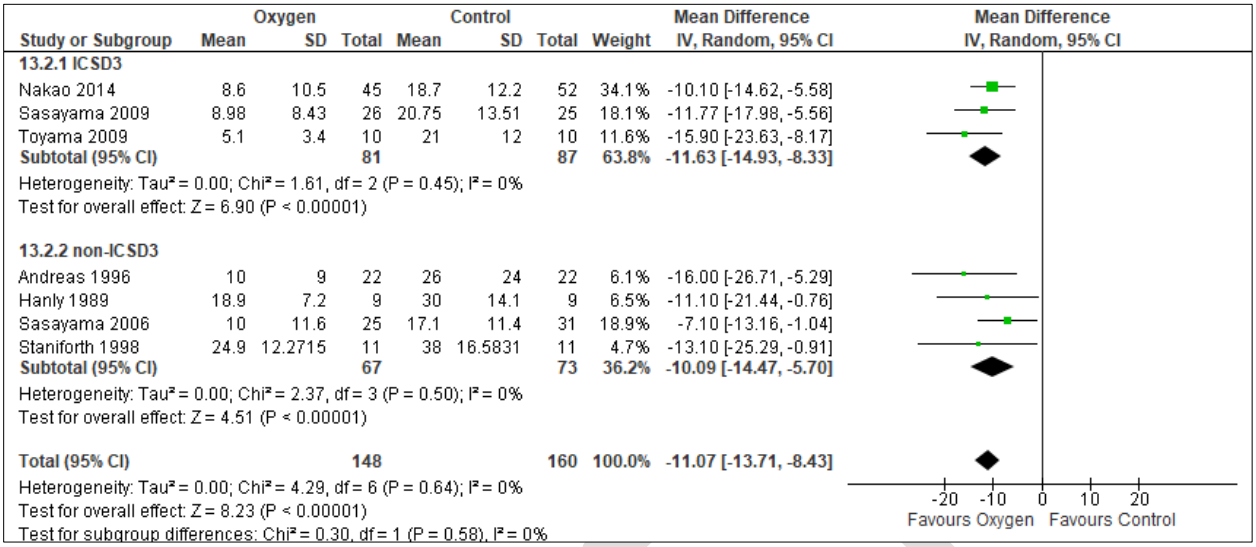
Critical Outcomes

Figure S131. Oxygen vs. Control (Excessive sleepiness, ESS) [CST= -2 pts], RCT



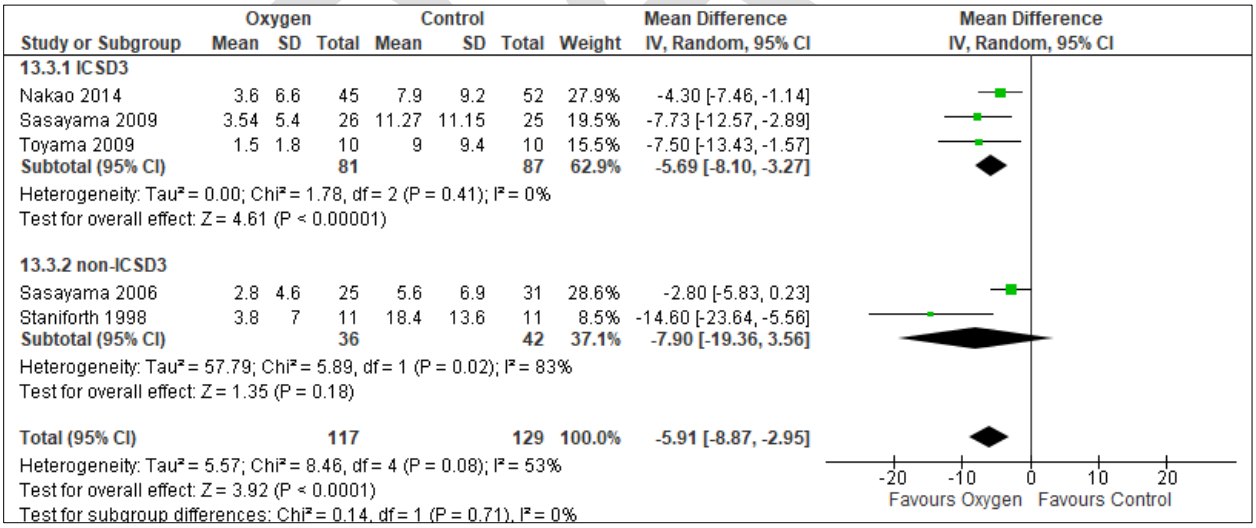
Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air delivered at a rate of 2 L/min via nasal cannula.

Figure S132. Oxygen vs. Control (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCTs



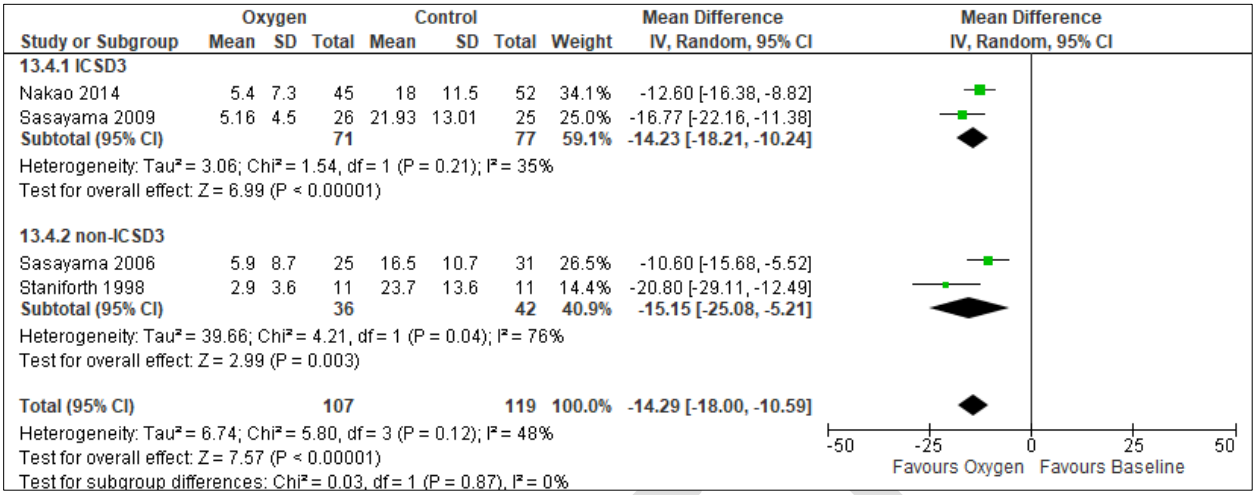
Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Andreas 1996: Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights; Hanly 1989: SEM converted to SD, AHI during total sleep time used, single night study, compressed air and oxygen were administered through nasal cannula at a rate of 2 to 3 L/min; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula; Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula; Disease severity (AHI): reduction from baseline O2=-55.3%.

Figure S133. Oxygen vs. Control (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCTs



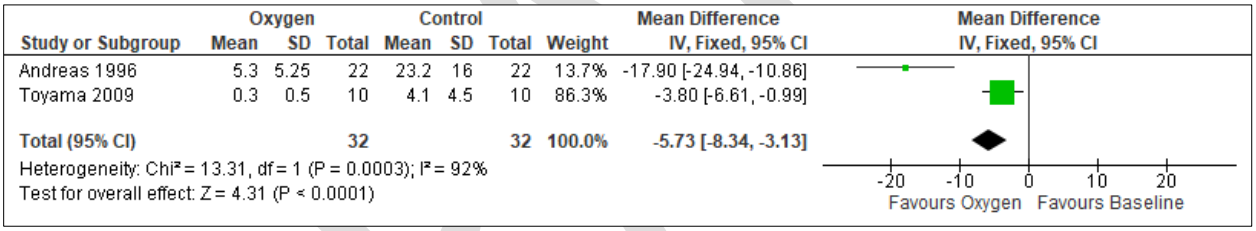
Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula; Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula; Disease severity (CAI): reduction from baseline O2=-67.1%

Figure S134. Oxygen vs. Control (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCTs



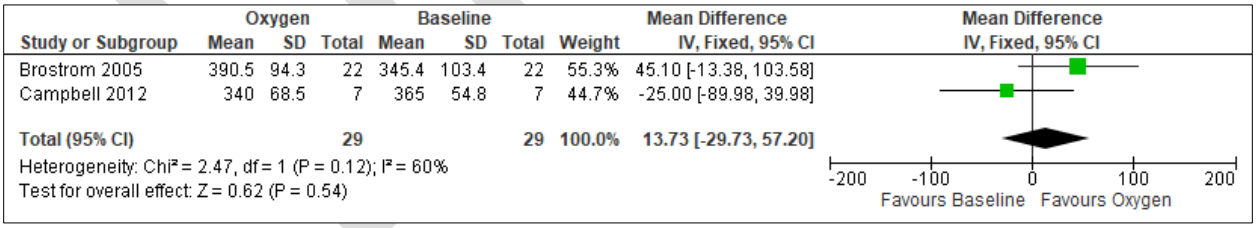
Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula; Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula

Figure S135. Oxygen vs. Control (Disease Severity, oxygen saturation <90%) [CST= ≥ 50% change from baseline], RCT



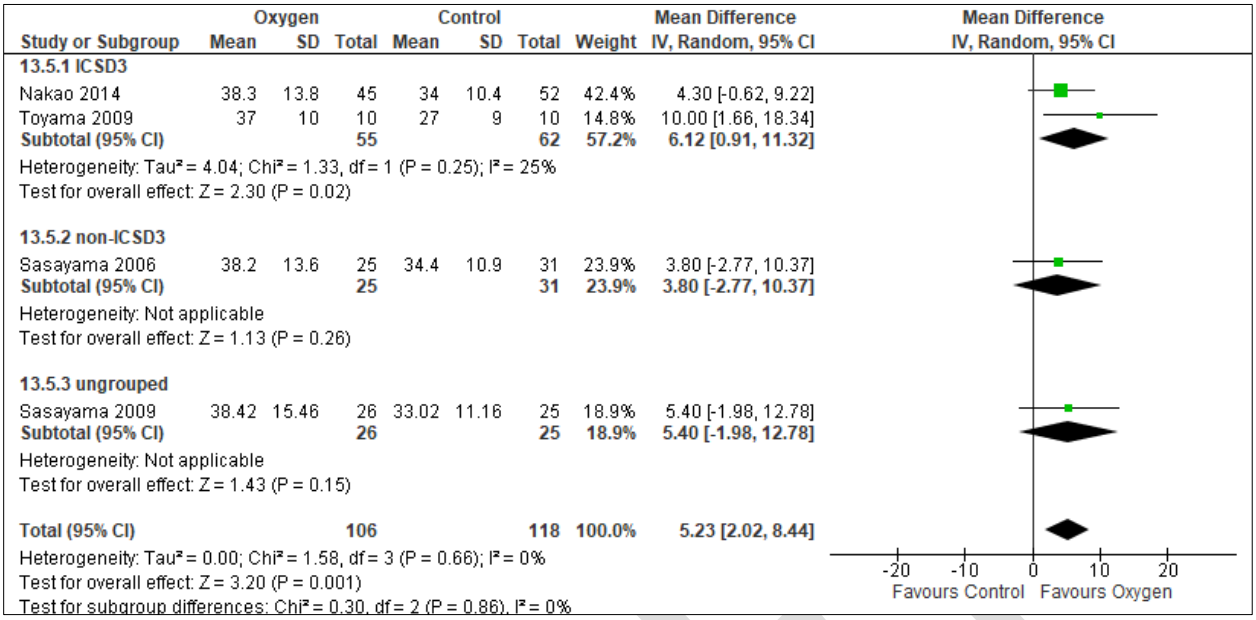
Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Andreas 1996: median and range converted to mean and SD, Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights

Figure S136. Oxygen vs. Baseline (Cardiovascular disease, 6MWD) [CST= + 32 meters], observational



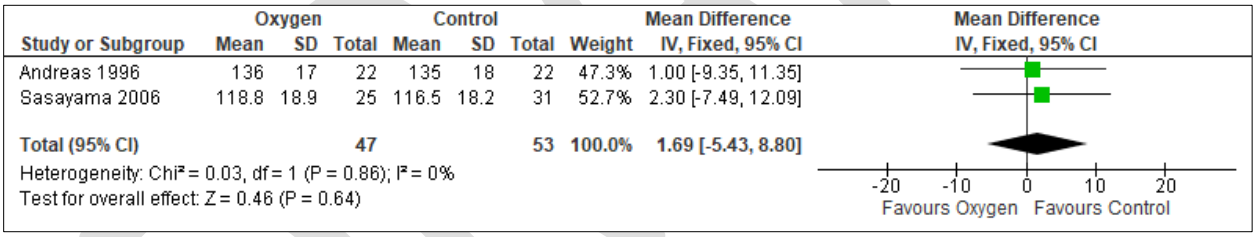
Brostrom 2005: mean and SD calculated from median and range

Figure S137. Oxygen vs. Control (Cardiovascular disease, LVEF (%)) [CST= 5%], RCTs



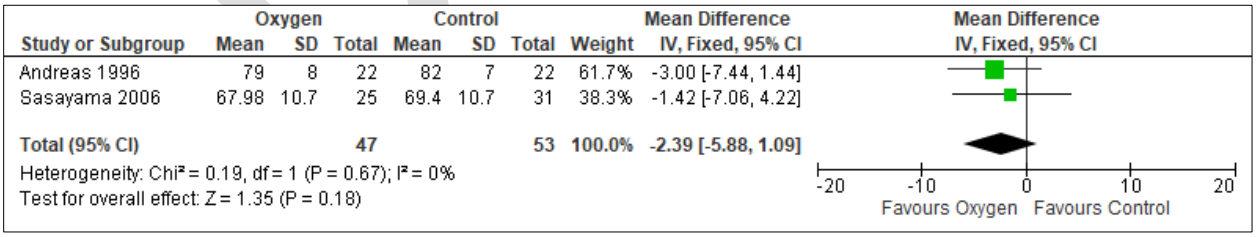
Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula

Figure S138. Oxygen vs. Control (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], RCTs



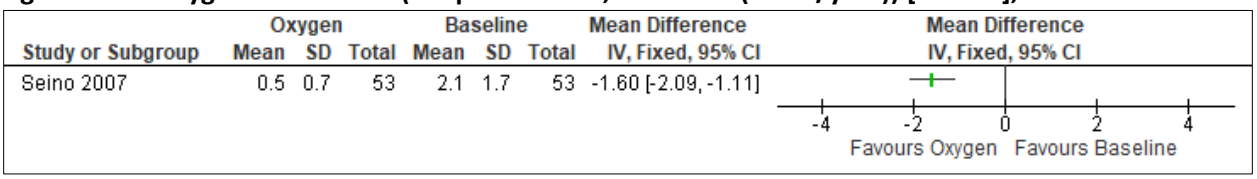
Andreas 1996: Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula

Figure S139. Oxygen vs. Control (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCT



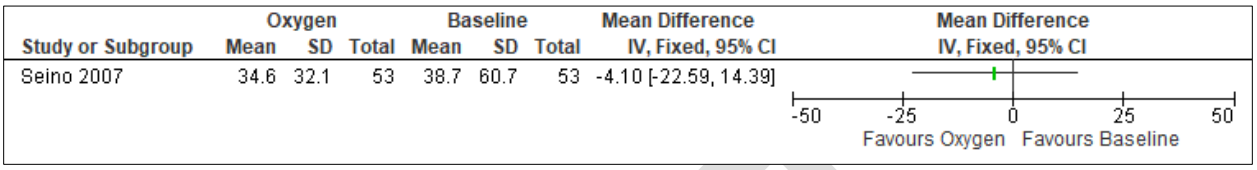
Andreas 1996: Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula

Figure S140. Oxygen vs. Baseline (Hospitalizations, Incidence (times/year)) [No CST], Observational



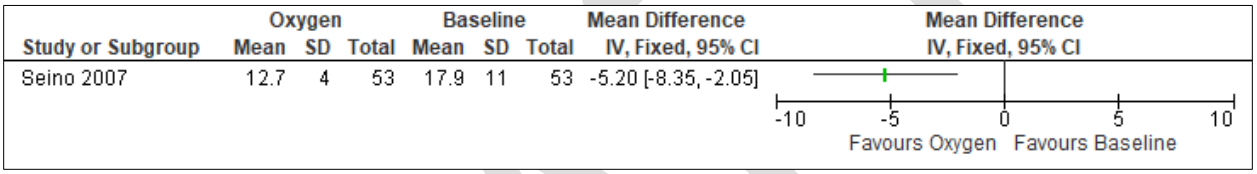
Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula.

Figure S141. Oxygen vs. Baseline (Hospitalizations, Length of stay (days)) [No CST], Observational



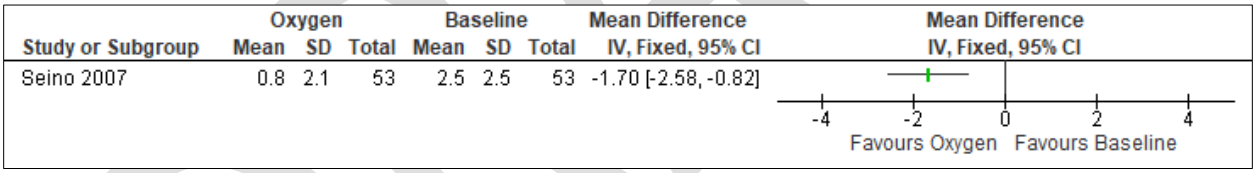
Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula

Figure S142. Oxygen vs. Baseline (Hospitalizations, Outpatient visits (times/year)) [No CST], Observational



Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula

Figure S143. Oxygen vs. Baseline (Hospitalizations, Emergency visits (times/year)) [No CST], Observational



Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula

Figure S144. Oxygen vs. Baseline (Sleep quality (Patient reported), sleep sufficiency index) [No CST], Observational

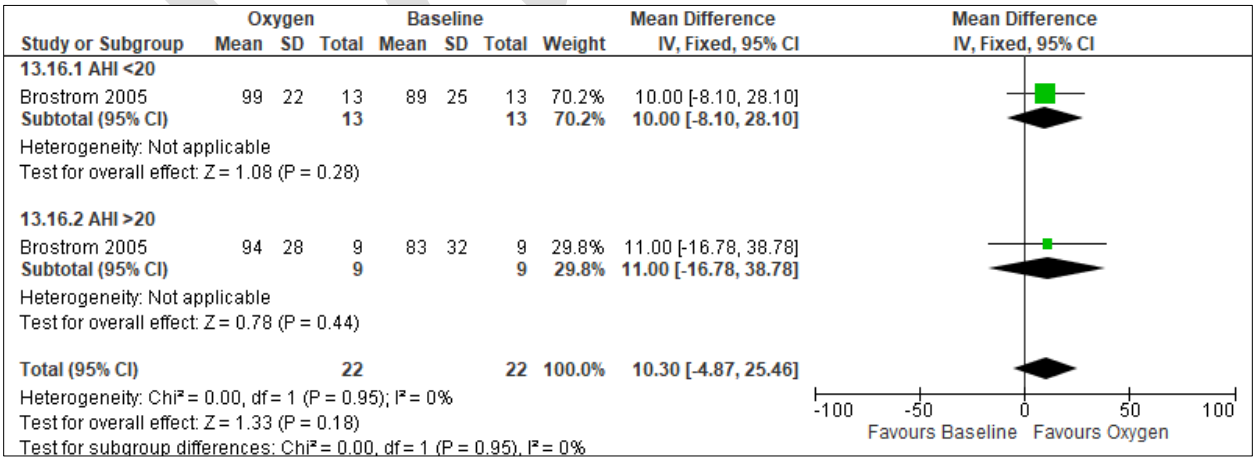
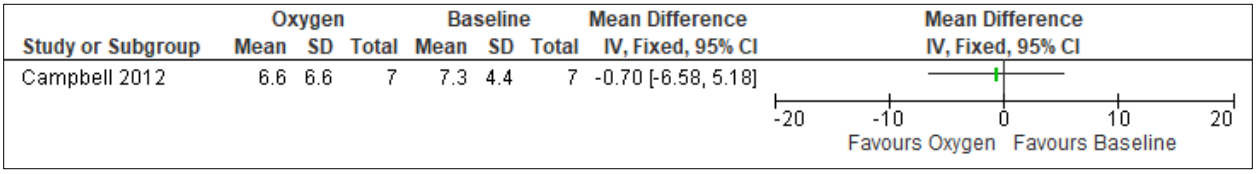
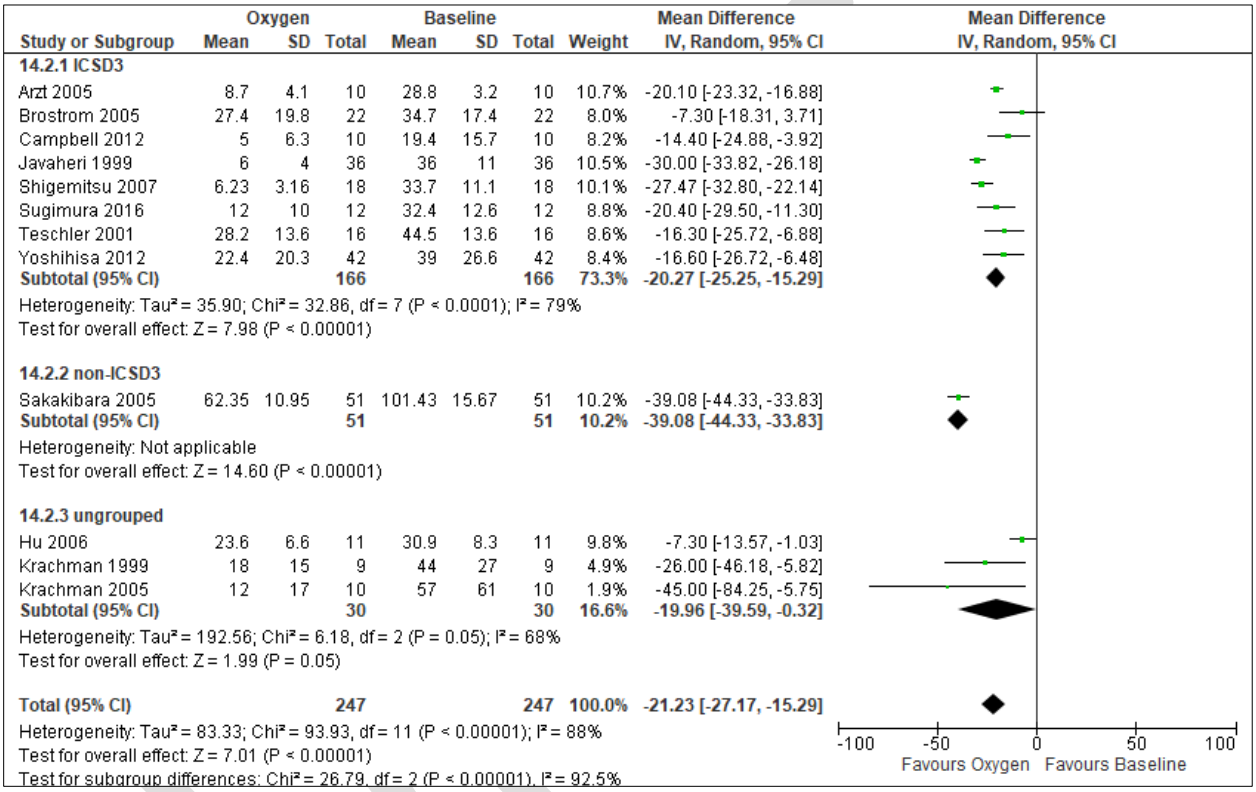


Figure S145. Oxygen vs. Control (Excessive sleepiness, ESS) [CST= 2 pts], Observational



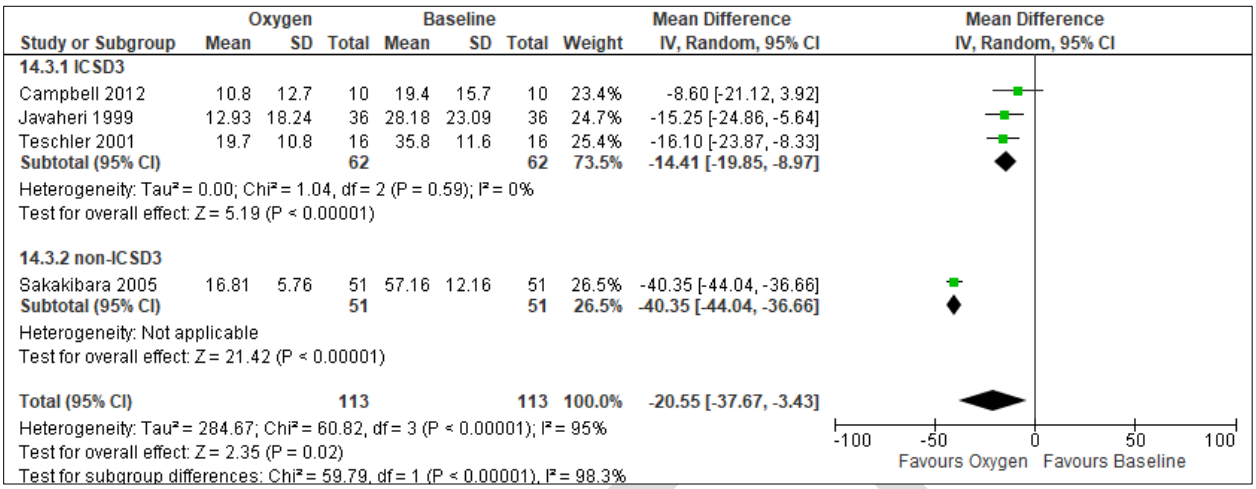
Campbell 2012: 8-week study, analysis included pre-post analysis of oxygen arm, Oxygen was delivered through nasal prongs at 2 L/min through an oxygen concentrator

Figure S146. Oxygen vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% change from baseline], Observational



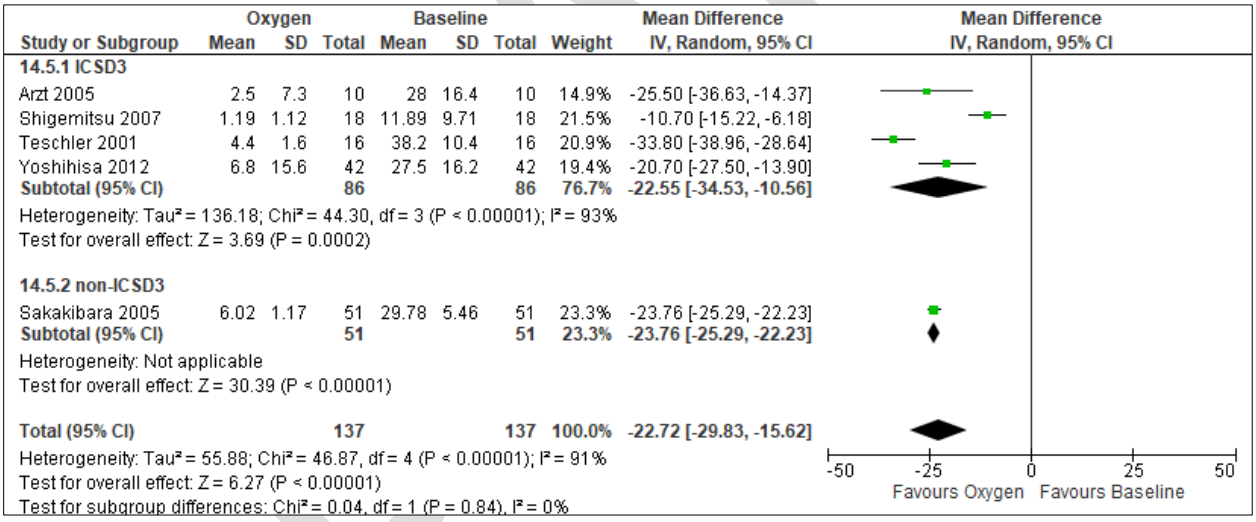
Arzt 2005: 12-week study, 2 L/min nasal oxygen; Brostrom 2005: 3-month study, oxygen administered at a fixed rate of 2 L/min by nasal cannula; Campbell 2012: 8-week study, analysis included pre-post analysis of oxygen arm, Oxygen was delivered through nasal prongs at 2 L/min through an oxygen concentrator; Javaheri 1999: Single night study, the final amount of O_2 were 2 to 2 ½ l/min in 14, 3 l/min in 10 and 4 l/min in 12 in subjects. ; Shigemitsu 2007: Single night study, nasal oxygen was administered at 2 l/min and was raised progressively to 3 l/min if disordered breathing resulted in ODI4% >4/h.; Sugimura 2016: two night study, Flow rate of O_2 therapy was 3 L/min via nasal cannula; Teschler 2001: SEM converted to SD, single night study, nasal oxygen (2 L/min); Yoshihisa 2012: single night study, administered oxygen at a rate of 3 L/min through a nasal cannula Sakakibara 2005: 2 nights, O_2 2 l/min; Hu 2006: single night study, nasal oxygen (4 L/min); Krachman 2005: night 2 (1 month of treatment) data used; Krachman 1999: SEM converted to SD, single night study, oxygen administered at 2 L/min by nasal cannula

Figure S147. Oxygen vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% change from baseline], Observational



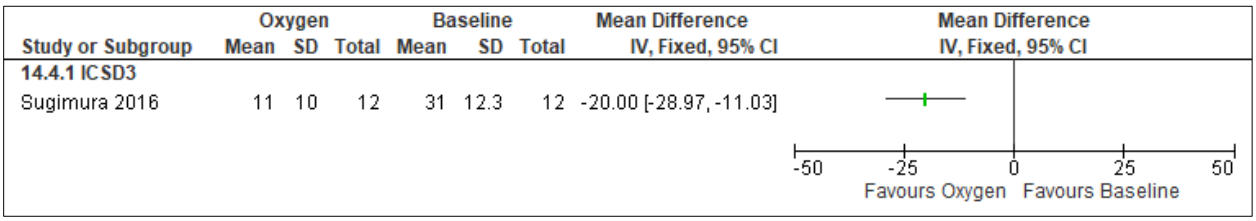
Campbell 2012: 8-week study, analysis included pre-post analysis of oxygen arm, Oxygen was delivered through nasal prongs at 2 L/min through an oxygen concentrator; Javaheri 1999: Single night study, the final amount of O_2 were 2 to 2 ½ l/min in 14, 3 l/min in 10 and 4 l/min in 12 in subjects. ; Teschler 2001: SEM converted to SD, single night study, nasal oxygen (2 L/min); Sakakibara 2005: 2 nights, O_2 2 l/min

Figure S148. Oxygen vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% change from baseline], Observational



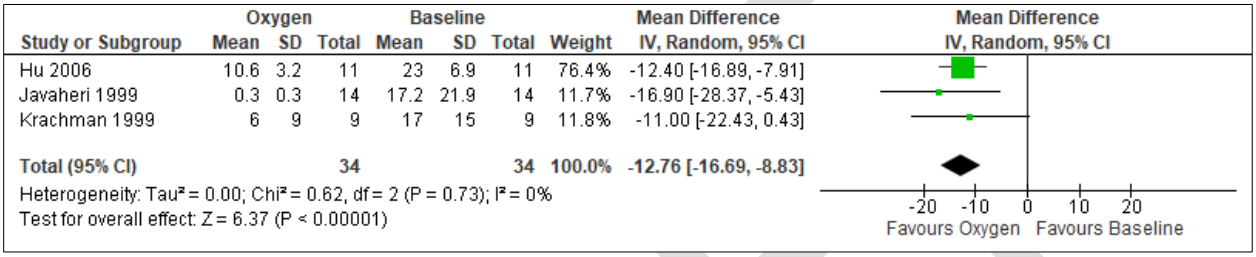
Arzt 2005: 12-week study, 2 L/min nasal oxygen; Shigemitsu 2007: Single night study, nasal oxygen was administered at 2 l/min and was raised progressively to 3 l/min if disordered breathing resulted in ODI4% >4/h.; Teschler 2001: SEM converted to SD, single night study, nasal oxygen (2 L/min); Yoshihisa 2012: single night study, administered oxygen at a rate of 3 L/min through a nasal cannula; Sakakibara 2005: 2 nights, O_2 2 l/min

Figure S149. Oxygen vs. Baseline (Disease Severity, CAHI) [CST= ≥ 50% change from baseline], Observational



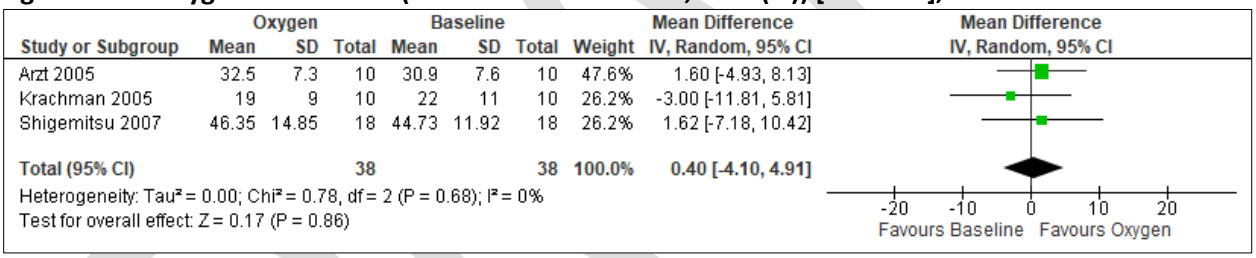
Sugimura 2016: two night study, Flow rate of O_2 therapy was 3 L/min via nasal cannula

Figure S150. Oxygen vs. Baseline (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% reduction from baseline], Observational



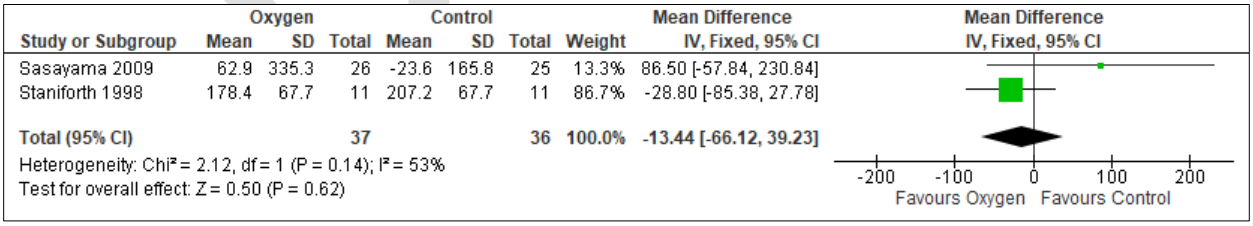
Javaheri 1999: data extracted from figure 3, fully responsive patients, Single night study, the final amount of O_2 were 2 to 2 ½ l/min in 14, 3 l/min in 10 and 4 l/min in 12 in subjects; Hu 2006: single night study, nasal oxygen (4 L/min); Krachman 1999: SEM converted to SD, single night study, oxygen administered at 2 L/min by nasal cannula

Figure S151. Oxygen vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= 5%], Observational



Arzt 2005: 12-week study, 2 L/min nasal oxygen; Shigemitsu 2007: Single night study, nasal oxygen was administered at 2 l/min and was raised progressively to 3 l/min if disordered breathing resulted in ODI4% >4/h.; Sakakibara 2005: 2 nights, O_2 2 l/min

Figure S152. Oxygen vs. Control (Cardiovascular disease, BNP (pg/mL)) [CST= 50% change from baseline], RCT



Sasayama 2009: 52-week study, change score reported in (pg/ml), oxygen delivered at a rate of 3 L/min through a nasal cannula; Staniforth 1998: 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula, serum BNP for oxygen group = 21.1 ±8 (pmol.L^-1) and air group = 24.5 ± 8 (pmol.L^-1) converted to pg/ml

Figure S153. Oxygen vs. Control (Cardiovascular disease, HR (beats/min)) [CST], RCT

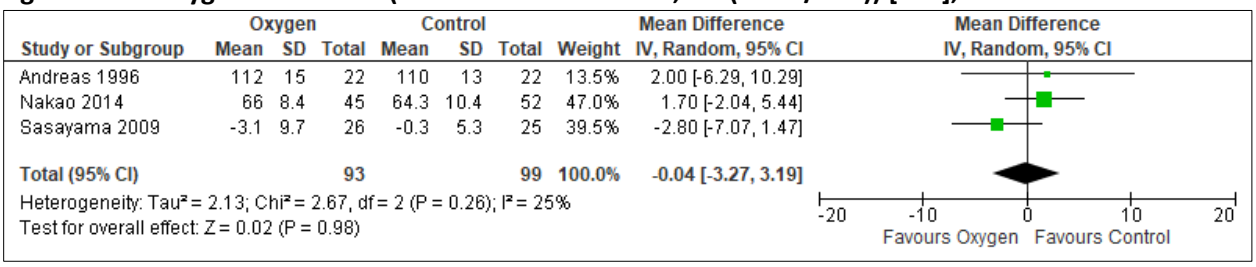
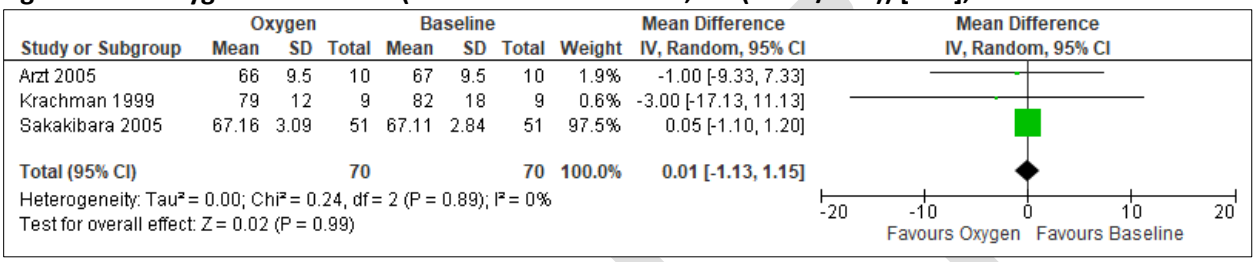


Figure S154. Oxygen vs. Baseline (Cardiovascular disease, HR (beats/min)) [CST], Observational



Krachman 1999: SEM converted to SD

Important Outcomes

Figure S155. Oxygen vs. Control (Daytime functioning, Specific Activity Scale (Mets)) [No CST], RCT

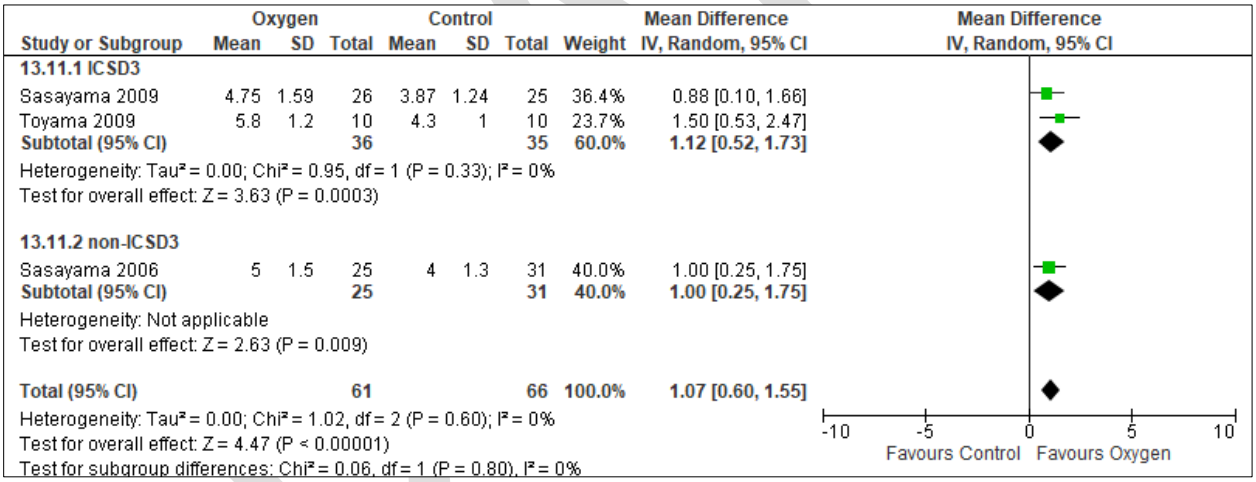


Figure S156. Oxygen vs. Control (Daytime functioning, Anaerobic threshold (AT VO2)) [No CST], RCT

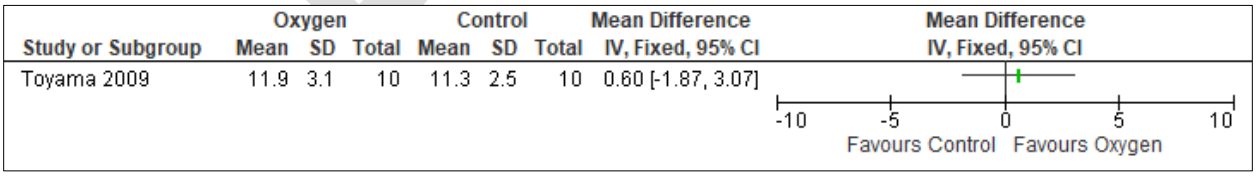


Figure S157. Oxygen vs. Control (Daytime functioning, Peak VO2) [No CST], RCT

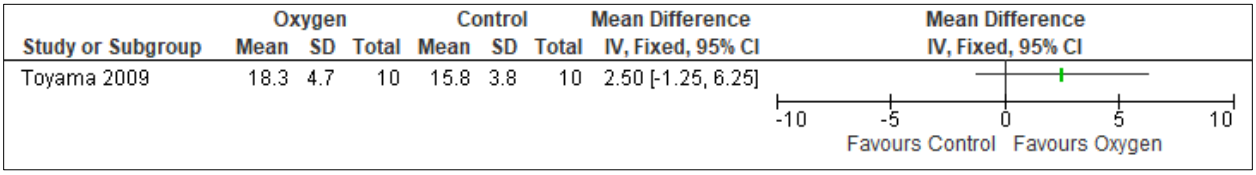


Figure S158. Oxygen vs. Control (Daytime functioning, Reitan trail making B (s)) [No CST], RCT

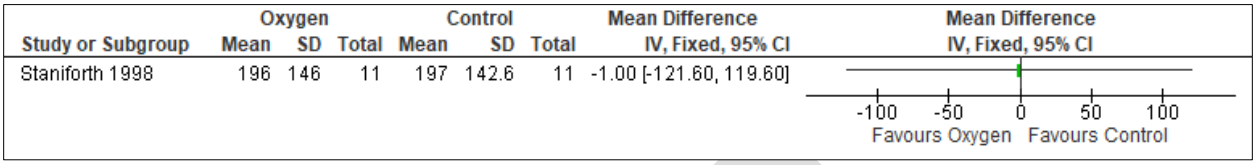


Figure S159. Oxygen vs. Control (Daytime functioning, Four choice reaction time (s)) [No CST], RCT

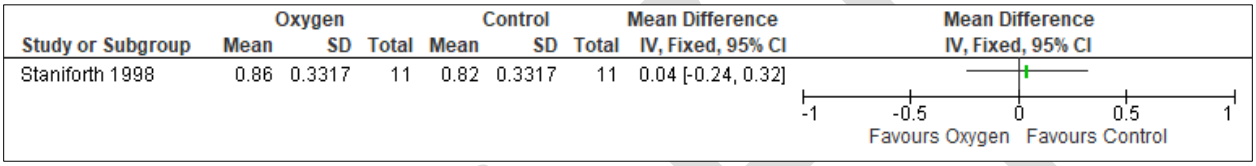


Figure S160. Oxygen vs. Control (Daytime functioning, PASAT 2 (s)) [No CST], RCT

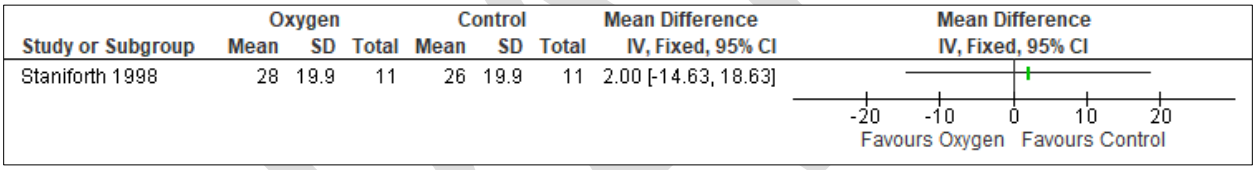


Figure S161. Oxygen vs. Control (Daytime functioning, PASAT 4 (s)) [No CST], RCT

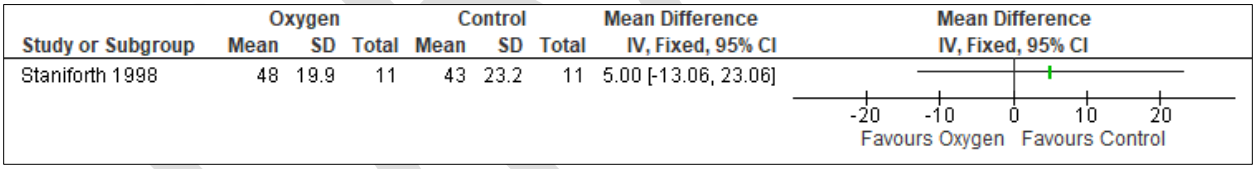


Figure S162. Oxygen vs. Control (Quality of Life, Quality of life score (max 240)) [No CST], RCT

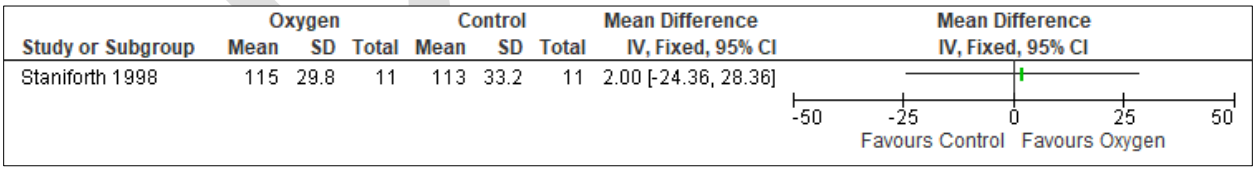
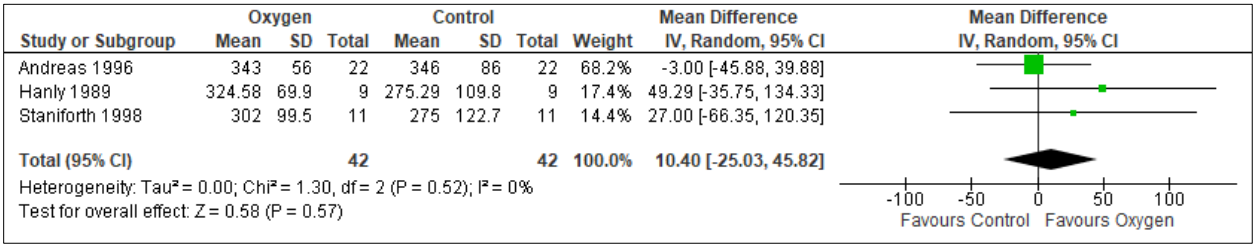


Figure S163. Oxygen vs. Control (Sleep architecture, PSG, Total Sleep Time) [CST= 15 min], RCT



Hanly 1989: SEM converted to SD

Figure S164. Oxygen vs. Control (Sleep architecture, PSG, REM (%)) [CST= 5% of TST], RCT

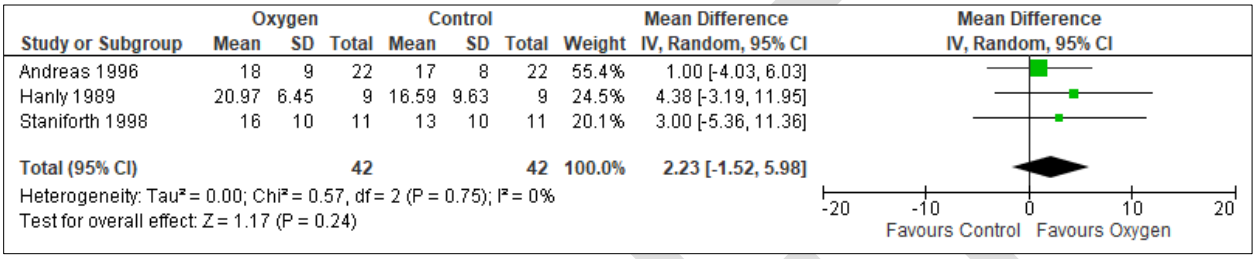
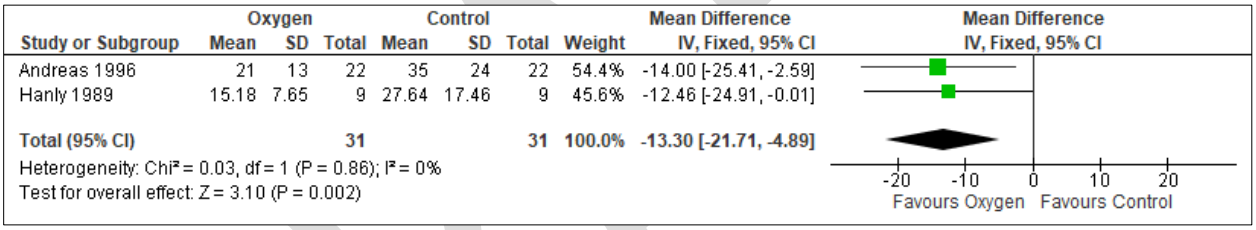


Figure S165. Oxygen vs. Control (Sleep architecture, PSG, Sleep stage N1%) [CST=5% of TST], RCT



Hanly 1989: SEM converted to SD

Figure S166. Oxygen vs. Control (Sleep architecture, PSG, Sleep stage N2%) [CST=5% of TST], RCT

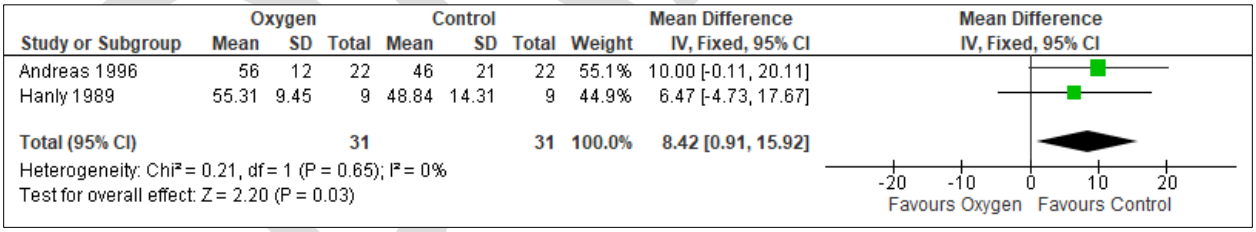
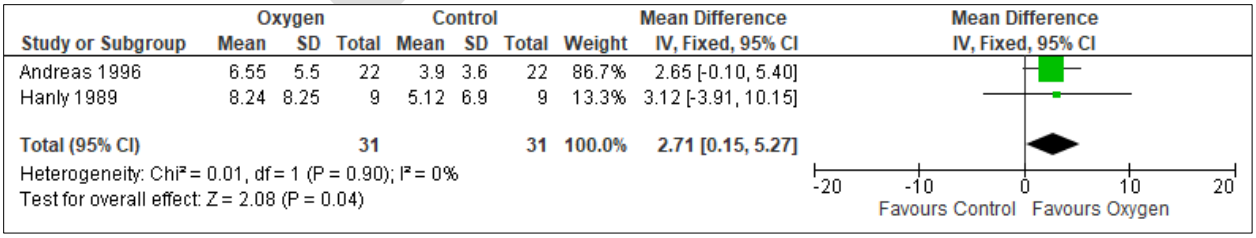


Figure S167. Oxygen vs. Control (Sleep architecture, PSG, SWS%) [CST=5% of TST], RCT



Andreas 1996: median and range converted to mean and SD

Figure S168. Oxygen vs. Control (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], RCTs

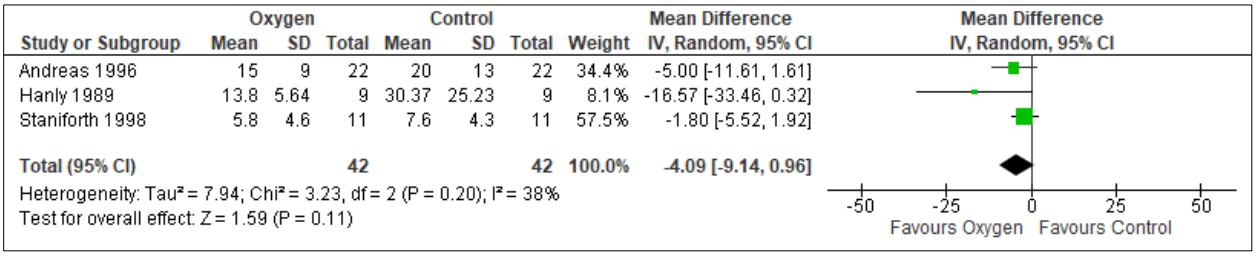


Figure S169. Oxygen vs. Control (Daytime functioning, Minnesota Living with Heart Failure) [CST], Observational

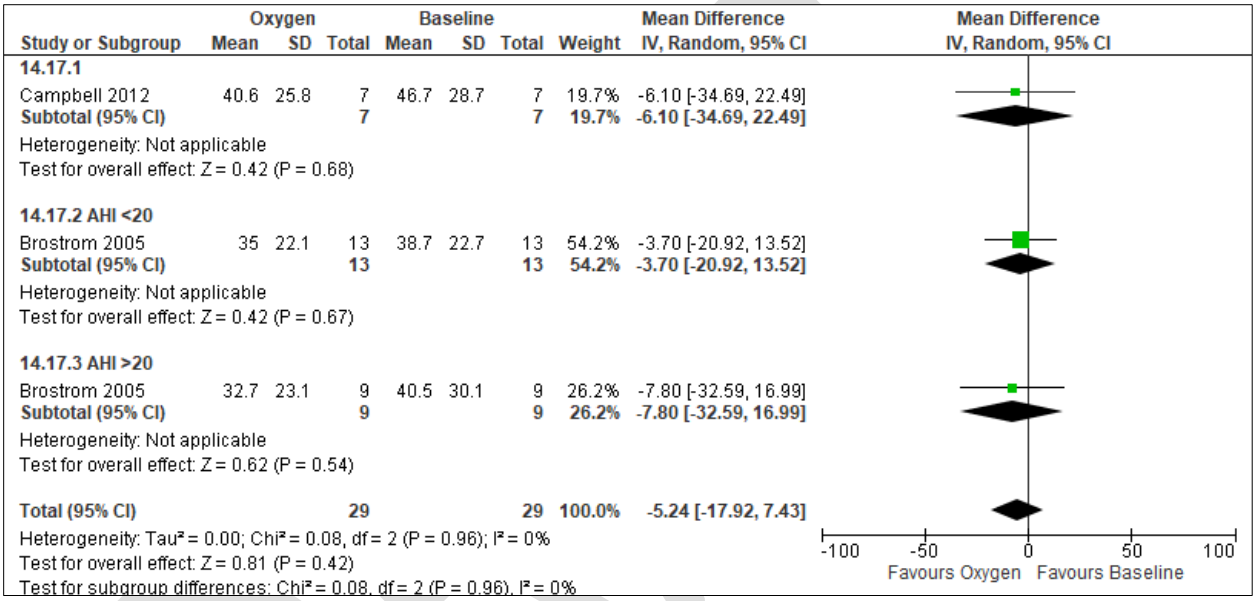
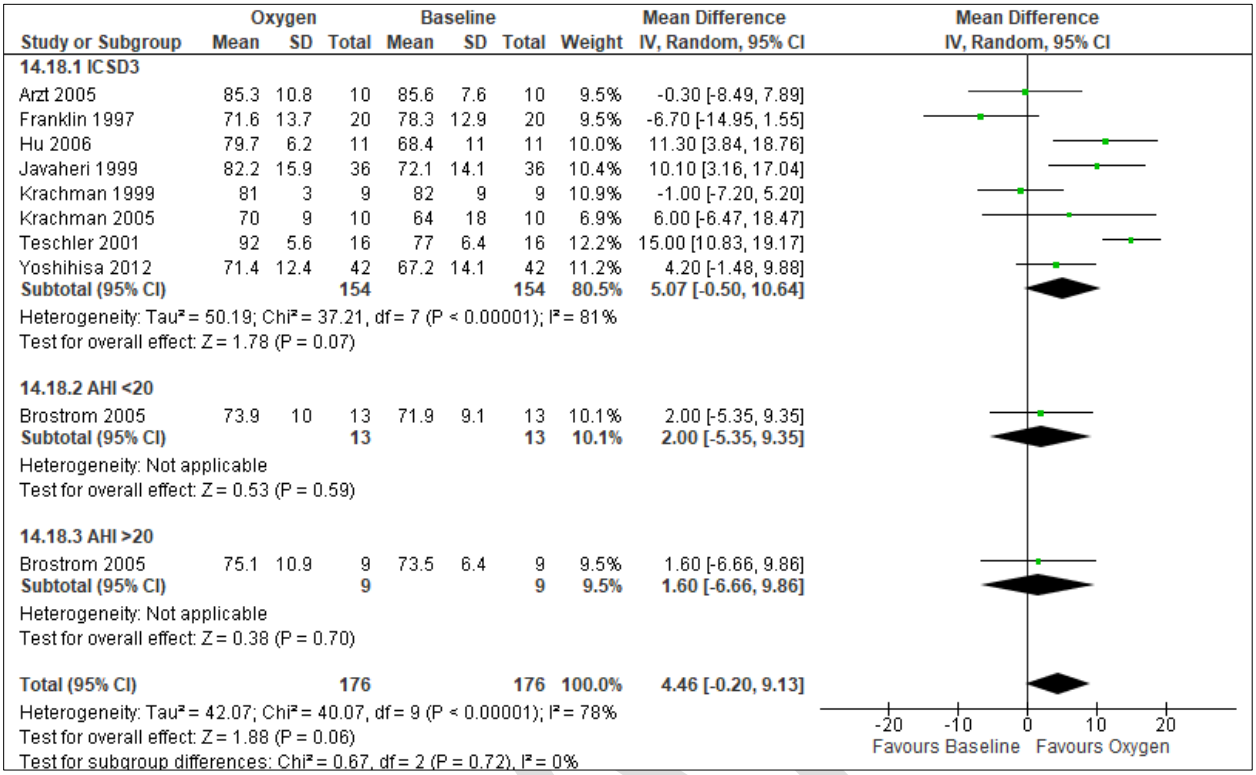
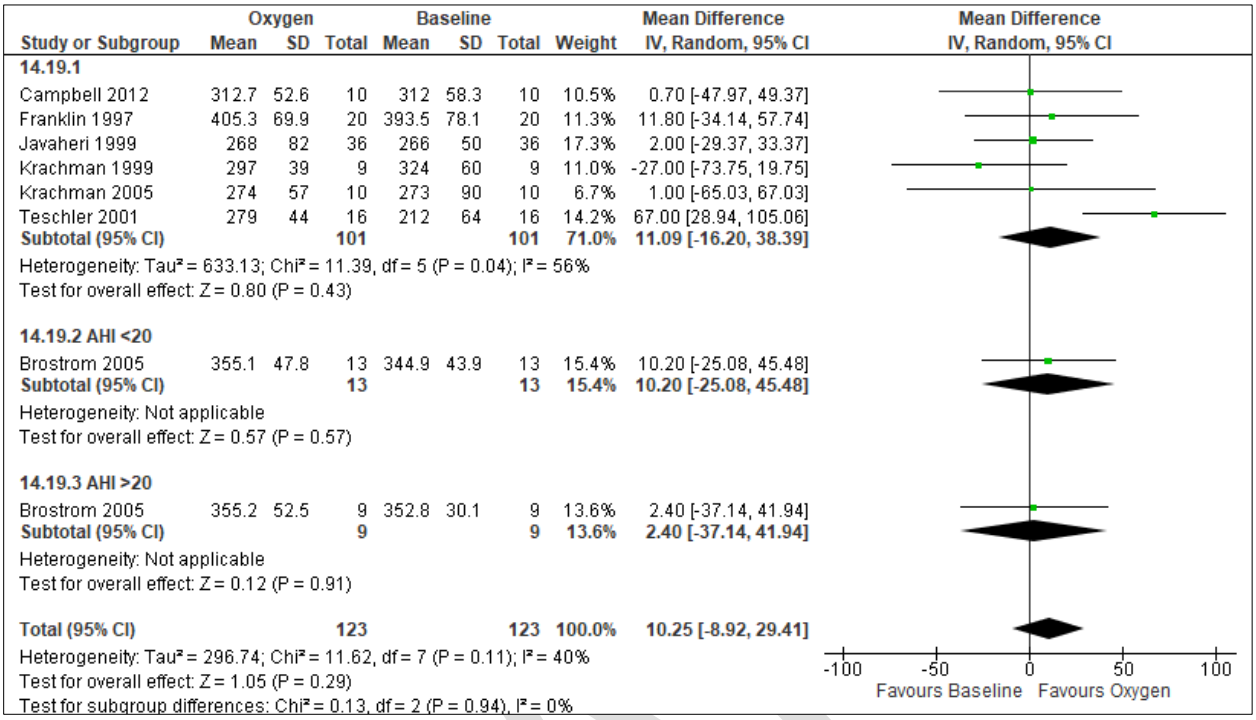


Figure S170. Oxygen vs. Baseline (Sleep architecture, PSG, Sleep efficiency) [CST=10%], Observational



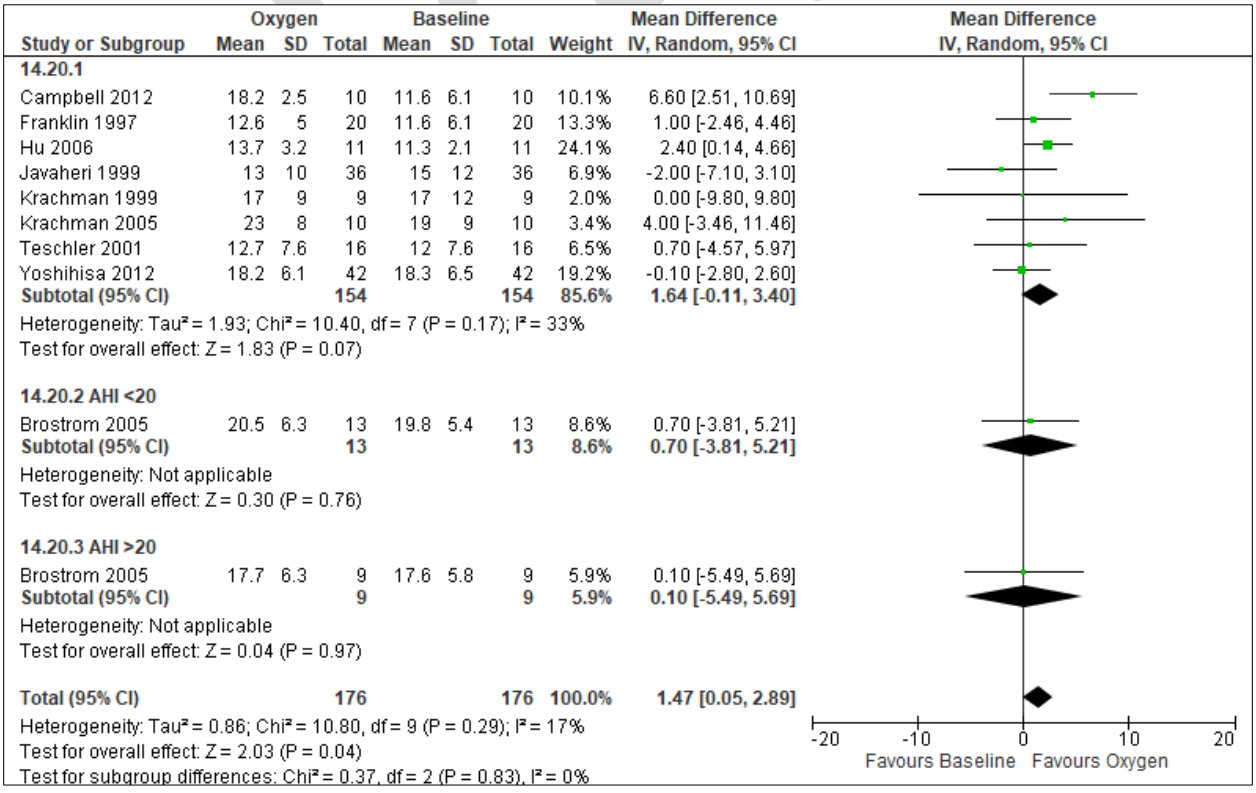
Arzt 2005: SEM converted to SD; Franklin 1997: median and range converted to mean and SD; Brostrom 2005: median and range converted to mean and SD; Javaheri 1999: data extracted from figure 3; Krachman 1999: SEM converted to SD; Teschler 2001: SEM converted to SD

Figure S171. Oxygen vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST= 15 min], Observational



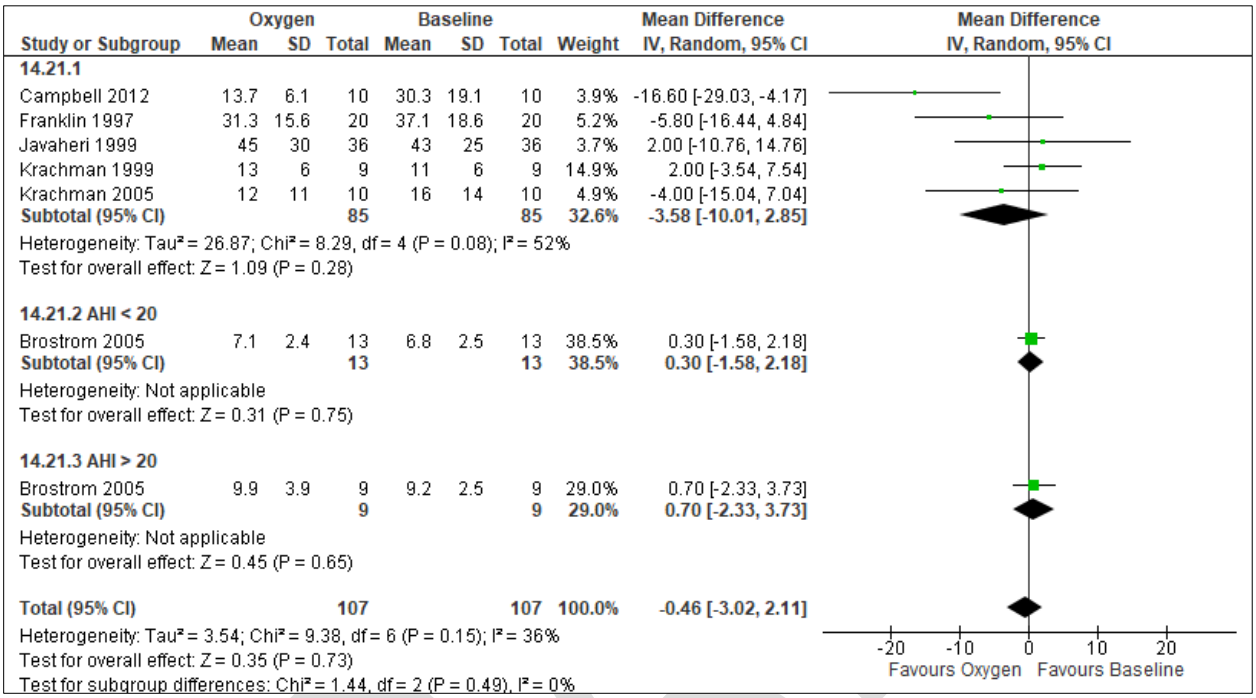
Teschler 2001: SEM converted to SD; Krachman 1999: SEM converted to SD; Campbell 2012: median and range converted to mean and SD Franklin 1997: median and range converted to mean and SD

Figure S172. Oxygen vs. Baseline (Sleep architecture, PSG, REM%) [CST=5% of TST], Observational



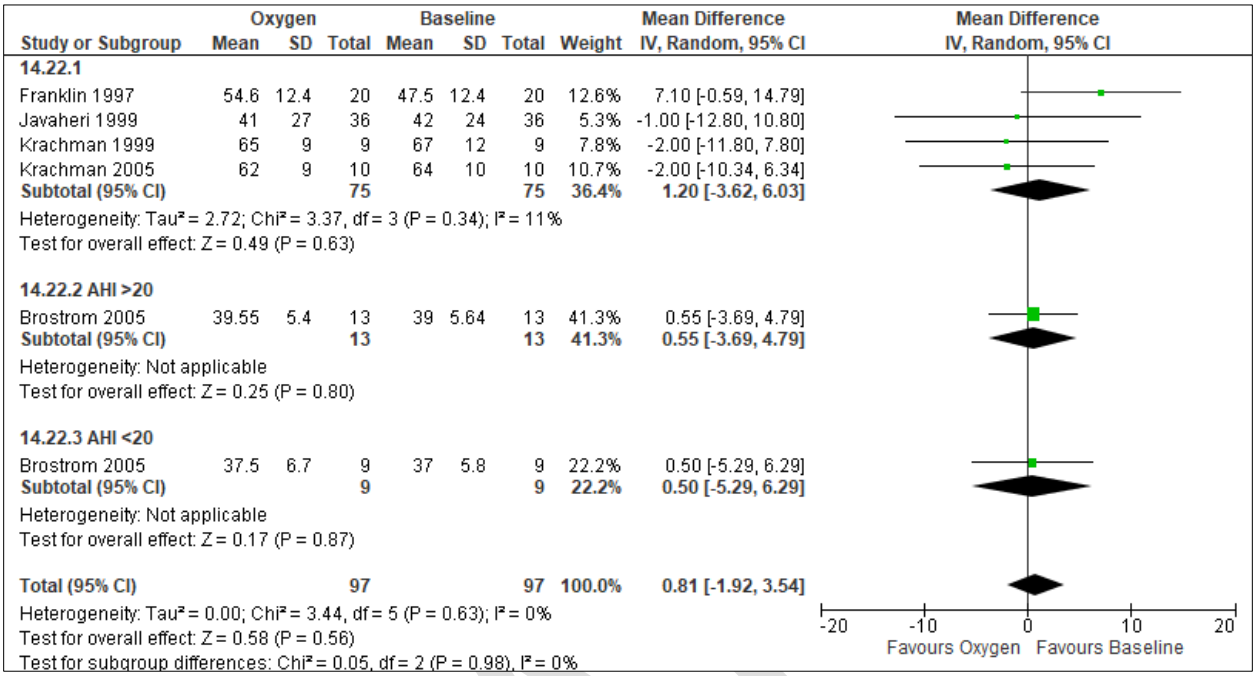
Krachman 1999: SEM converted to SD; Krachman 2005 oxygen data from night 2; Teschler 2001: SEM converted to SD; Franklin 1997: median and range converted to mean and SD

Figure S173. Oxygen vs. Baseline (Sleep architecture, PSG, Sleep stage N1%) [CST=5% of TST], Observational



Krachman 1999: SEM converted to SD; Franklin 1997: median and range converted to mean and SD

Figure S174. Oxygen vs. Baseline (Sleep architecture, PSG, Sleep stage N2%) [CST=5% of TST], Observational



Franklin 1997: median and range converted to mean and SD

Figure S175. Oxygen vs. Baseline (Sleep architecture, PSG, SWS%) [CST=5% of TST], Observational

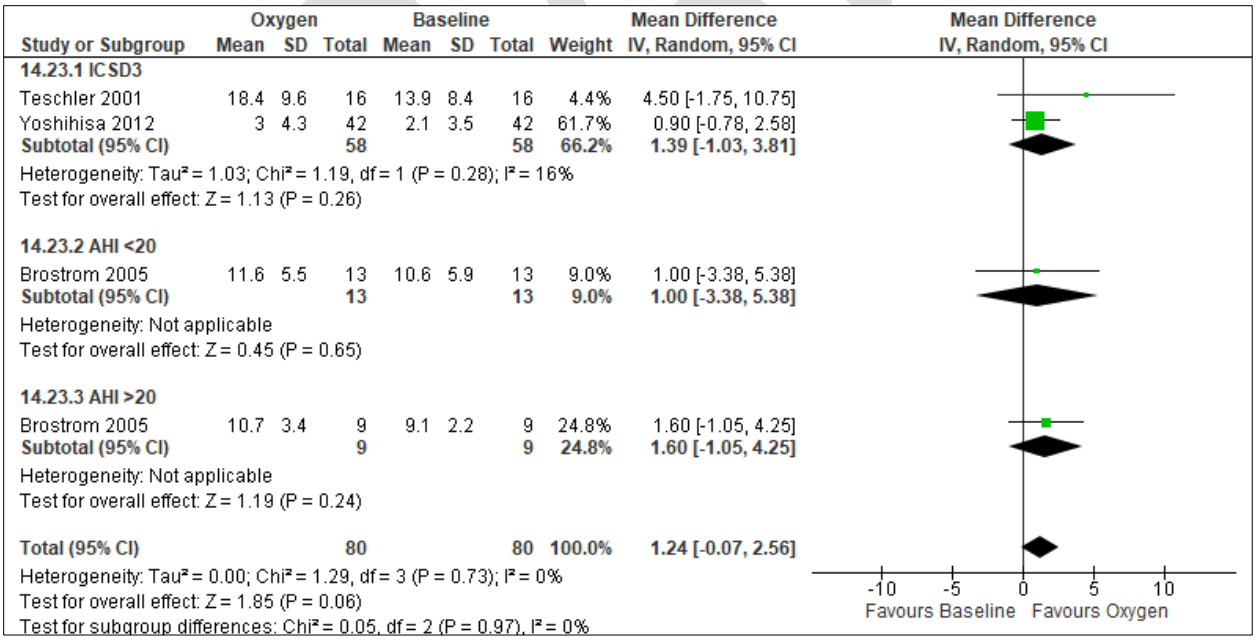
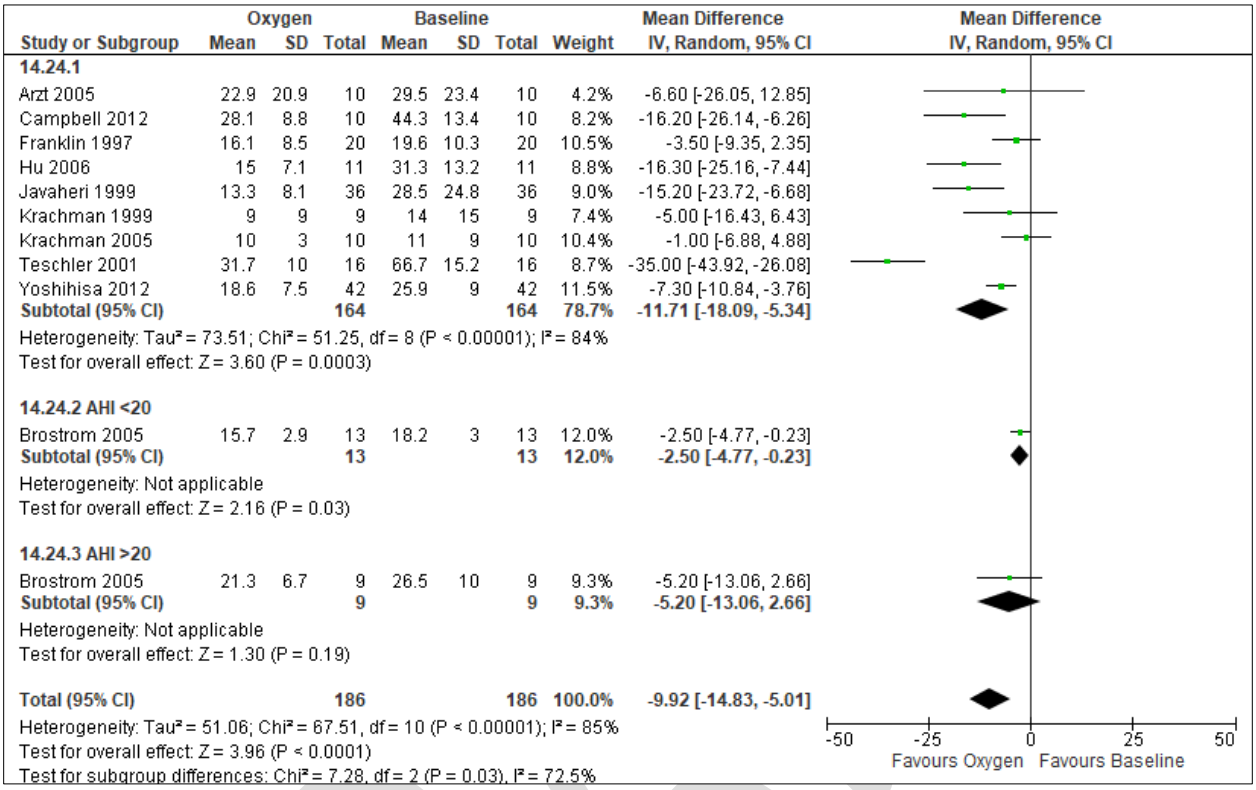


Figure S176. Oxygen vs. Baseline (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], Observational



Teschler 2001: SEM converted to SD; Franklin 1997: median and range converted to mean and SD

Acetazolamide

Summary of Findings (GRADE)

Table S6 Acetazolamide in adults with CSA

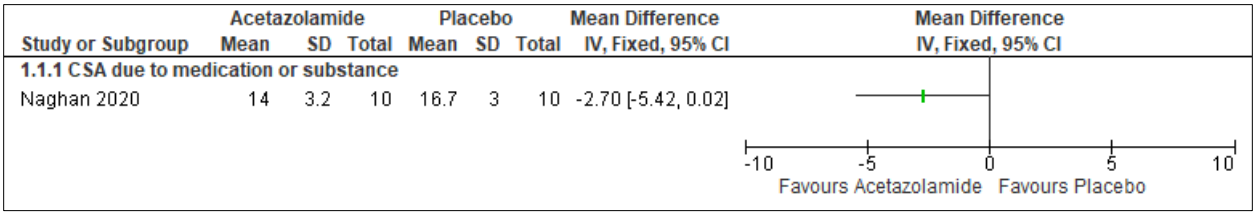
References: Ginter 2020, Javaheri 2006, Naghan 2020

Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **Acetazolamide vs. placebo**	**No of Participants (studies)**
Excessive sleepiness [ESS]	⨁⨁◯◯ **LOW**[a,b]	The mean difference in the acetazolamide group was **2.7 points lower (5.42 lower to 0.02 higher)** compared to placebo	20 (1 RCT)
Disease severity [AHI]	⨁⨁⨁◯ **MODERATE**[b]	The mean difference in the acetazolamide group was **16.57 events/hour lower (28.43 lower to 4.71 lower)** compared to placebo	76 (3 RCTs)
Disease severity [CAI]	⨁⨁◯◯ **LOW**[a,b]	The mean difference in the acetazolamide group was **7.65 events/hour lower (13.8 lower to 1.51 lower)** compared to placebo	56 (2 RCTs)
Cardiovascular disease [LVEF]	⨁⨁◯◯ **LOW**[a,b]	The mean difference in the acetazolamide group was **1 percent higher (-5.81 lower to 7.81 higher)** compared to placebo	24 (1 RCTs)

a. Imprecision due to the 95% CI includes possibility for important benefit and no effect
b. Imprecision due to small sample size (<200 participants)

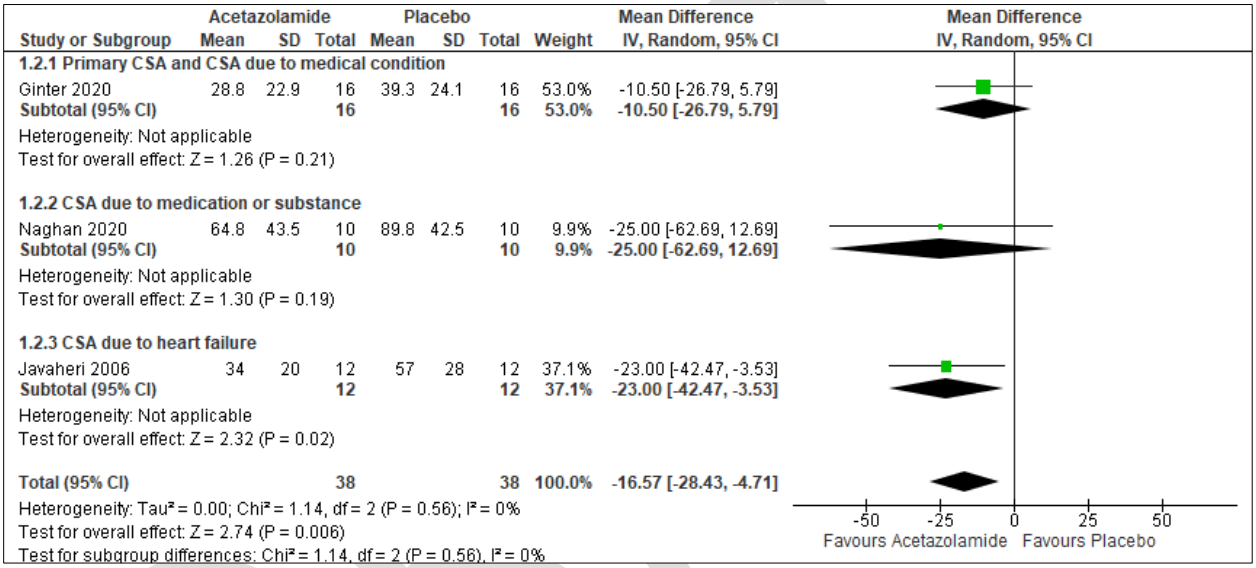
Critical Outcomes

Figure S177. Acetazolamide vs. Placebo (Excessive sleepiness, ESS) [CST= - 2 points], RCT



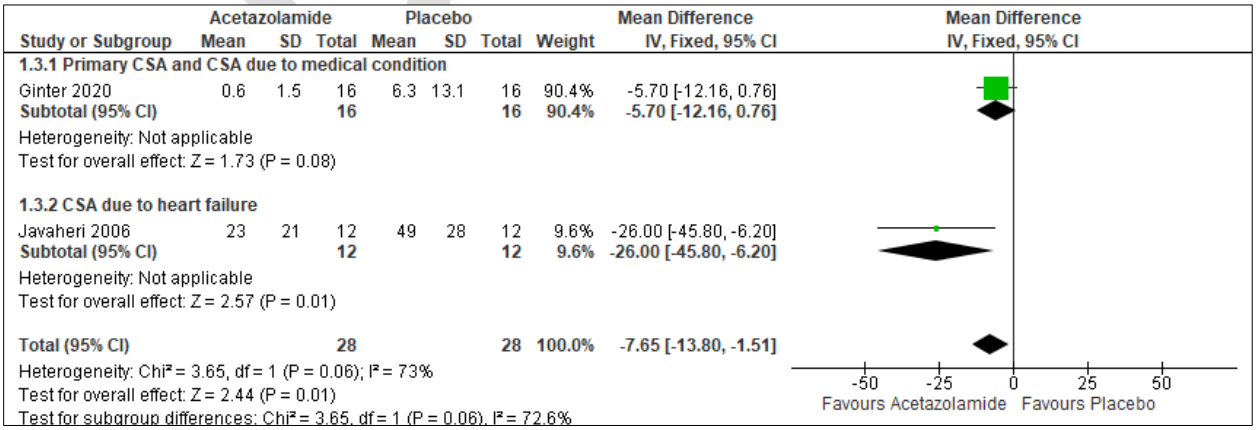
Naghan 2020: Acetazolamide 250 mg 1 h before sleep for 6 nights, the Epworth sleepiness scale results range from 0 to 24

Figure S178. Acetazolamide vs. Placebo (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCT



Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period Baseline AHI: Able-bodied= 21 ± 13.8, SCI=27.2 ± 32; Naghan 2020: Acetazolamide was prescribed one dose 250 mg and just 1 h before sleep for 6 nights; Javaheri 2006: Patients received three identical capsules of either placebo or one acetazolamide and two potassium chloride capsules. Potassium chloride (total, 30 mEq) was given to compensate for acetazolamide-induced urinary potassium loss. Acetazolamide was administered at 3.5 mg/kg and increased to 4 mg/kg AHI change from baseline was -56% reduction.

Figure S179. Acetazolamide vs. Placebo (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCT



Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period, Baseline CAI: Able-bodied= 2.8 ± 4.5, SCI= 7.3 ± 14.6; Javaheri 2006: Patients received three identical capsules of either placebo or one acetazolamide and two potassium chloride capsules. Potassium chloride (total, 30 mEq) was given to compensate for acetazolamide-induced urinary potassium loss. Acetazolamide was administered at 3.5 mg/kg and increased to 4 mg/kg; CAI change from baseline was -49% reduction.

Figure S180. Acetazolamide vs. Placebo (Cardiovascular disease, LVEF (%)) [CST= +5%], RCT

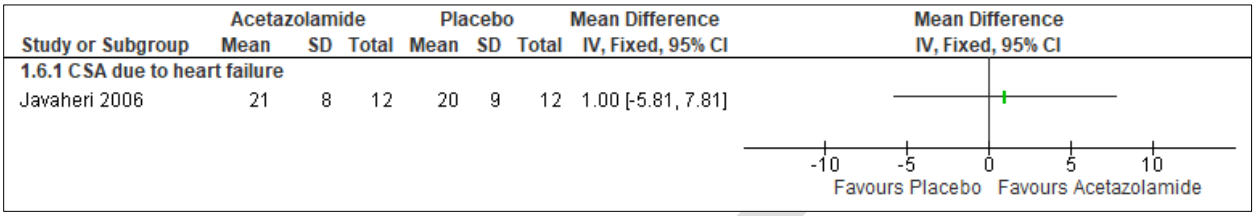
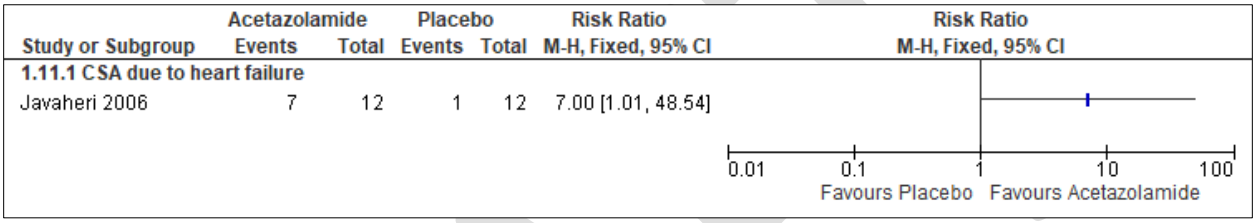
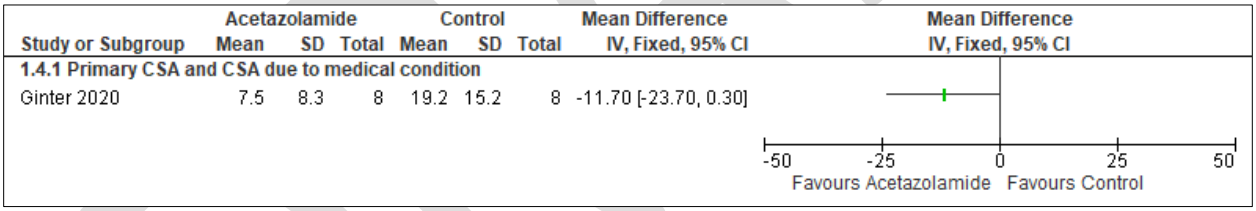


Figure S181. Acetazolamide vs. Placebo (Sleep Quality, Subjective Questionnaire) [No CST], RCT



Javaheri 2006: improvement of sleep quality on placebo vs acetazolamide, higher number represents an improvement, patients were asked specifically if they felt improved in comparing the first arm versus the second arm of the study

Figure S182. Acetazolamide vs. Placebo (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCT



Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period, Baseline ODI: Able-bodied= 8.9 ± 13, SCI= 19.9 ± 34.1

Figure S183. Acetazolamide vs. Placebo (Disease Severity, oxygen saturation < 90%) [CST= ≥ 50% change from baseline], RCT

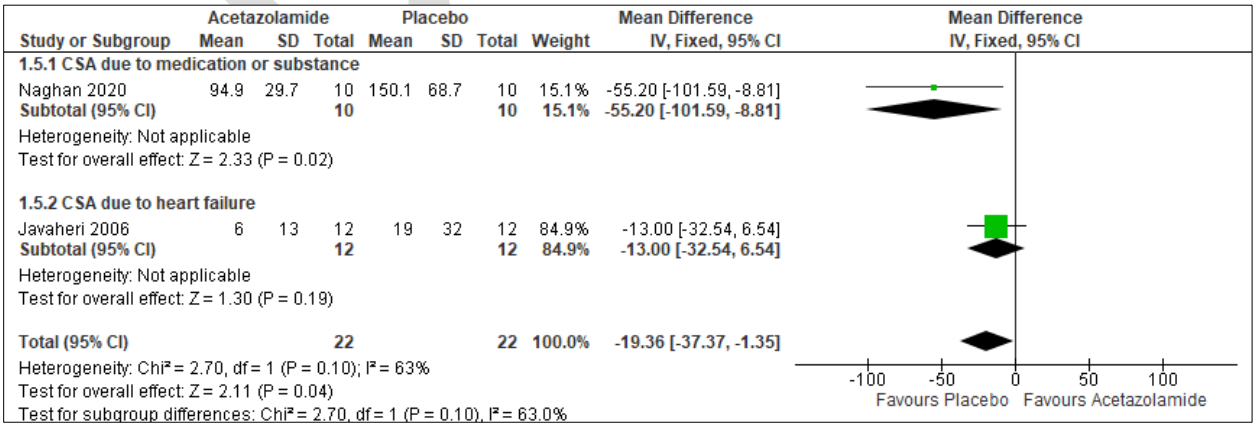


Figure S184. Acetazolamide vs. Placebo (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], RCT

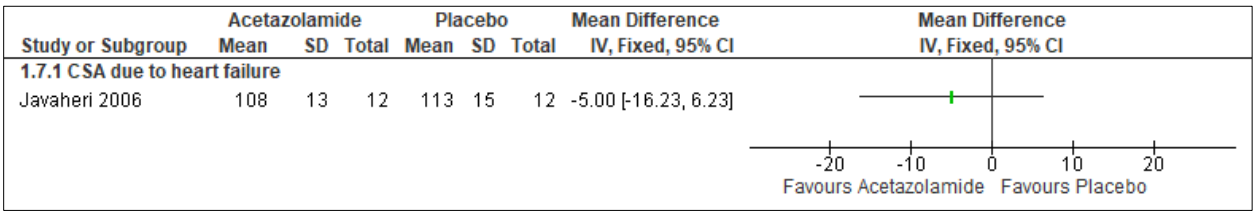


Figure S185. Acetazolamide vs. Placebo (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCT

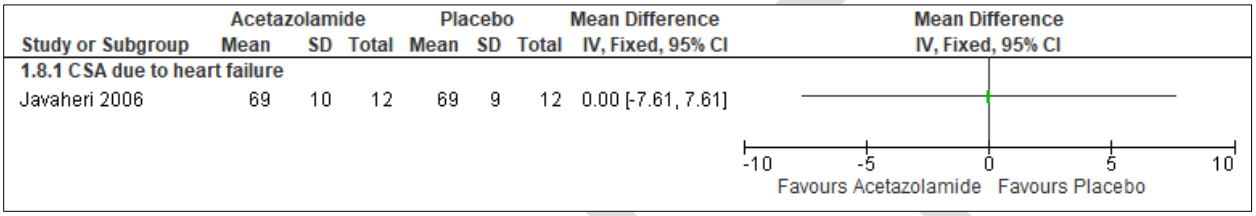


Figure S186. Acetazolamide vs. Placebo (Cardiovascular disease, HR (beats/min)) [No CST], RCT

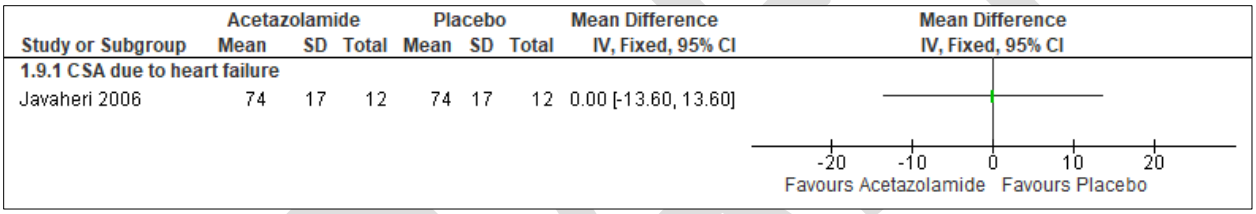
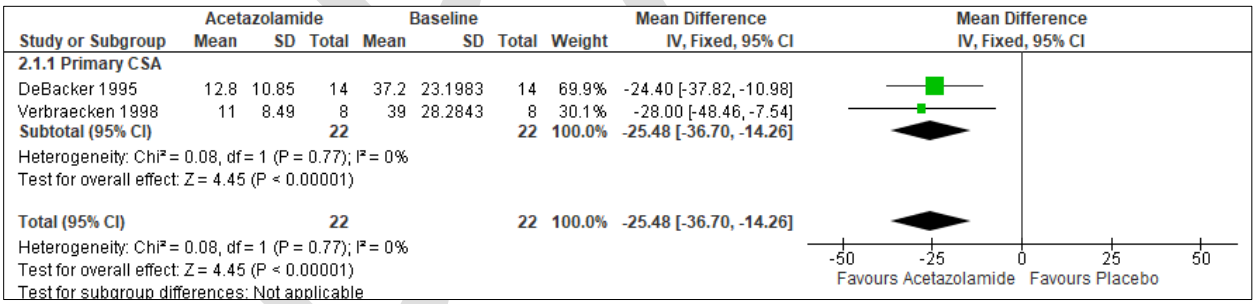
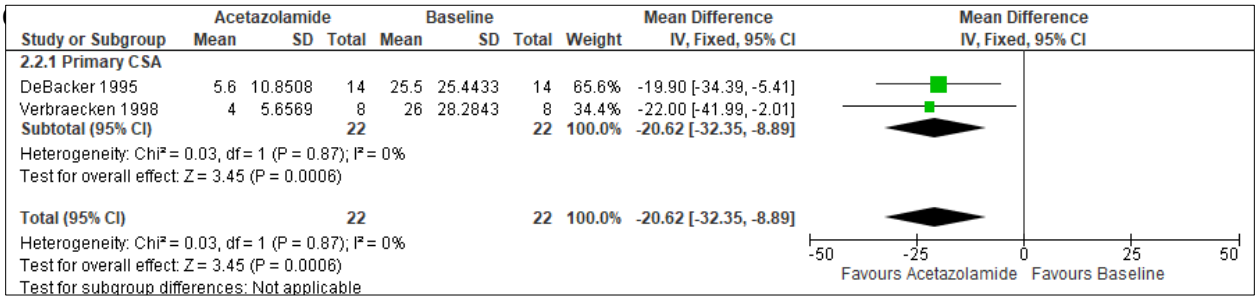


Figure S187. Acetazolamide vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% change from baseline], Observational



DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=65.6%; Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=71.8%

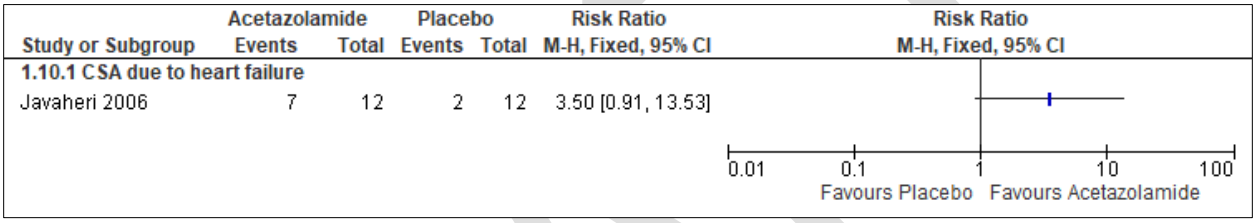
Figure S188. Acetazolamide vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% change from baseline],



DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=78%; Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=84.6%

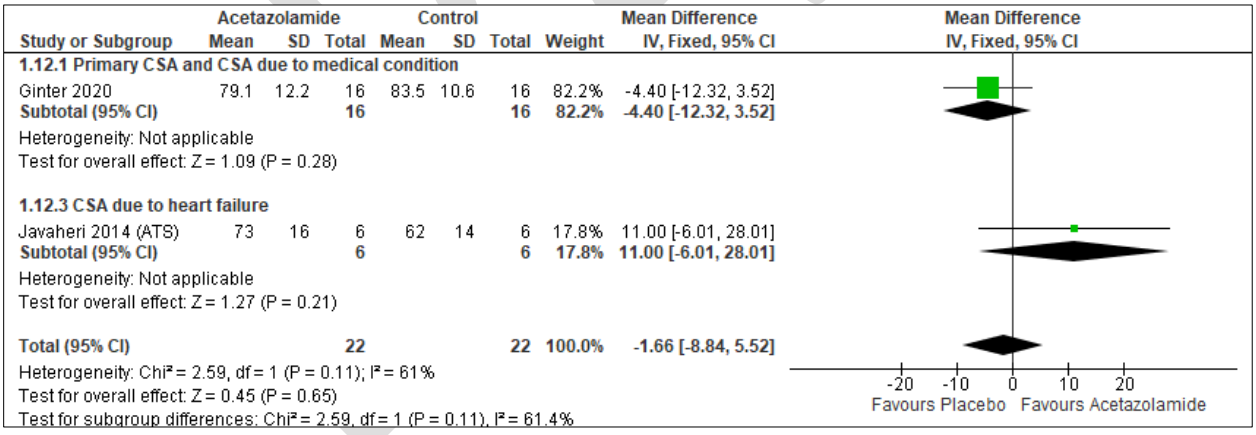
Important Outcomes

Figure S189. Acetazolamide vs. Placebo (Fatigue, Subjective Questionnaire) [No CST], RCT



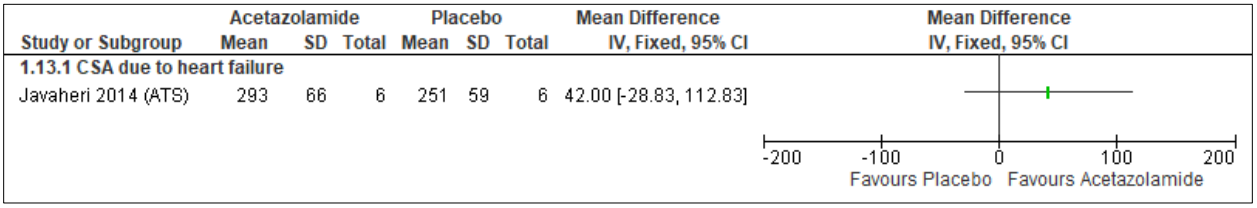
Javaheri 2006: improvement of daytime fatigue on placebo vs acetazolamide, higher number represents an improvement, patients were asked specifically if they felt improved in comparing the first arm versus the second arm of the study

Figure S190. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep efficiency) [CST=10%], RCT



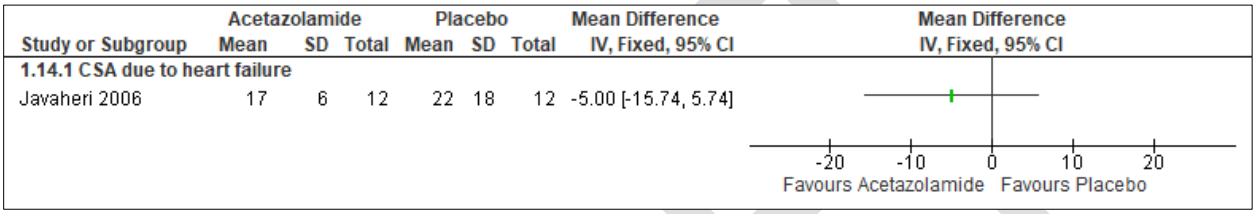
Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period; Javaheri 2014: patients received three identical capsules that were received orally 1 hour before bedtime for six nights; the three capsules consisted of three placebos or one acetazolamide (3.5 mg/kg) and two potassium chloride capsules (total 30 mEq) to compensate for acetazolamide-induced urinary potassium loss. Crossover studies were performed after a 2-week washout period.

Figure S191. Acetazolamide vs. Placebo (Sleep architecture, PSG, Total sleep time) [CST=15 min], RCT



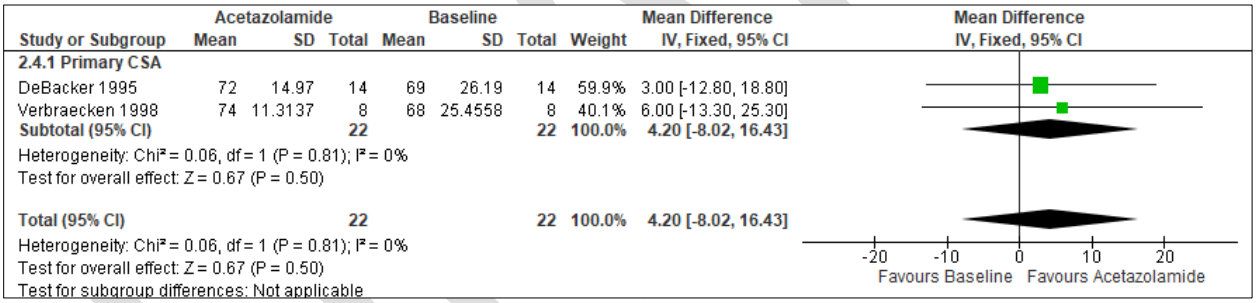
Javaheri 2014: patients received three identical capsules that were received orally 1 hour before bedtime for six nights; the three capsules consisted of three placebos or one acetazolamide (3.5 mg/kg) and two potassium chloride capsules (total 30 mEq) to compensate for acetazolamide-induced urinary potassium loss. Crossover studies were performed after a 2-week washout period.

Figure S192. Acetazolamide vs. Placebo (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], RCT



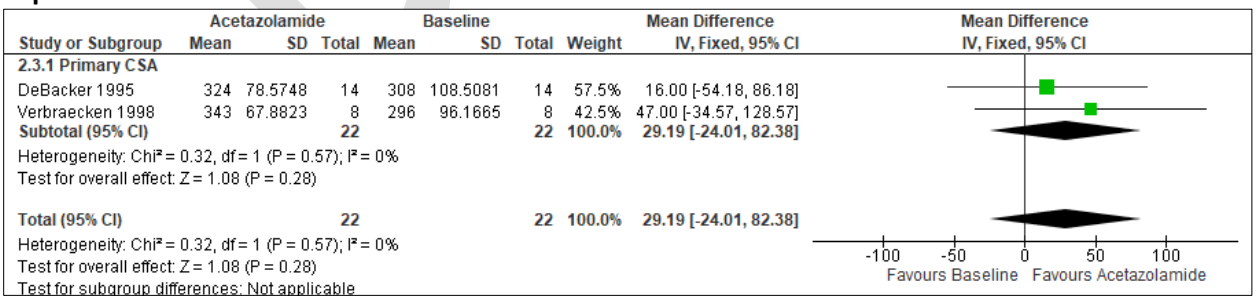
Baseline arousal index for acetazolamide group was 30(25).

Figure S193. Acetazolamide vs. Baseline (Sleep architecture, PSG, Sleep efficiency) [CST=10%], Pre- vs post-treatment non-randomized studies



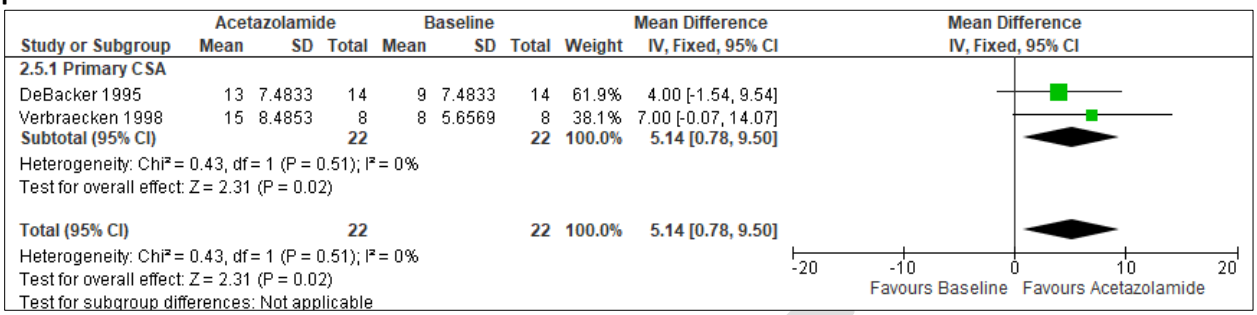
DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD
Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD

Figure S194. Acetazolamide vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST=15 min], Pre- vs post-treatment non-randomized studies



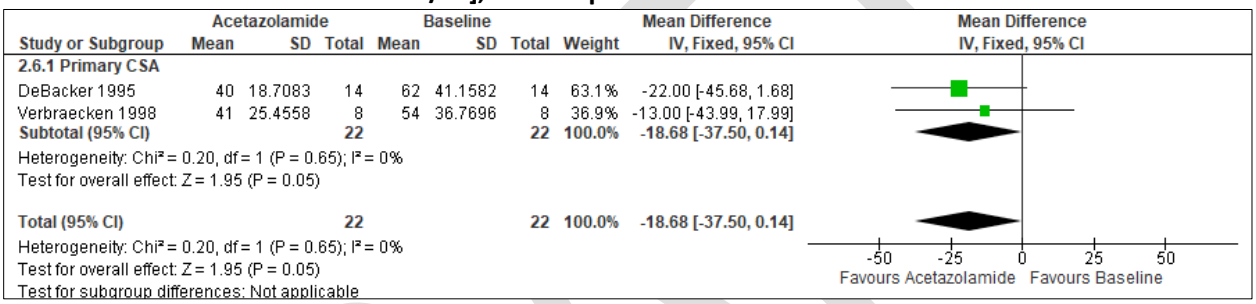
* DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD
Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD

Figure S195. Acetazolamide vs. Baseline (Sleep architecture, PSG, REM (%)) [CST=5% of TST], Pre- vs post-treatment non-randomized studies



DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD
Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD

Figure S196. Acetazolamide vs. Baseline (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], Pre- vs. post-treatment non-randomized studies



DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD
Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD
Approximately a 43% reduction from baseline

TPNS

Summary of findings (GRADE)

Table S7 TPNS for adults with CSA

References: Costanzo 2016, Potratz 2021

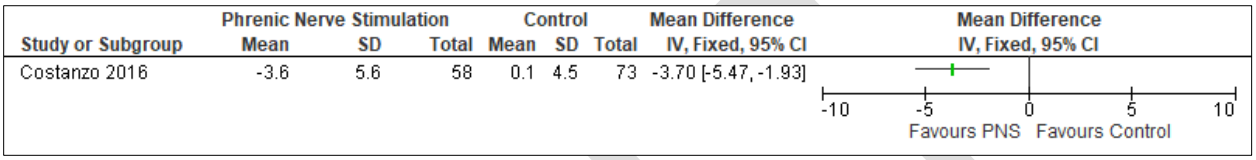
Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **TPNS vs. baseline or control**	**No of Participants (studies)**
Excessive sleepiness [ESS]	⨁⨁◯◯ **LOW**[a,b]	The mean difference in the TPNS group was **3.7 points lower (5.47 lower to 1.93 lower)** compared to control	131 (1 RCT)
Disease severity [AHI]	⨁⨁◯◯ **LOW**[a,b]	The mean difference in the TPNS group was **25 events/hour lower (31.26 lower to 18.74 lower)** compared to control	131 (1 RCT)
Disease severity [CAI]	⨁⨁⨁◯ **MODERATE**[b]	The mean difference in the TPNS group was **17.3 events/hour lower (21.94 lower to 12.66 lower)** compared to control	131 (1 RCT)
Disease severity [ODI]	⨁⨁◯◯ **LOW**[a,b]	The mean difference in the TPNS group was **16.2 events/hour lower (23.49 lower to 8.91 lower)** compared to control	131 (1 RCT)
Cardiovascular disease [6MWD]	⨁◯◯◯ **VERY LOW**[b,c,d]	The mean difference in the TPNS group was **40.5 meters higher (53.79 lower to 134.78 higher)** compared to baseline	24 (1 non-RCT)

Cardiovascular disease [LVEF]	⨁◯◯◯ **VERY LOW**[b,c,d]	The mean difference in the TPNS group was **0.5% lower (8.46 lower to 7.46 higher)** compared to baseline	24 (1 non-RCT)
Mortality [reported deaths]	⨁⨁◯◯ **LOW**[b,d]	The risk ratio in the TPNS group was **1.07 (0.15 to 7.39)** with an absolute risk of **2 more per 1,000 (22 fewer to 164 more)** compared to control	151 (1 RCT)

a. Imprecision due to the 95% CI includes possibility for important benefit and no effect
b. Imprecision due to small sample size (<200 participants)
c. Downgraded quality of evidence due to data analyzed using pre- and posttreatment values
d. Imprecision due to the 95% CI includes possibility for important benefit and harm

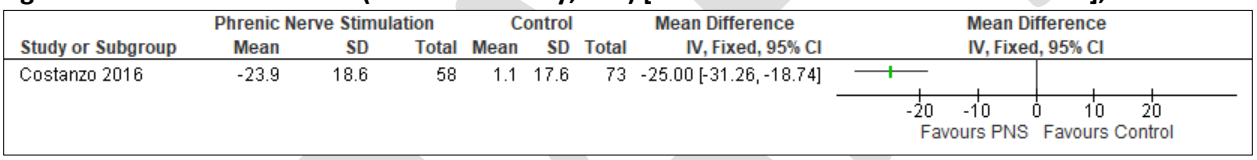
Critical Outcomes

Figure S197. TPNS vs. Control (Sleepiness during the day, ESS) [CST= -2 points], RCT



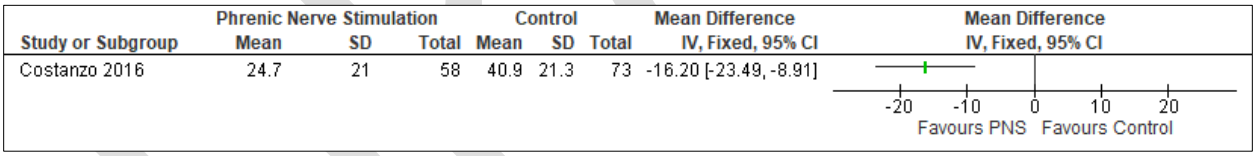
Costanzo 2016: change scores

Figure S198. TPNS vs. Control (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCT



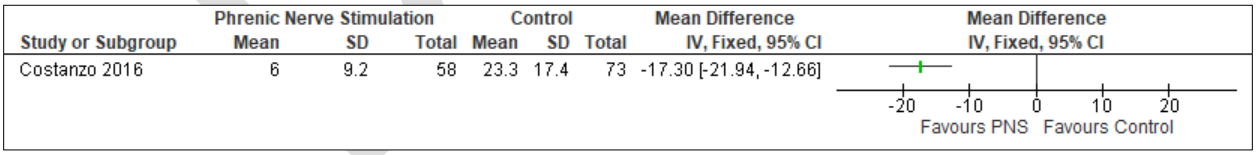
Costanzo 2016: change scores

Figure S199. TPNS vs. Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT



* Costanzo 2016: change from baseline

Figure S200. TPNS vs. Control (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCT



* Costanzo 2016: change from baseline

Figure S201. TPNS vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= +5%], single-arm pre- and post-treatment

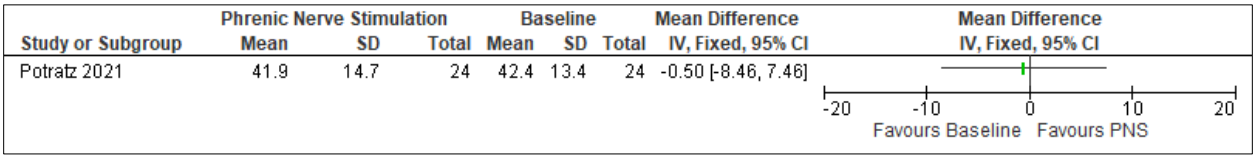


Figure S202. TPNS vs. Baseline (Cardiovascular disease, 6MWD) [CST=+ 32 meters], single-arm pre- and post-treatment

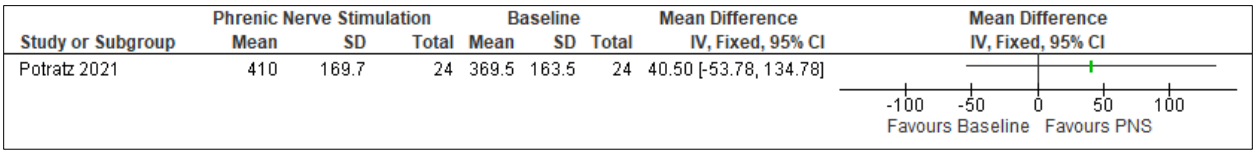


Figure S203. TPNS vs. Control (Mortality, Number of deaths) [CST= risk ratio of 0.8], RCT

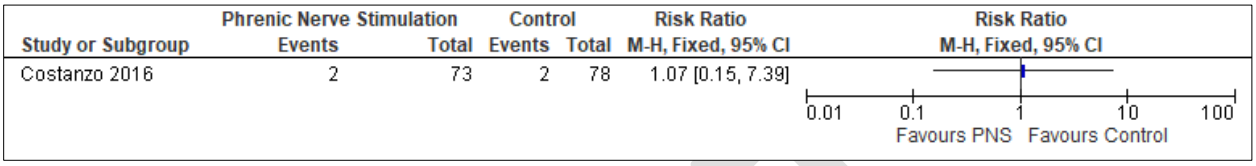
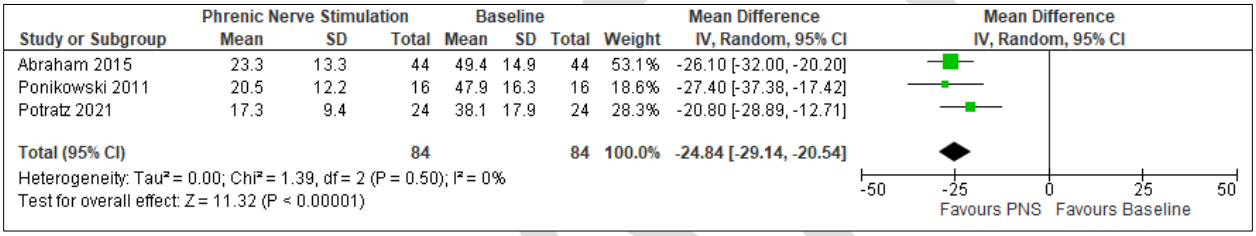
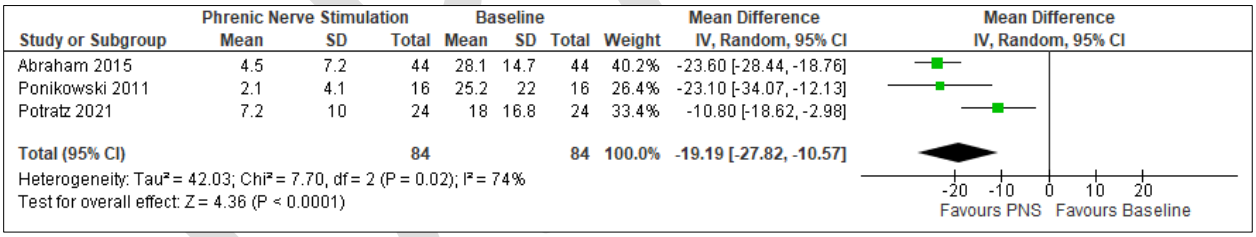


Figure S204. TPNS vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], single-arm pre- and post-treatment, observational studies



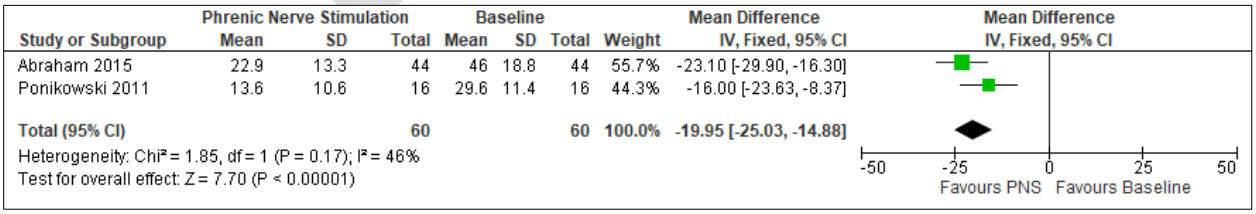
Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S205. TPNS vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], single-arm pre- and post-treatment, observational studies



Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S206. TPNS vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], single-arm pre- and post-treatment, observational studies



Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S207. TPNS vs. Baseline (Disease Severity, Percentage of sleep with oxygen saturation <90%) [CST= ≥ 50% reduction from baseline], single-arm pre- and post-treatment, observational studies

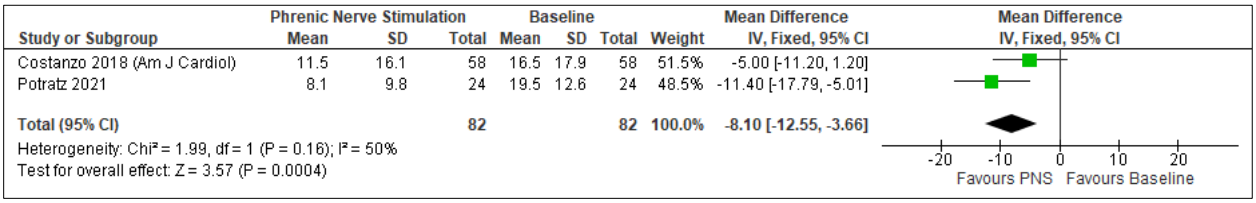
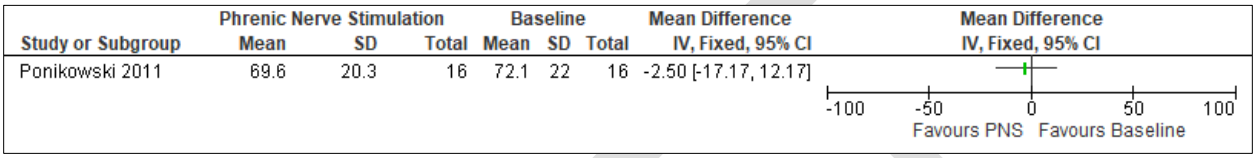
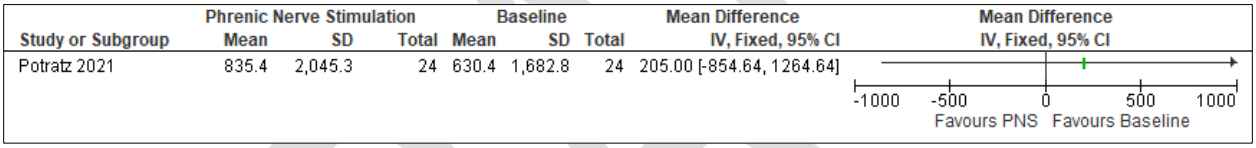


Figure S208. TPNS vs. Baseline (Cardiovascular disease, HR (beats/min)) [No CST], single-arm pre- and post-treatment



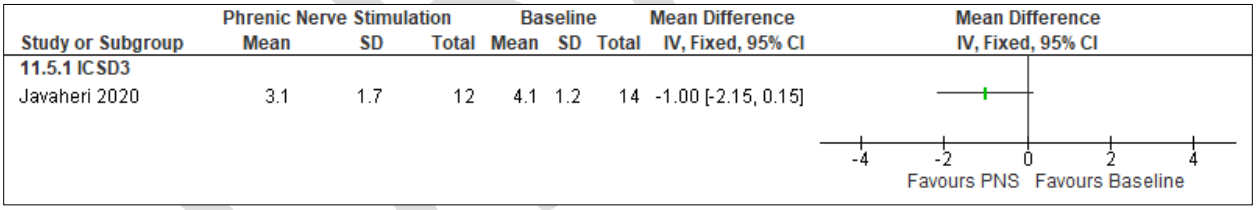
*Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S209. TPNS vs. Baseline (Cardiovascular disease, BNP, pg/mL) [CST= 50% reduction], single-arm pre- and post-treatment



BNP pg/ml

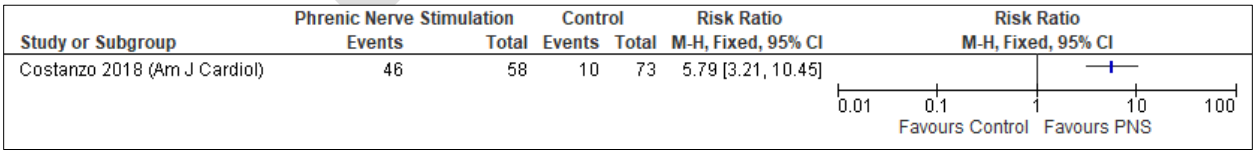
Figure S210. TPNS vs. Baseline (Fatigue, FSS) [CST= - 0.5 point], observational studies



Javaheri 2020, 6-month data, median and inter-quartile range converted to SD

Important Outcomes

Figure S211. TPNS vs. Control (Quality of Life, Patient Global Assessment) [No CST], RCT



6-month data for percentage of patient showing mild or marked/moderate improvement, data from figure 6

Figure S212. TPNS vs. Control (Sleep architecture, PSG, REM%) [CST=+5% of TST], RCT

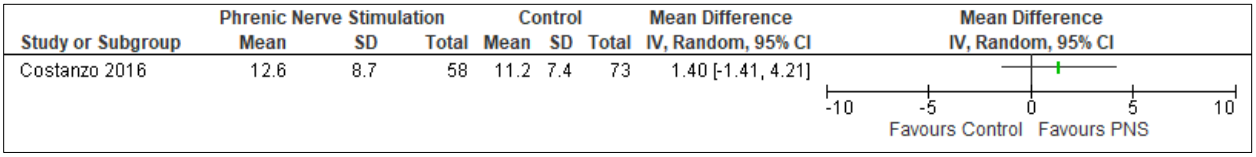
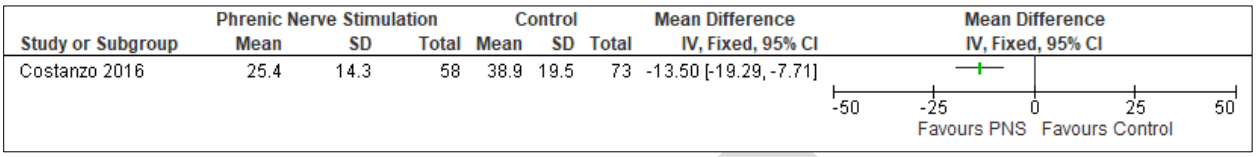
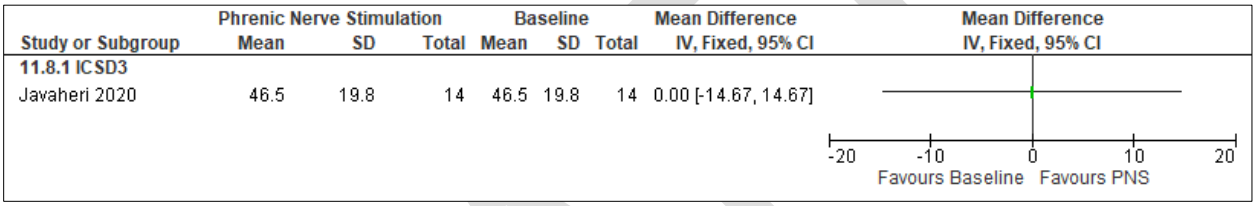


Figure S213. TPNS vs. Control (Sleep architecture, PSG, Arousal Index) [CST=25% reduction from baseline or reduction to ≤12 events/hr], RCT



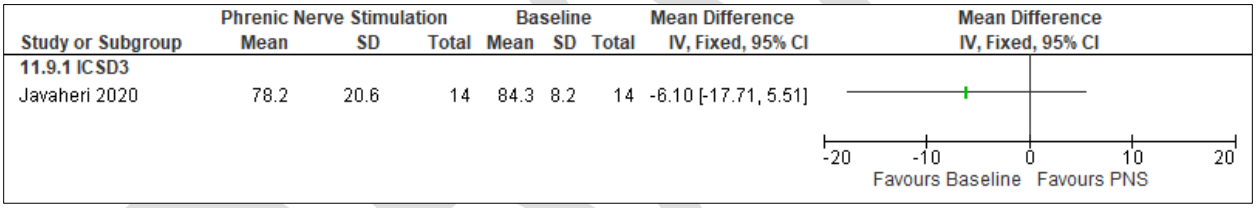
Baseline arousal index for TPNS was 45.6 (18.9)

Figure S214. TPNS vs. Baseline (Quality of Life, SF-12) [CST= + 4 points], Observational study



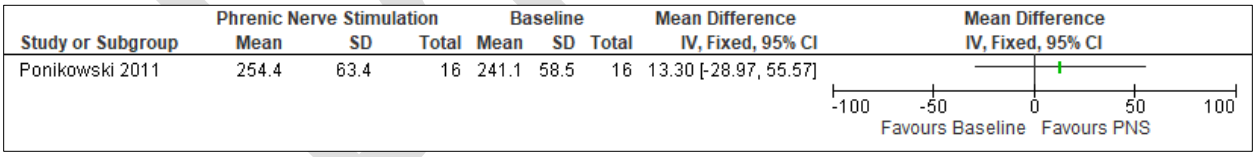
Javaheri 2020, 6-month data, median and inter-quartile range converted to SD

Figure S215. TPNS vs. Baseline (Quality of Life, EQ-5D) [No CST], Observational study



Javaheri 2020, 6-month data, median and inter-quartile range converted to SD

Figure S216. TPNS vs. Baseline (Total Sleep Time, PSG) [CST=+15 min], single-arm pre- and post-treatment, observational studies



Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S217. TPNS vs. Baseline (Sleep architecture, PSG, Sleep Efficiency) [CST=+15 min], single-arm pre- and post-treatment, observational studies

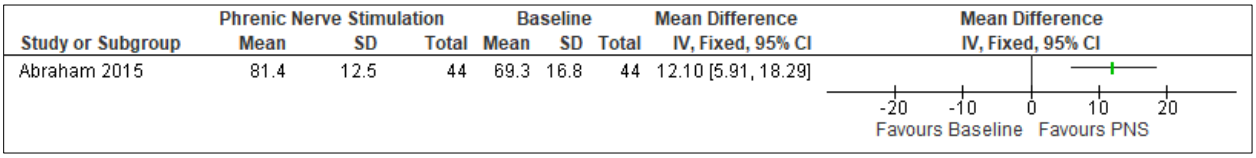
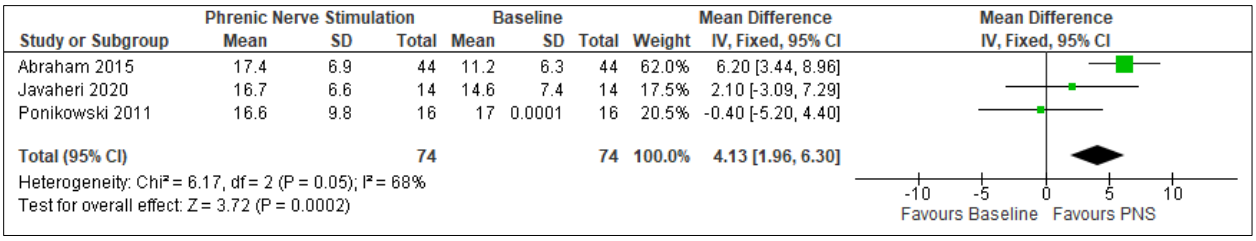
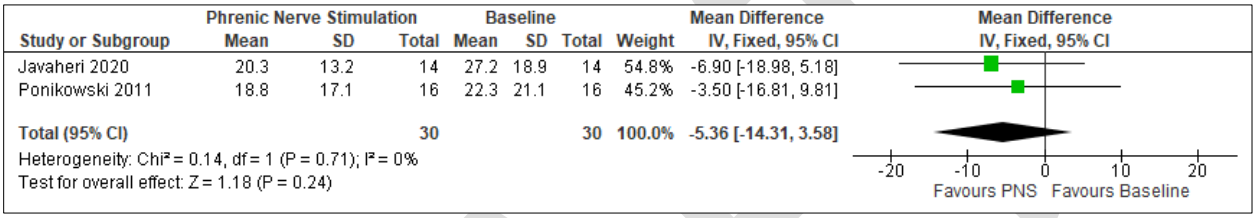


Figure S218. TPNS vs. Baseline (Sleep architecture, PSG, REM%) [CST=+5% of TST], single-arm pre- and post-treatment, observational studies



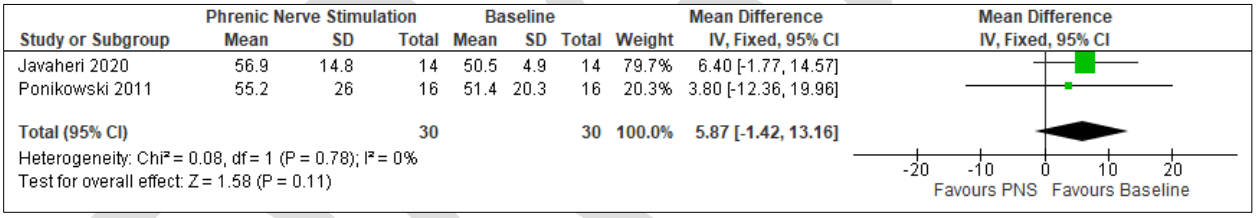
Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S219. TPNS vs. Baseline (Sleep architecture, PSG, Sleep stage N1%) [CST=-5% of TST], single-arm pre- and post-treatment, observational studies



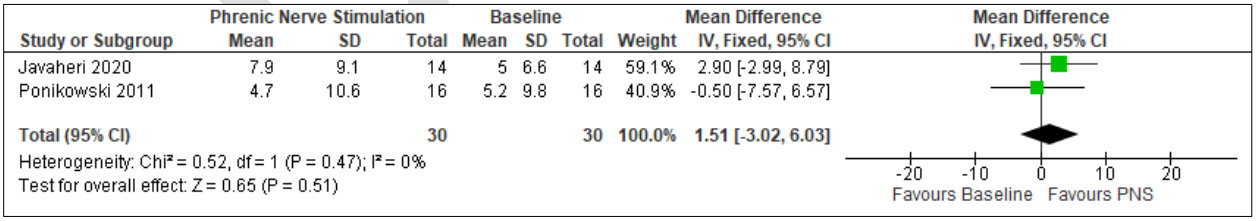
Javaheri 2020, 6-month data, median and inter-quartile range converted to SD; Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S220. TPNS vs. Baseline (Sleep architecture, PSG, Sleep stage N2%) [CST=-5% of TST], single-arm pre- and post-treatment, observational studies



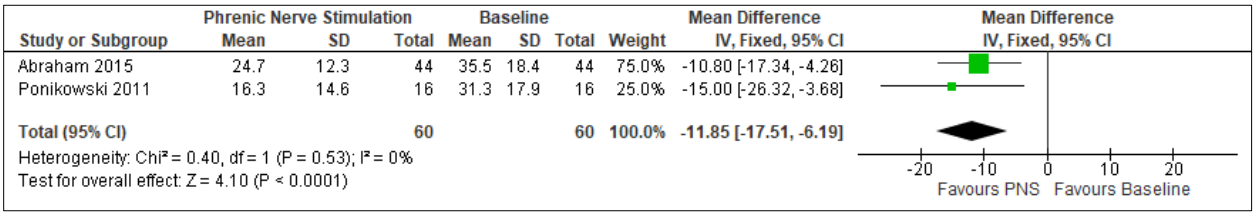
Javaheri 2020, 6-month data, median and inter-quartile range converted to SD; Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S221. TPNS vs. Baseline (Sleep architecture, PSG, Sleep stage N3%) [CST=+5% of TST], single-arm pre- and post-treatment, observational studies



Javaheri 2020, 6-month data, median and inter-quartile range converted to SD; Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S222. TPNS vs. Baseline (Sleep architecture, PSG, Arousal Index) [CST=25% reduction from baseline or reduction to ≤12 events/hr], single-arm pre- and post-treatment, observational studies



Javaheri 2020, 6-month data, median and inter-quartile range converted to SD, reduction from baseline=50.8%; Ponikowski 2011: median and inter-quartile range converted to mean and SD

PICO 2: Adults with CSA due to high altitude

Low-flow oxygen

Summary of findings table (GRADE)

Table S8. Low-flow oxygen for adults with CSA due to high altitude

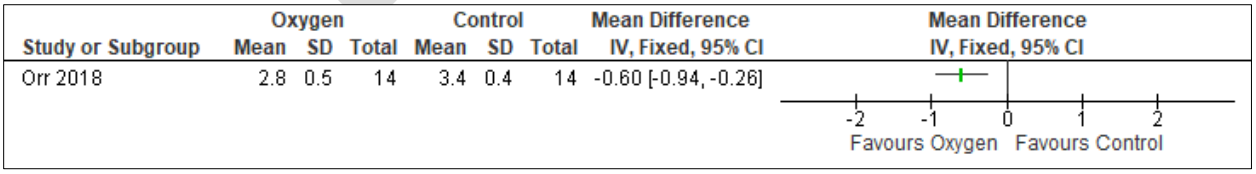
References: Heinrich 2019, Orr 2018

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Low-flow oxygen vs. control	No of Participants (studies)
Excessive sleepiness [SSS]	⨁◯◯◯ **VERY LOW**[a,b]	The mean difference in the low-flow oxygen group was **0.6 points lower (0.94 lower to 0.26 lower)** compared to control	14 (1 RCT)
Disease severity [ODI]	⨁⨁◯◯ **LOW**[b]	The mean difference in the low-flow oxygen group was **14.7 events/hour lower (23.72 lower to 5.68 lower)** compared to control	14 (1 RCT)
Daytime functioning* [AMS]	⨁⨁◯◯ **LOW**[b]	The mean difference in the low-flow oxygen group was **1 point lower (2.27 lower to 0.27 higher)** compared to control	14 (1 RCT)
Quality of life* [POMS-A confusion]	⨁◯◯◯ **VERY LOW**[a,b]	The mean difference in the low-flow oxygen group was **1.1 points lower (1.91 lower to 0.29 lower)** compared to control	17 (1 RCT)
Quality of life* [POMS-A fatigue]	⨁◯◯◯ **VERY LOW**[a,b]	The mean difference in the low-flow oxygen group was **3.2 lower (6.28 lower to 0.12 lower)** compared to control	17 (1 RCT)

a. Risk of bias due to lack of blinding of patients
b. Imprecision due to small sample size (<200 participants)
* No CST

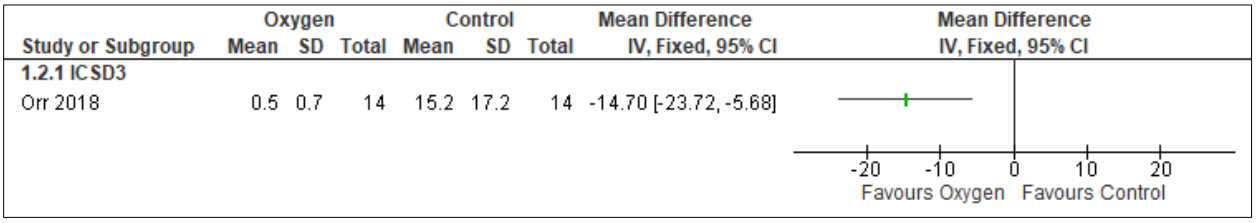
Critical Outcomes

Figure S223. Oxygen vs. Control (Excessive sleepiness, SSS) [CST=-1 points], RCT



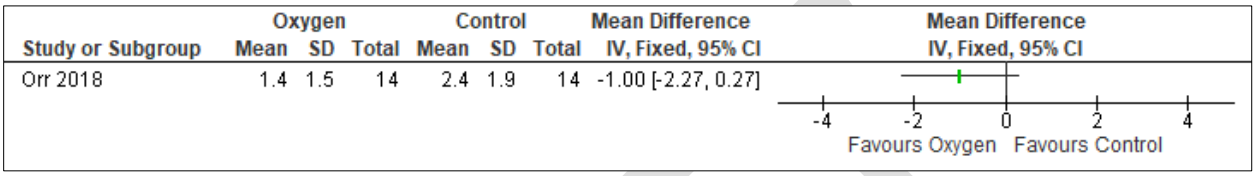
Orr 2018: SEM converted to SD, single night per arm

Figure S224. Oxygen vs. Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT



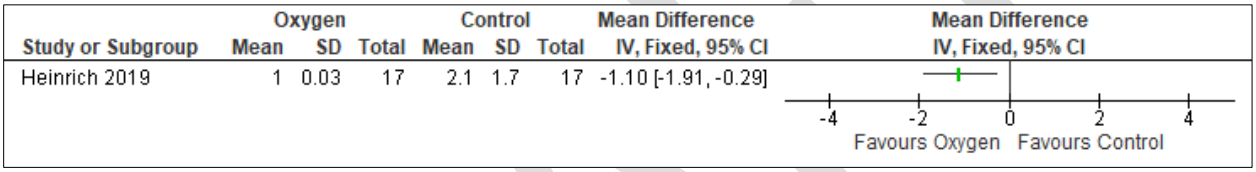
Orr 2018: SEM converted to SD, single night per arm

Figure S225. Oxygen vs. Control (Daytime Functioning, AMS) [No CST], RCT



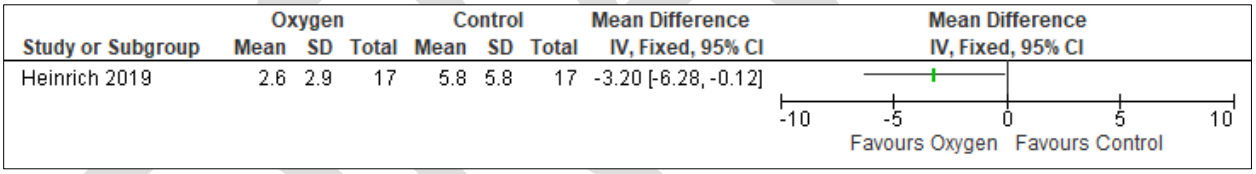
Orr 2018: SEM converted to SD, single night per arm

Figure S226. Oxygen vs. Control (Quality of Life, POMS-A (Confusion Score) [No CST], RCT



Heinrich 2019: data extracted from graph; CI interval converted to SD

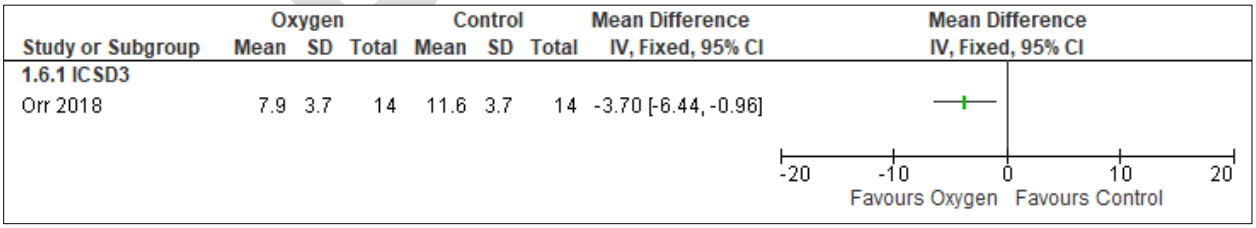
Figure S227. Oxygen vs. Control (Quality of Life, POMS-A (Fatigue Score) [No CST], RCT



Heinrich 2019: data extracted from graph; CI interval converted to SD

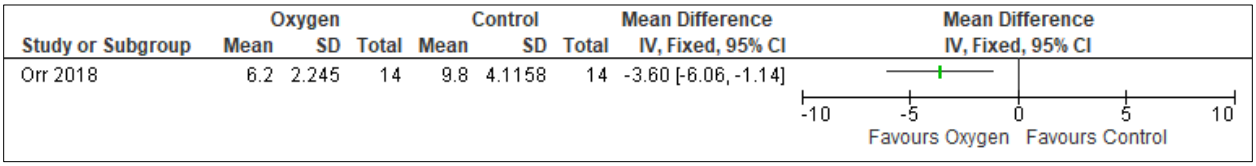
Important Outcomes

Figure S228. Oxygen vs. Control (Sleep architecture, PSG, Arousal Index) [CST=25% reduction from baseline or reduction to ≤12 events/hr], RCT



Orr 2018: SEM converted to SD, single night per arm

Figure S229. Oxygen vs. Control (Sleep architecture, PSG, Sleep stage N1%,) [CST= +5% of TST], RCT



Orr 2018: SEM converted to SD, single night per arm

Acetazolamide

Summary of Findings (GRADE)

Table S9 Acetazolamide in adults with CSA due to high altitude

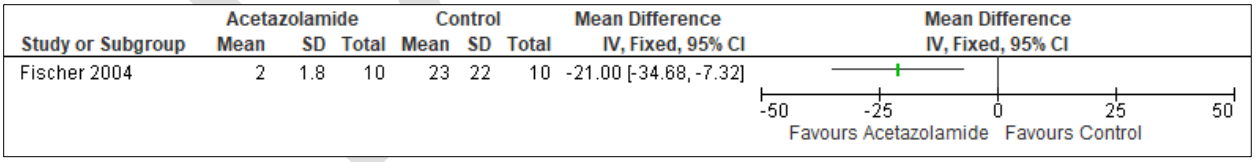
References: Hackett 1987, Fisher 2004

Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **Acetazolamide vs. control**	**No of Participants (studies)**
Disease severity [AHI]	⨁⨁◯◯ **LOW**[a]	The mean difference in the acetazolamide group was **21 events/hour lower (34.68 lower to 7.32 lower)** compared to control	20 (1 RCT)
Disease severity [Desaturation index]	⨁⨁◯◯ **LOW**[a]	The mean difference in the acetazolamide group was **30.3 events/hour lower (45.19 lower to 15.41 lower)** compared to control	20 (1 RCT)
Disease severity [% time with periodic breathing]	⨁◯◯◯ **VERY LOW**[a,b,c]	The mean difference in the acetazolamide group was **23.7 percent lower (49.55 lower to 2.15 higher)** compared to control	4 (1 RCT)
Disease severity [oxygen saturation <70%]	⨁◯◯◯ **VERY LOW**[a,b]	The mean difference in the acetazolamide group was **11.82 percent lower (17.73 lower to 5.91 lower)** compared to control	4 (1 RCT)

a. Imprecision due to small sample size (<200 participants)
b. Indirectness in the measurement of the outcome
c. Imprecision due to the 95% CI includes possibility for important benefit and no effect

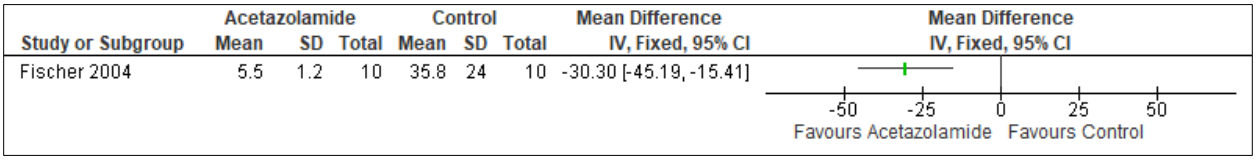
Critical Outcomes

Figure S230. Acetazolamide vs. Control (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCT



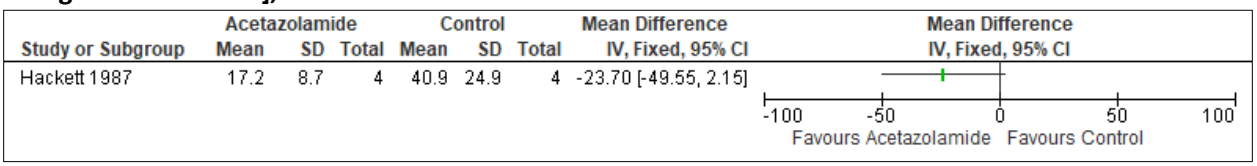
Fischer 2004: median and range converted to mean and SD, Night 2 data used.

Figure S231. Acetazolamide vs. Control (Disease Severity, Desaturation Index) [CST= ≥ 50% change from baseline], RCT



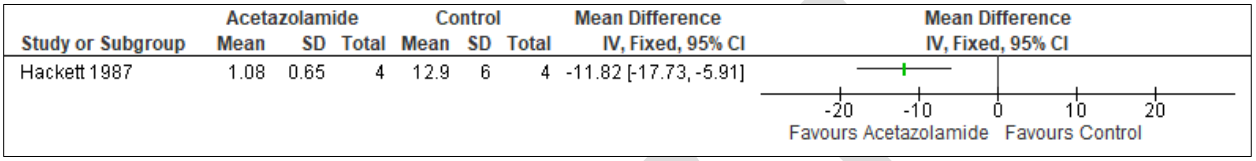
Fischer 2004: median and range converted to mean and SD, Night 2 data used.

Figure S232. Acetazolamide vs. Control (Disease Severity, % time with periodic breathing) [CST= ≥ 50% change from baseline], RCT



Hackett 1987: data extracted from graph

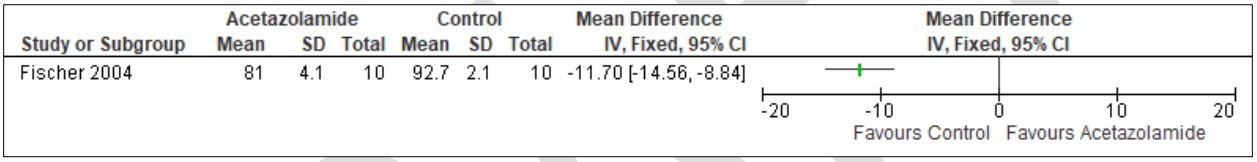
Figure S233. Acetazolamide vs. Control (Disease Severity, oxygen saturation < 70%) [CST= ≥ 50% change from baseline], RCT



Hackett 1987: data extracted from graph

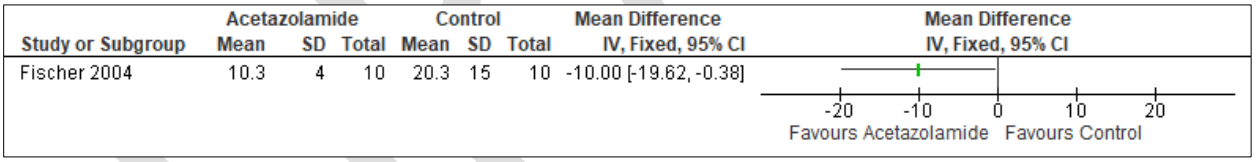
Important Outcomes

Figure S234. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep efficiency) [CST= + 10%], RCT



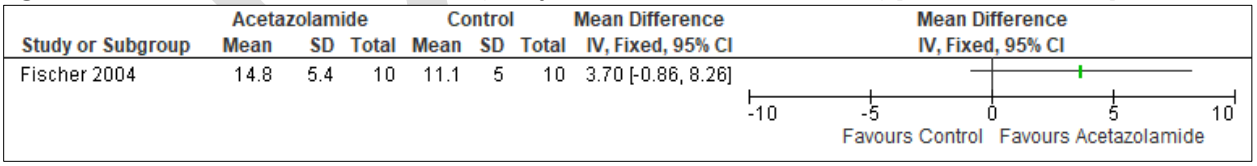
Fischer 2004: Night 1 data

Figure S235. Acetazolamide vs. Control (Sleep architecture, PSG, Arousal Index) [CST= - 25% change from baseline or reduction to ≤12 events/hr], RCT



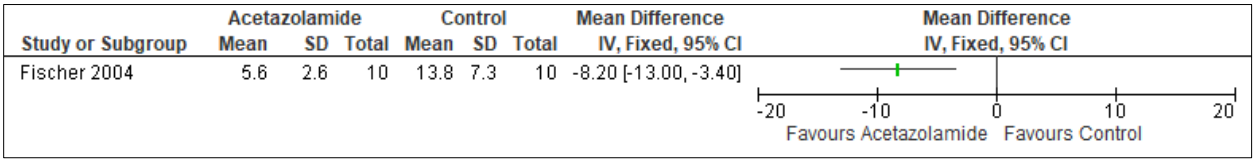
Fischer 2004: Night 2 data

Figure S236. Acetazolamide vs. Control (Sleep architecture, PSG, REM %,) [CST= + 5% of TST], RCT



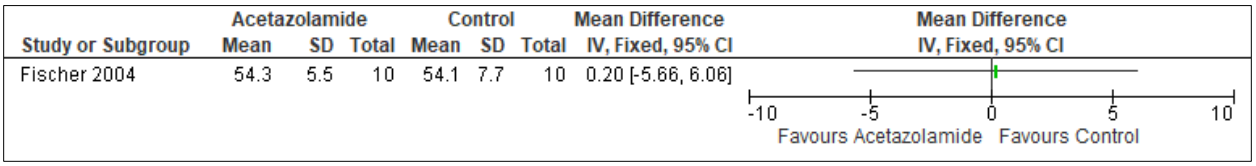
Fischer 2004: Night 1 data

Figure S237. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N1%) [CST= - 5% of TST], RCT



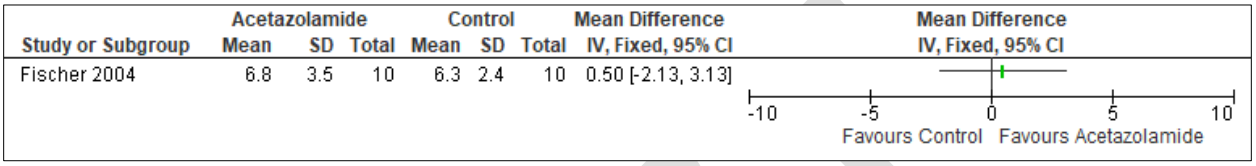
Fischer 2004: Night 1 data

Figure S238. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N2%) [CST= - 5% of TST], RCT



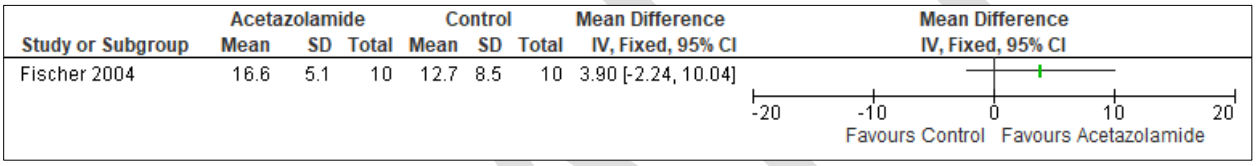
Fischer 2004: Night 1 data

Figure S239. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N3%) [CST= + 5%], RCT



Fischer 2004: Night 1 data

Figure S240. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N4%) [No CST], RCT



Fischer 2004: Night 1 data

ASV

Summary of Findings (GRADE)

Table S10 ASV for adults with CSA due to high altitude

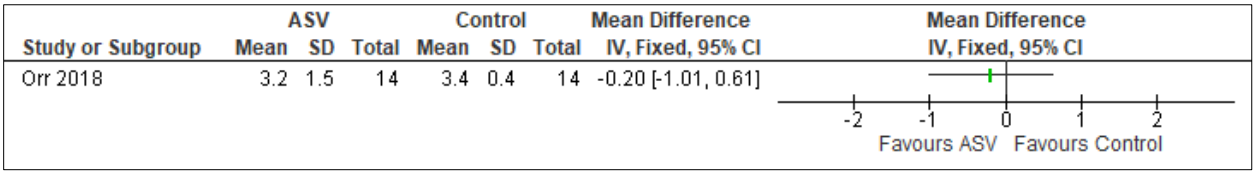
References: Heinrich 2019, Orr 2018

Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **ASV vs. control**	**No of Participants (studies)**
Excessive sleepiness [SSS]	⊕◯◯◯ **VERY LOW**[a,b,c]	The mean difference in the ASV group was **0.2 points lower (1.01 lower to 0.61 higher)** compared to control	14 (1 RCT)
Disease severity [ODI]	⊕◯◯◯ **VERY LOW**[a,b]	The mean difference in the ASV group was **6.9 events/hour lower (16.73 lower to 2.93 higher)** compared to control	14 (1 RCT)
Daytime functioning* [AMS]	⊕⊕◯◯ **LOW**[a]	The mean difference in the ASV group was **0.3 points lower (1.45 lower to 0.85 higher)** compared to control	14 (1 RCT)
Quality of life* [POMS-A confusion]	⊕◯◯◯ **VERY LOW**[a,c]	The mean difference in the ASV group was **0.6 points lower (1.47 lower to 0.27 higher)** compared to control	17 (1 RCT)
Quality of life* [POMS-A fatigue]	⊕◯◯◯ **VERY LOW**[a,c]	The mean difference in the ASV group was **1 point lower (4.73 lower to 2.73 higher)** compared to control	17 (1 RCT)

a. Imprecision due to small sample size (<200 participants)
b. Imprecision due to the 95% CI includes possibility for important benefit and no effect
c. Risk of bias due to lack of blinding of the participants
* No CST

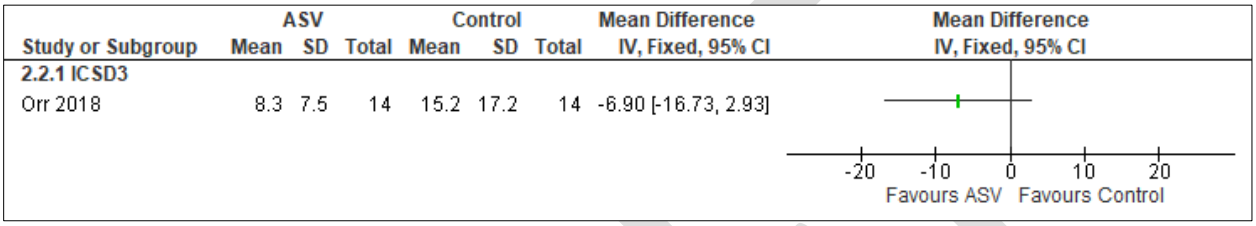
Critical Outcomes

Figure S241. ASV vs. Control (Excessive sleepiness, SSS) [CST= -1 points], RCT



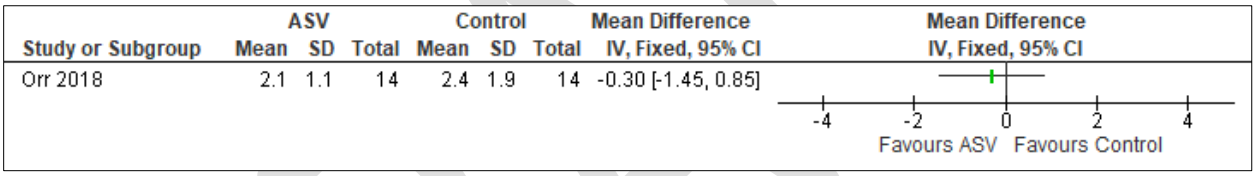
Orr 2018: SEM converted to SD, single night per arm

Figure S242. ASV vs. Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT



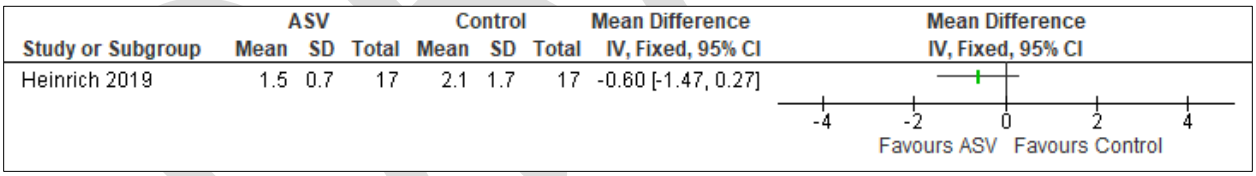
Orr 2018: SEM converted to SD, single night per arm

Figure S243. ASV vs. Control (Daytime Functioning, AMS) [No CST], RCT



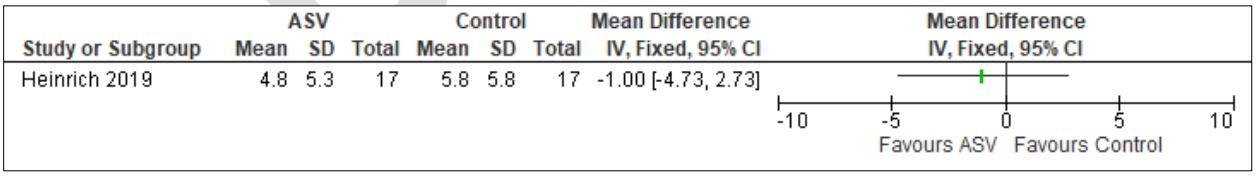
Orr 2018: SEM converted to SD, single night per arm

Figure S244. ASV vs. Control (Quality of Life, POMS-A (Confusion Score)) [No CST], RCT



Heinrich 2019: data extracted from graph; CI interval converted to SD

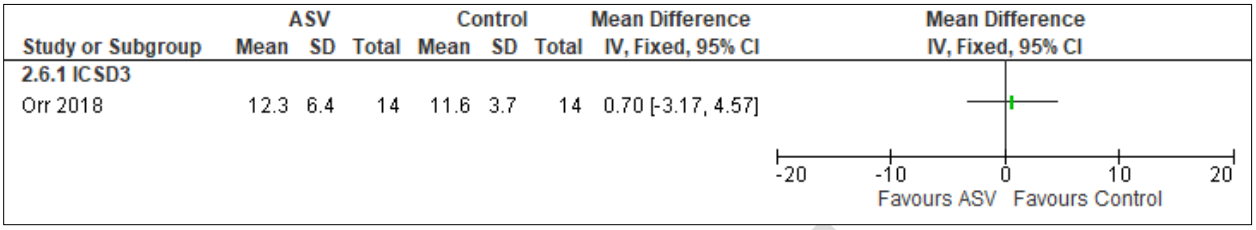
Figure S245. ASV vs. Control (Quality of Life, POMS-A (Fatigue Score)) [No CST], RCT



Heinrich 2019: data extracted from graph; CI interval converted to SD

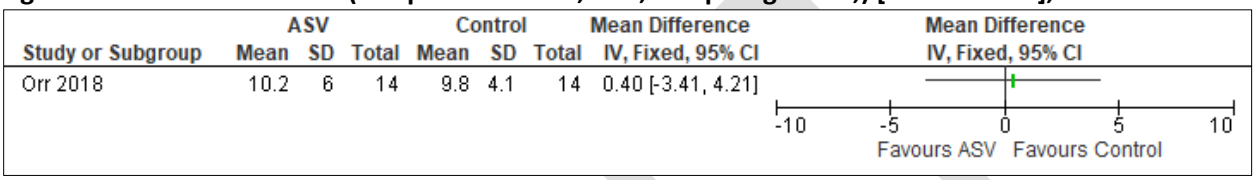
Important Outcomes

Figure S246. ASV vs. Control (Sleep architecture, PSG, Arousal Index, PSG) [CST= ≥25% reduction from baseline or reduction to ≤12 events/hr], RCT



Orr 2018: SEM converted to SD, single night per arm

Figure S247. ASV vs. Control (Sleep architecture, PSG, Sleep stage N1%,) [CST = +5 TST], RCT



Orr 2018: SEM converted to SD, single night per arm

Table S11. List of studies using ICSD* vs. non-ICSD diagnostic criteria**

Short Citation	Intervention(s)	Diagnostic Criteria
Abraham 2015	TPNS	ICSD
Andreas 1996	Oxygen	non-ICSD
Arzt 2005	CPAP, Oxygen	ICSD
Arzt 2007	CPAP	non-ICSD
Arzt 2008	ASV, BPAP with backup rate, CPAP	ICSD
Arzt 2009	CPAP	non-ICSD
Arzt 2013	ASV	non-ICSD
Bradley 2005	CPAP	ICSD
Bradley 2023	ASV	ICSD
Brill 2014	ASV	non-ICSD
Broström 2005	Oxygen	ICSD
Campbell 2012	ASV, Oxygen	ICSD
Cao 2014	ASV, BPAP with backup rate	non- ICSD
Carnevale 2011	ASV	ICSD
Correia 2015	ASV	non-ICSD
Costanzo 2016	TPNS	ICSD
Cowie 2015	ASV	ICSD
Daubert 2018	ASV	non-ICSD
DeBacker 1995	Acetazolamide	ICSD
D'Elia 2013	ASV	ICSD
Dellweg 2013	ASV, BPAP with backup rate	ICSD
Dohi 2008	BPAP with backup rate, CPAP	non-ICSD
Fietze 2008	ASV, BPAP with backup rate	ICSD
Fischer 2004	High altitude Acetazolamide	ICSD
Franklin 1997	Oxygen	ICSD
Ginter 2020	Acetazolamide	non-ICSD
Gorbachevski 2020	ASV, CPAP	ICSD
Granton 1996	CPAP	ICSD
Hackett 1987	High altitude Acetazolamide	ICSD
Hanly 1989	Oxygen	non-ICSD

Hastings 2010	ASV	non-ICSD
Heider 2018	ASV	ICSD
Heinrich 2019	High altitude ASV, High altitude Oxygen	ICSD
Hetland 2017	ASV	ICSD
Hetzenecker 2016	ASV, CPAP	ICSD
Hetzenecker 2016 (Sleep Med)	ASV	ICSD
Hu 2006	BPAP with backup rate, CPAP, Oxygen	non-ICSD
Iliou 2018	ASV	ICSD
Jaffuel 2019	ASV	ICSD
Javaheri 1999	Oxygen	ICSD
Javaheri 2006	Acetazolamide	ICSD
Javaheri 2011	ASV	non-ICSD
Javaheri 2014 (JCSM)	ASV	ICSD
Javaheri 2014	Acetazolamide	ICSD
Javaheri 2015	ASV	ICSD
Javaheri 2020	TPNS	ICSD
Karavidas 2011	CPAP	ICSD
Kasai 2005	BPAP with backup rate	non-ICSD
Kasai 2010	ASV, CPAP	ICSD
Kasai 2013	ASV, CPAP	ICSD
Köhnlein 2002	CPAP	ICSD
Koyama 2013	ASV	ICSD
Krachman 1999	Oxygen	ICSD
Krachman 2005	Oxygen	ICSD
Miyata 2012	ASV	ICSD
Morgenthaler 2007	ASV, BPAP with backup rate	ICSD
Morgenthaler 2014	ASV, CPAP	ICSD
Naghan 2020	Acetazolamide	non-ICSD
Nakao 2014	Oxygen	ICSD
Naughton 1994	CPAP	ICSD
Naughton 1995	CPAP	ICSD
Naughton 1995 (Am J Respir Crit Care Med)	CPAP	ICSD
Noda 2007	BPAP	ICSD
O'Connor 2017	ASV	non-ICSD
Oldenburg 2015	ASV	ICSD
Oldenburg 2018	ASV	ICSD
Orr 2018	High altitude ASV, High altitude Oxygen	ICSD
Pepperell 2003	ASV	ICSD
Philippe 2006	ASV, CPAP	non-ICSD
Ponikowski 2012	TPNS	ICSD
Potratz 2021	TPNS	ICSD
Ramar 2012	ASV	ICSD
Randerath 2012	ASV, CPAP	ICSD
Randerath 2009	ASV	non-ICSD
Roder 2020	ASV	ICSD
Ruttanaumpawan 2009	CPAP	ICSD
Sakakibara 2005	Oxygen	non-ICSD
Sasayama 2006	Oxygen	non-ICSD
Sasayama 2009	Oxygen	ICSD
Seino 2007	Oxygen	ICSD
Shapiro 2015	ASV, CPAP	ICSD

Shigemitsu 2007	Oxygen	non-ICSD
Sin 2000	CPAP	ICSD
Staniforth 1998	Oxygen	ICSD
Sugimura 2016	Oxygen	ICSD
Szollosi 2006	ASV	ICSD
Tamisier 2022	ASV	non-ICSD
Terziyski 2016	CPAP	ICSD
Teschler 2001	ASV, BPAP with backup rate, CPAP, Oxygen	ICSD
Tkacova 1997	CPAP	ICSD
Toyama 2009	Oxygen	ICSD
Toyama 2017	ASV	non-ICSD
Troitino 2014	ASV, BPAP with backup rate, CPAP	non-ICSD
Verbraecken 1998	Acetazolamide	ICSD
Verbraecken 2002	CPAP	ICSD
Willson 2001	BPAP with backup rate	ICSD
Yoshihisa 2012	ASV, Oxygen	ICSD
Yoshihisa 2013	ASV	non-ICSD
Yoshihisa 2013 (Eur J Heart Fail)	ASV	non-ICSD
Zhang 2021	CPAP	non-ICSD

ICSD - International Classification of Sleep Disorders
*Five or more central respiratory events (central apneas or central hypopneas) per hour of sleep. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas.
** The total number of central apneas plus central hypopneas is 20-50% of the total number of apneas and hypopneas.
TPNS – transvenous phrenic nerve stimulation; CPAP – continuous positive airway pressure; ASV – adaptive servo-ventilation; BPAP – bilevel positive airway pressure
CPAP = 76% of studies met ICSD criteria; BPAP without a backup rate = 45%; BPAP = 100%; ASV = 69%; Oxygen = 71%; Acetazolamide = 67%; TPNS = 100%; high altitude = 100%