An Official American Thoracic Society Research Statement: Impact of Mild Obstructive Sleep Apnea in Adults

Online supplement

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Table E1. OSA Prognosis Studies Medline Strategy

1. sleep apnea, obstructive/ or (sleep adj3 (apneic or apn?ea$) adj3 obstruct$).tw.
2. ((Sleep adj3 disorder$ adj3 breath$) and obstruct$).tw.
3. (obstruct$ adj3 (apn?ea$ or apneic or hypersomni$ or hypopn?ea$ or hypercapni$ or hypoxi$ or hypoventilat$ or polycythemi$)).tw.
4. (osa or osah or osahs or sahs).tw.
5. sleep apnea syndromes/ and (mixed or obstruct$).tw.
6. (obesity hypoventilation syndrome/ or (obes$ adj hypoventilat$ adj syndrome$).tw. or pickwickian$.tw.) and (mixed or obstruct$).tw.
7. Snoring/ or (snore$ or snoring$).tw.
8. or/1-7 [OSA]
9. ..l/ 8 lg=en or ab=y
10. limit 9 to human

11. limit 10 to animals
12. 9 not 10 not 11 [not indexed with human or animal]
13. 10 or 12 [indexed with human or not indexed]
14. limit 13 to "all child (0 to 18 years)"
15. limit 13 to "all adult (19 plus years)"
16. 13 not 14 not 15 [not indexed with age]
17. 15 or 16 [OSA Adult or not Indexed]
18. epidemiologic studies/ or case-control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/ or incidence/ or mortality/ or "cause of death"/ or fatal outcome/ or hospital mortality/ or mortality, premature/ or survival rate/ or disease progression/ or Comorbidity/ or risk/ or risk factors/
19. (prognos$ or risk$ or predict$ or cohort$ or mortalit$ or between group$).tw.
20. 17 and 18
21. 17 and 19
22. 20 or 21
23. limit 22 to (comment or editorial or interview or lectures or letter or patient education handout)
24. 22 not 23

Table E2. OSA Therapy Studies Medline Strategy

1. sleep apnea, obstructive/ or (sleep adj3 (apneic or apn?ea$) adj3 obstruct$).tw.
2. ((Sleep adj3 disorder$ adj3 breath$) and obstruct$).tw.
3. (obstruct$ adj3 (apn?ea$ or apneic or hypersomni$ or hypopn?ea$ or hypercapni$ or hypoxi$ or hypoventilat$ or polycythemi$)).tw.
4. (osa or osah or osahs or sahs).tw.
5. sleep apnea syndromes/ and (mixed or obstruct$).tw.
6. (obesity hypoventilation syndrome/ or (obes$ adj hypoventilat$ adj syndrome$).tw. or pickwickian$.tw.) and (mixed or obstruct$).tw.
7. Snoring/ or (snore$ or snoring$).tw.
8. or/1-7 [OSA]
9. ..l/ 8 lg=en or ab=y
10. limit 9 to human
11. limit 10 to animals
12. 9 not 10 not 11 [not indexed with human or animal]
13. 10 or 12 [indexed with human or not indexed]
14. limit 13 to "all child (0 to 18 years)"
15. limit 13 to "all adult (19 plus years)"
16. 13 not 14 not 15 [not indexed with age]
17. 15 or 16 [OSA Adult or not Indexed]
18. positive-pressure respiration/ or continuous positive airway pressure/ or intermittent positive-pressure breathing/ or intermittent positive-pressure ventilation/
19. (Continuous Positive Airway Pressure$ or (nppv or cpap or ncpap or aprv)).tw.
20. ((positive or airway$) adj2 pressure$).tw.
21. or/18-20 [CPAP]
22. 17 and 21 [OSA + CPAP]
23. Weight Loss/ or Diet Therapy/ or (diet$2 or dietary or dieting).tw.

24. (weigh$ adj3 (loss$ or lose$1 or losing or lost or less)).tw.

25. exp Adipose Tissue/ or body fat distribution/ or adiposity/ or body mass index/ or body size/ or body weight/ or overweight/ or obesity/ or obesity, morbid/ or waist circumference/ or skinfold thickness/ or waist-hip ratio/

26. ((body adj3 (fat or mass or size$ or weigh$)) or (bmi$ or overweigh$ or obes$ or adipos$)).tw.

27. or/23-26 [Weight Loss]

28. 17 and 27 [OSA + Weight Loss]

29. orthodontics/ or orthodontic appliances/ or occlusal splints/ or orthodontic appliances, functional/ or activator appliances/ or orthodontic appliances, removable/ or orthodontic brackets/ or orthodontic retainers/ or orthodontic wires/ or dental prosthesis/ or crowns/ or dental abutments/ or dental clasps/ or dental implants/ or dental implants, single-tooth/ or dental prosthesis, implant-supported/ or dental restoration, permanent/ or dental restoration, temporary/ or dentures/ or denture, complete/ or denture, complete, immediate/ or denture, complete, lower/ or denture, complete, upper/ or denture, partial/ or denture, partial, fixed/ or denture, partial, immediate/ or denture, partial, removable/ or denture, partial, temporary/ or denture precision attachment/ or inlays/ or palatal obturators/

30. (orthodontic$ or applianc$ or splint$ or brace$1 or bracket$ or retainer$ or wire$ or prosthe$ or device$ or splint$ or denture$ or clasp$2 or crown$2 or inlay$2).tw.

31. 29 or 30 [Oral Appliance]

32. 17 and 31 [OSA + Oral Appliance]

33. oral surgical procedures/ or apicoectomy/ or gingivectomy/ or gingivoplasty/ or glossectomy/ or jaw fixation techniques/ or mandibular advancement/ or maxillofacial prosthesis implantation/ or mandibular prosthesis implantation/ or oral surgical procedures, preprosthetic/ or alveolar ridge augmentation/ or alveolectomy/ or alveoloplasty/ or dental implantation/ or dental implantation, endosseous/ or blade implantation/ or dental implantation, endosseous, endodontic/ or immediate dental implant loading/ or dental implantation, subperiosteal/ or vestibuloplasty/ or tooth extraction/ or serial extraction/ or tooth replantation/

34. otorhinolaryngologic surgical procedures/ or adenoidectomy/ or laryngectomy/ or laryngoplasty/ or laryngoscopy/ or nasal surgical procedures/ or rhinoplasty/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or tonsillectomy/

35. (surgical$ or surger$ or dental$).mp.

36. (apicoectom$ or gingivectom$ or gingivoplast$ or glossectom$ or adenoidectom$ or laryng$ or rhinoplast$ or pharyng$ or tonsillectom$ or tracheostom$ or tracheotom$ or septoplast$ or polypectom$).tw.

37. ((prosthe$ or dental$ or orthodont$ or blade$ or tooth or teeth) adj3 (implant$ or replant$)).tw.

38. (vestibuloplast$ or alveolectom$ or alveoloplast$).tw.
39. ((alveol$ ridge or sinus floor) adj3 augment$).tw.
40. ((le fort or sagittal split ramus) adj3 osteotom$).tw.
41. ((tooth or serial or teeth) adj3 extract$).tw.
42. ((maxill$ or genioglos$ or palat$ or mandib$) adj3 advanc$).tw.
43. ((neck adj3 dissect$) or (jaw adj3 fixat$) or (palat$ adj3 implant$) or (pillar adj3 procedur$) or (nasal adj3 reduc$) or (palat$ adj3 obdurat$) or (dental adj3 restor$)).tw.
44. ((radiofrequency adj3 (ablat$ or reduc$)) or (RFA or RFAP or RFTVR or TCRFTA)).tw.
45. (uvulopalato$ or UPPP or LAUP).tw.
46. su.fs.
47. or/33-45 [Surgery]
48. 17 and 47 [OSA + Surgery]
49. 22 or 28 or 32 or 48 [OSA + (CPAP or Weight Loss or Oral Appliance or Surgery)]
50. clinical trial$.mp.
51. random$.mp.
52. tu.xs.
53. or/50-52 [Clinical Queries Sensitive RCT hedge]
54. review$.pt.
55. (medline or medlars or embase or pubmed or cochrane or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl).tw,sh.
56. ((hand or manual$) adj2 search$).tw,sh.
57. ((electronic$ or bibliograph$ or computer$ or online$) adj database$).tw,sh.
58. (pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect).tw,sh.
59. (retraction of publication or retracted publication).pt.
60. or/55-59
61. 54 and 60
62. meta-analysis.pt.
63. (meta-analys$ or metaanalys$).tw,sh.

64. (systematic$ adj5 review$).tw,sh.
65. (systematic$ adj5 overview$).tw,sh.
66. (quantitativ$ adj5 review$).tw,sh.
67. (quantitativ$ adj5 overview$).tw,sh.
68. (quantitativ$ adj5 synthes$).tw,sh.
69. (methodologic$ adj5 overview$).tw,sh.
70. (methodologic$ adj5 review$).tw,sh.
71. (integrat$ research review$ or research integrat$).tw.
72. or/62-71
73. 61 or 72 [BMJ Clinical Evidence SR hedge]
74. guideline$.pt.
75. practice guideline$.tw.
76. 74 or 75 [practice guidelines]
77. 53 or 73 or 76
78. 49 and 77

Table E3. Studies pertinent to the question*: Does mild OSA in comparison to absence of OSA contribute to adverse long-term neurocognitive outcomes such as daytime sleepiness, poor attention/memory loss, motor vehicle accidents, and poor quality of life?*

Author/ Year	Study Type	Participants*	Event Identification Methodology	Major Results*
Agha, 2014(1)	Cross-sectional	Clinic Sample; Obese Control 10 (mean age: 52.80±8.40 years); 29 OSA (mean age: 53.34±11.53 years). "Mild" OSA N=8; mild AHI= 9.31±2.63	Hypopneas identified using nasal pressure catheter and thermistor; Defined using 30% decline in nasal pressure+4% desaturation or 50% decline in nasal pressure+3% desaturation	Obese Control ESS: 3.40±1.64; mild OSA: 10.25±1.28; moderate OSA: 12.66±1.0; severe OSA: 13.08±1.56; p<0.001 by ANOVA
Balsevicius, 2012(2)	Cross-sectional	Clinic Sample: Total 74 (mean age: 41.83±11.01 years); mild OSA N=32; snorers N=20 from ENT clinic	Hypopnea identification method not provided; Defined using 50% decline+3% desaturation or an arousal	No significant differences in self-reported sleepiness, ESS, SAQLI or BDI among snorers, mild, moderate OSA.

Baldwin, 2001(3)	Cross-sectional	Total 5816 subjects from a general population, (mean ages men: 64.2±10.6 years; women: 66.6±10.8years), number in mild OSA subgroup not provided	Hypopnea identification using a thermistor; Defined using 30% decline in thermistor and 4% oxygen desaturation	Mild OSA was associated with reduction in vitality on SF36 (OR 1.2; 95%CI: 1.02-1.43) but not for overall QOL.
Batool-Anwar, 2014(4)	Cross-sectional	Total 61 subjects from a sleep clinic (mean age: 46±15 years); mild OSA N=19, no OSA N=18	Hypopneas identified with a thermistor and nasal pressure catheter; Defined using a 50% decline in airflow and 3% desaturation or arousal	No differences in PVT parameter among categories of OSA.
Cui, 2008(5)	Cross-sectional	3523 female subjects (mean age: 46±15 years) from an urban community population, mild OSA N=619	Events identified with only pulse oximetry and defined as the number per hour with a 3% desaturation (ODI3%)	Higher OR (95%CI) for excessive daytime sleepiness in those with ODI3% 5-9: 1.9 (1.2-3.0) and ODI3% 10-14: 2.2 (1.0-4.6)
Duran, 2001(6)	Cross-sectional	Age 30 to 70, white, AHI 5-14.9, mild OSA N=115 from a general community population	Hypopnea identified by nasal and oral thermistor; defined as 50% reduction in airflow and >4% desaturation and/or an arousal.	Daytime hypersomnolence, OR 1.37 (95% CI 0.6 to 3.3)

Franklin, 2013(7)	Cross-sectional	Total 400 females (weighted mean 48 years; 95% CI: 46–49) from the general population; number in mild OSA subgroup not provided	Hypopneas identified with a thermistor and nasal pressure catheter; defined using a 50% decline in airflow and 3% desaturation or arousal	Percentage of females with ESS $\geq$10 not greater in mild OSA
Gottlieb, 2000(8)	Cross-sectional	5,777 subjects (mean age: 64±11 years) from a general population cohort, mild OSA N=1672	Hypopnea identification using a thermistor; Defined using 30% decline in thermistor and 4% oxygen desaturation	RDI trend for ESS Score and % with ESS $\geq$ 11 are significant, but no comparison of mild (ESS=7.8) to no OSA (ESS=7.1). Data is irrespective of snoring status.
Howard, 2004(9)	Cross-sectional	244 randomly selected truck drivers (mean age: 47.8$\pm$9.3 years), mild N=OSA 36	Hypopnea identification using nasal pressure; Defined using 50% reduction in nasal pressure lasting at least 10 seconds or a clear reduction of less than 50% in association with a fall in oxygen saturation of 3% or an arousal	Significant trend for ESS to increase with OSA severity, but no comparison of no OSA (ESS=6.8) and mild OSA (ESS=7.4) No relationship between AHI and accident risk (OR 0.82, 95% CI 0.15–3.57 for change in RDI of 1 SD)
Ibrahim, 2007(10)	Cross-sectional	191 Snorers from a clinic population (mean age: 48.1±9.8 years), mild OSA N=30 (mean age: 47.8±9.5 years)	Hypopneas identified using a thermistor; Defined using 50% decline in a thermistor and 4% oxygen desaturation	Linear increase ($p<0.001$) in ESS from no OSA (ESS=7.2$\pm$4.3) through mild (9.6$\pm$5) and severe OSA (12.6$\pm$4.1), but no specific comparison of mild OSA vs. no OSA.

Isodoro, 2013(11)	Cross-sectional	198 subjects from a sleep clinic (mean age 52.7 ± 12.8 years); mild OSA N= 37, no N=OSA 30	Hypopnea identification method not provided; Defined as discernible reductions in airflow or thoraco-abdominal movements and desaturation >3%	No difference in Psychological General Well-Being Index (PGWBI) global or subscales by severity class; AHI inversely associated with SF-12, but no comparison between OSA severity categories. Regression adjusted for age, BMI and ESS
Ishman, 2010(12)	Cross-sectional	53 participants from an ENT clinic (mean age, range: 47.4, 24–72 years), mild OSAN=15, controls N=51	Hypopnea methodology and definition not provided	No difference between mild OSA and snorers with respect to BDI and ESS.
Kasai, 2010(13)	Cross-sectional	50 males; mild OSA N=23 (mean age: 51.0 $\pm$11.3 years), controls N=25 (mean age 50.9$\pm$12.4 years)	Hypopnea methodology and definition not provided; Citation to AASM 1999 report	ESS greater in mild vs. no OSA; 6.6$\pm$4.5 vs. 10.0$\pm$5.1; $p<0.05$
Kezerian, 2007(14)	Cross-sectional	461 elderly females from the general population (mean age: 82.9±3.5 years); mild OSA N=178, control N=153	Hypopneas identified using nasal pressure catheter and thermistor; Defined as a 30% reduction in respiratory sensors and 3% oxygen desaturation	Weak relationship of ESS to AHI on multivariate regression (β=0.44, 95%CI: 0.10-0.78); No relationship with FOSQ; tertile analysis without specific comparisons among tertiles. Regression adjusted for age, race, BMI, physician-diagnosed depression and self-reported health.

Kezirian, 2009(15)	Cross-sectional	2849 elderly males (mean age: 76.4± 5.5 years) from the general population, mild OSA N=949, control N=948	Hypopneas identified using nasal pressure catheter and thermistor; Defined as a 30% reduction in respiratory sensors and 3% oxygen desaturation	Weak relationship of ESS to AHI on multivariate regression (β =0.18, 95%CI: 0.04-0.32); No relationship with FOSQ; Tertile analysis without specific comparisons among tertiles. Regression adjusted for age, race, BMI, Geriatric Depression Scale, Goldberg Anxiety Scale, Self-reported Health.
Kinoshita, 2012(16)	Cross-sectional	Vietnam-era veterans (mean age 61.3±4.0 years, 100% male); mild OSA N=33; recruited from the general community	Unattended PSG, Hypopnea identified by nasal and oral thermistor and nasal air pressure transducer ; defined as 50% reduction in airflow and >3% desaturation	Test of auditory learning and memory - Rey Auditory Verbal Learning Test (RAVLT)-Word mild OSA vs. no-OSA group significant difference in mean RAVLT scores 44.7±7.5 vs. 41.7±8.4 No significant difference between groups for the Color-Word Interference Test (CWIT).
Lecube, 2010(17)	Cross-sectional	88 morbidly obese premenopausal women (mean age: 38.3±8.1) undergoing bariatric surgery evaluation, mild OSA N=25, no OSA N=22	Hypopneas identified using a nasal pressure catheter; Defined as a 50% reduction in nasal pressure catheter and 3% oxygen desaturation	No difference in ESS between Mild OSA and no OSA.
Lopes, 2008(18)	Cross-sectional	Adults > 18 years from sleep clinic; mild OSA N=506 (mean age: 45±12 years), no OSA N=508 (mean age: 40±12 years)	Hypopneas identified using nasal pressure catheter and thermistor; Definition not provided	AHI <5 ESS: 10.54$\pm$5.37 vs. AHI 5-15: 10.22$\pm$5.17; p=NS

Mason, 2011(19)	Cross-sectional	127 subjects from an aortic aneurysm register (mean age: 67.9 ±6 years); mild OSA N=43, no OSA N=47	Hypopneas identified using nasal pressure catheter; Defined as a 50% reduction in nasal pressure catheter and 4% oxygen desaturation	No association of ESS with AHI.
Minoguchi, 2005(20)	Case Control	36 men with OSA, obese controls N=16 (mean age: 48.6±3.9 years); mild OSA N=13 (mean age: 46.5±3.8 years [SE]); sample source not provided	Hypopnea methodology and definition not provided	ESS in mild OSA>than obese controls; 10.4±1.4 vs. 7.8±1.1, p<0.01
Minoguchi, 2007(21)	Cross-sectional	50 obese males with OSA, mild (n=26, mean age: 47.6 ±1.9 [SE] years) moderate/severe(N=24; mean age: 50.5±1.7 years) and matched controls N=15 (mean age: 48.5±3.1 years); sample source not provided	Hypopnea methodology and definition not provided	ESS in mild OSA>than obese Controls; 9.7±0.7 vs. 7.7±0.4, p<0.05
Mulgrew, 2008(22)	Cross-sectional	783 subjects referred for suspected sleep disordered breathing (mean age: 49.9±11.6 years); mild OSA N=235, controls N=140 matched by age, sex, driver license type and	Hypopneas identified using oronasal flow canula; Defined as a 50% decrease in airflow or a clear but lesser decrease in airflow if associated with either a 3%	MVA risk increased in mild (RR: 2.6, 95%CI 1.7-3.9); No differences in ESS between mild OSA and no OSA. Regression adjusted for AHI group, ESS, BMI, gender, age, kilometers driven and use of alcohol, sedatives or caffeine.

		residence	desaturation or an arousal	
Nazzaro, 2008(23)	Cross-sectional	Age 52±8 years; mild OSA N=33, no OSA N=32; recruited from a hypertension clinic	Hypopnea identified by nasal and oral thermistor; defined as 2/3 reduction in airflow with ≥3% desaturation or awakening	No significant difference in ESS between mild OSA and no OSA groups. But severe OSA had significantly higher ESS compared with mild OSA (13·46±5·33 vs. 9·93±5·24, p<0.01).
Peppard, 2006 (24)	Mixed cross-sectional and longitudinal analyses	1408 subjects from a general population sample; mild OSA mean age 53 years, range 31-73, [PSG N=405]; no OSA mean age: 46 years, range: 30-63 [PSG N=140]	Hypopneas identified using nasal pressure catheter and oral and nasal thermistor and RIP; defined as an discernible reduction in the sum amplitude of the rib-cage plus the abdominal excursions on respiratory inductance plethysmography and with 4 percent desaturation	Mild OSA associated with Zung Score ≥50 (adjusted OR=2.0, 95% CI:1.4-2.9); Regression adjusted for age, body mass index, antihypertensive medication use, education, history of cardiovascular disease, usual alcoholic beverage consumption, physical exercise habits, and intrasubject correlation owing to the use of multiple studies per participant. Longitudinal association of change in AHI severity category with change in depression status was significant (OR-1.8, 95% CI: 1.3-2.6), but no data on mild OSA.
Quan, 2011(25)	Cross-sectional analysis of RCT at baseline	1204 subjects recruited from sleep clinics and the community (mean age: 50.7 ±12.6 years); N=92 with AHI<10 and N=144 with AHI 10-15	Hypopneas identified using a thermistor and nasal pressure canula; Defined if there was a 50% decrease in nasal pressure signal or a clear reduction in nasal pressure associated with either a 3% desaturation or	No correlation between ESS and any of a large number of neurocognitive tests, adjusted for demographics, sleep architecture, oxygen desaturation.

			an arousal	
Quan, 2014(26)	Cross-sectional analysis of RCT at baseline	239 subjects recruited from sleep clinics and the community; mild OSA N=199 (47.1±13.1 years), no OSA N=40 (mean age: 42.1±15.1 years)	Hypopneas identified using a thermistor and nasal pressure canula; Defined if there was a 50% decrease in nasal pressure signal or a clear reduction in nasal pressure associated with either a 3% desaturation or an arousal	No differences between No OSA and Mild OSA on ESS, SSS, HAM-D, POMS, SAQLI.
Ronksley, 2009(27)	Cross-sectional	2149 subjects with OSA referred for sleep testing (mean age: 50.1±12.9 years), mild OSA N=738, no OSA N=432	Hypopneas identified using a nasal pressure catheter; Defined if there was a 30% reduction in thoracoabdominal movement or airflow and associated with 4% oxygen desaturation	ESS increased with OSA severity per analysis, but means of mild vs. no OSA were not compared, but also do not appear different; ESS no OSA: 10.9 (5.1) vs. mild OSA 10.7 (5.3).
Samson, 2012(28)	Cross-sectional retrospective chart review; clinic sample	Total subjects; 596 Veterans who had undergone PSG (Mean age: 56.0±11.6 years), mild OSA N=136, moderate OSA N=105	Hypopneas identified using a nasal/oral thermocouple; Defined as 30% reduction in airflow and a 4% oxygen desaturation	ESS was not statistically higher in mild OSA vs. no OSA; no OSA: 11.5 (5.7), mild OSA: 12.2 (5.1).
Serafini, 2000(29)	Cross-sectional	66 bariatric surgery patients (mean age: 43 ± 9.5 years [SE]), mild OSA N=13	Hypopnea methodology and definition not provided	No correlation of AHI with ESS.

Sharkey, 2013(30)	Cross-sectional	Total subjects: 296 bariatric surgery patients (mean age: 42.0±9.5 years), mild OSA N=97, moderate/severe OSA N=158	Hypopneas identified using a nasal pressure catheter and oral/nasal thermistors; Defined as 50% decrease in nasal pressure and 3% oxygen desaturation or arousal	No changes in ESS according to OSA severity.
Shiomi, 2002(31)	Cross-sectional retrospective chart review	Total subjects: 554 from a sleep center (mean age 49.2±14.3 years), mild OSA: N=155; snorers: N=106;moderate/ severe OSA: N=293	Hypopnea methodology and definition not provided	Motor vehicle accidents: Snorers: 3.8% Mild OSA: 5.8% Mod OSA: 9.9% Severe OSA: 11.0% P<0.05 snorers vs. severe OSA only
Svensson, 2008(32)	Cross-sectional	400 women from a general population with oversampling of snorers (mean age: 50±11 years); mild OSA N=128	Hypopneas identified using nasal pressure catheter; Defined as a 50% reduction in the airflow with an arousal or ≥ 3% oxygen desaturation	In comparison to AHI<5, mild OSA not related to ESS, excessive daytime sleepiness, falling asleep involuntarily during the daytime or daytime fatigue. Adjusted for Age, BMI, habitual snoring, smoking, total sleep time, percentage of REM sleep, and percentage of slow-wave sleep.
Tregear, 2009(33)	Meta analysis of motor vehicle crash risk	Not provided from 3 studies included	Not applicable	Non significant trend toward greater severity of the AHI among individuals with OSA who crashed.

Utriainen, 2012(34)	Cross-sectional	82 vascular surgery patients (mean age 67±9 years): mild OSA N=23, no OSA N=12	Hypopneas identified using a nasal pressure catheter; Defined as a 50% decrease in tidal volume and a 4% oxygen desaturation	No association of ESS with OSA severity.
Ward, 2013(35)	Cross-sectional	2,673 patients referred to a sleep disorders center with N=286 men (mean age: 50.0±13.6 years) and N=278 women (mean age: 50.0±13.5 years) with mild OSA	Hypopnea methodology not provided, but reference made to 1999 AASM "Chicago" criteria; Defined as ≥ 50% decrease in airflow, or a clear but lesser decrease in airflow associated with either 3% desaturation or arousal	In comparison to controls without OSA, there was increased in risk for MVA in men and women with mild OSA. Regression adjusted for neck circumference, proportion of time spent with an arterial oxygen saturation of < 90%, age, sex, and alcohol and caffeine intake
Wachter, 2013(36)	Cross-sectional	398 subjects at risk for heart failure; mild OSA N=140 (mean age 67±6 years), no OSA N=136, mean age 64±7 years	Hypopneas identified using a nasal pressure catheter; Defined as a 50% reduction in tidal volume and a 3% oxygen desaturation	No difference in ESS between mild OSA and no OSA.
Xiromeritis, 2011(37)	Cross-sectional	161 subjects (mean age: 48.5±10.5 years); mild OSA N=28, no OSA N=30; sample source not provided	Hypopneas identified using a thermistor; Hypopnea definition not provided	No difference in ESS between mild OSA and no OSA.

Yeh, 2010, (38)	Cross-sectional retrospective analysis	101 bariatric surgery patients (mean age 30.3±8.5 years); mild OSA N=32, no OSA N=18	Hypopnea methodology and definition not provided	AHI correlates with ESS (r=0.305, p<0.01), but no difference between mild OSA and no OSA.
Young, 1997(39)	Cross-sectional analysis	AHI 5-15/hour, age for entire sample 45.1±7.8 years; mild OSA N=133, no OSA N=318; general population sample	Hypopneas indentified using nasal end-tidal carbon dioxide(capnograph) and oral thermistry; defined as reduction in respiratory effort and ≥4% desaturation	Increased risk for any MVA in men in 5 years, OR, 95% CI 4.2, 1.6-11.3, but not significant in women; however, risk for multiple MVAs in 5 years was not significant.

*Data given as Mean±SD unless otherwise stated.

AASM American academy of sleep medicine; ANOVA Analysis of variance; AHI Apnea-hypopnea index; BDI Beck depression inventory; BMI Body mass index; CI Confidence interval; CPAP Continuous positive airway pressure; ESS= Epworth sleepiness scale; FOSQ Functional outcomes of sleep questionnaire; MVA Motor vehicle accident; N Sample size; ODI Oxygen desaturation index; OR Odd ratio; PVT Psychomotor vigilance testing; QOL Quality of life; RCT Randomized controlled trial; RDI Respiratory disturbance index; SSS Stanford sleepiness scale, HAM-D Hamilton depression rating scale; POMS Profile of Mood States; PSG Polysomnography; SAQLI Sleep apnea quality of life index; SF 12 12-Item Short Form Survey; SF-36 Short Form Medical Outcomes Survey: SE Standard error

Table E4. Studies pertinent to the question: *Does treatment of mild OSA in comparison to no treatment prevent or reduce adverse neurocognitive consequences, motor vehicle accidents, and improve quality of life?*

Author Year	Study Type	Participants*	Event Identification Methodology	Intervention and Comparator	Major Results*
Avlonitou 2012(40)	Observational, non-randomized	Adults (Mean age: 50±12 years), from sleep clinic; mild OSA N= 8, only CPAP adherent subjects included	Hypopneas identified using nasal pressure and thermistor; Defined using 4% desaturation and/or arousal	6 months on CPAP vs. baseline No control group	ESS: baseline=12.3±7.7 to 3.3±4.6 on CPAP, p=0.011 SAQLI: baseline= 3.3±0.9 to 5.5±1. on CPAP, diff 2.2±0.7 p<0.001 Domain A Daily functioning: baseline= 3.5±1.2 to 5.8±0.9 on CPAP, p<0.001 Domain B Social interactions: baseline= 4.4±1.7 to 5.8±1.3 on CPAP, p<0.001 Domain C Emotional functioning: baseline=3.7±1.0 to 5.2±1.0 on CPAP, p<0.001 Domain D Symptoms: baseline= 1.4±0.7 to 5.7±1.4 on CPAP, p<0.001

Barnes, 2004(41)	Randomized 3- way Crossover Clinical Trial	Adults >18 yrs from sleep clinic; mild OSA N= 47; Mean age: 46.4±1.1 [SE] years	Hypopneas identified using oral/nasal thermistor and abdominal and thoracic effort bands; defined as >50% reduction from baseline in at least two of the three signals: airflow, thoracic or abdominal movement. (oxygen desaturation or arousal confirmation not needed)	CPAP vs. Oral Appliance vs. Placebo tablet for 3 months each.	No raw data provided ESS: CPAP vs. placebo , p≤0.05 Oral Appliance vs. placebo, p≤0.05 FOSQ: CPAP vs. placebo , p≤0.05 Oral Appliance vs. placebo, p≤0.05 SF 36: CPAP vs. placebo , p≤0.05 Oral Appliance vs. placebo, p≤0.05 Neurophysiologic Function: CPAP vs. placebo , p=NS and Oral Appliance vs. placebo, p=NS
Back, 2009(42)	Randomize d controlled trial	N=32 patients in ENT clinic with mild OSA, only velopharyngeal obstruction were considered, age not provided	Events identified using oral and nasal thermistor; hypopnea was not defined; automated scoring Follow up after 4 months (range 4-6 months)	Intervention: Radiofrequenc y surgery of soft palate Comparator: Placebo applicator 'Cure' defined as AHI <5, ESS <8, increase in the mental and the physical component scores in SF-36	Baseline values were matched in the 2 arms. Surgery vs. placebo: No significant differences in the change in AHI, ESS, SF- 36 scores on follow-up. Only one patient in the surgery group was cured.

Engleman, 1997(43)	Randomized Clinical Trial with Crossover	16 Adults from sleep clinic; mild OSA N=16; mean age: 52±2 [SE] years	Hypopneas identified using oronasal thermistor and abdominal and thoracic effort bands; defined as 50% reduction in respiratory movement. (Oxygen desaturation or arousal confirmation NOT needed)	4 weeks CPAP vs. 4 weeks Oral Tablet Placebo	Mean (SE): CPAP Symptom score: no baseline; CPAP 2.0 (0.3), vs. placebo 3.7 (0.4), p<0.01 Trail making B (secs): no baseline, CPAP 64.1 (5.5) vs. placebo = 77.7 (9.2), p=0.02; HADS depression score: No baseline, CPAP= 3.4 (0.9) vs. placebo=5.0 (1.0), p= 0.03 The following tests were not significant (p>0.05): ESS, MSLT, UMACL energetic arousal score, IQ Decrement Score, Steer Clear, PASAT, RVIPT, Median 8 Choice Reaction Time, Verbal Fluency, BVRT, HADS Anxiety Score, GHQ-28, NHP Part 2

Engleman, 1999(44)	Randomized Clinical Trial with Crossover	Adults from sleep clinic; mild OSA N= 34; mean age: 44±6 years	Hypopneas identified using oronasal thermistor and abdominal and thoracic effort bands; defined as 50% reduction in respiratory movement. (oxygen desaturation or arousal confirmation NOT needed)	4 weeks CPAP vs. 4 weeks Oral Tablet Placebo	ESS: baseline =13±3, CPAP = 8±4 vs. placebo = 11±4 ; p=0.008; Digit symbol (correct): baseline= 54±12, CPAP = 59±12 vs. placebo= 57±14, p=0.004 PASAT-2 (correct): baseline =31±12, CPAP = 40±11 vs. placebo= 36±14, p=0.02 HADS Depression Score: baseline= 7.4±4.1, CPAP= 4.0±3.0 vs. placebo = 5.7±3.9 ,p=0.003 Total Symptom Score: baseline =22/6; CPAP =11/7 vs. placebo =16/7 , p=0.003; SF-36 Health Transition: baseline =3.1±0.6, CPAP= 2.6±0.9 vs. placebo=3.0±0.7, p = 0.03 SF-36 Role—physical: baseline= 58±36, CPAP= 81±27 vs. placebo=64±34, p = 0.03 SF-36 Bodily pain: baseline= 68±31, CPAP= 75±23 vs.

					placebo= 68±27, p = 0.02 SF-36 Social function: baseline= 60±27, CPAP= 84±17 vs. placebo=73±25, p < 0.01 SF-36 Vitality: baseline=33±19, CPAP= 58±19 vs. placebo= 46±23, p< 0.001 The following tests were not significant (p>0.05): MWT, UMACL Energetic Arousal Score, Steer Clear, Trailmaking A&B, Block Design, Performance IQ, HADS Anxiety Score, NHP Part 2, SF-36 Physical Function, Role Emotional, Mental Health, General Health
Giannasi, 2013(45)	Observational, non-randomized	Adults in sleep clinic (mean age: 48±11 years); mild OSA N= 11	Hypopneas identified using thermistor; Definition not specified	OA for 7.2 months (Range 6-9 months) vs. baseline No control group	Median (range) ESS baseline= 9.5 (4-14) to 5.8 (1-9) on OA, P=NS

Kushida, 2012(46)	Randomized Clinical Trial	Adults ≥ 18 years recruited from the community and sleep clinic (mean ages: Active-52.2±12.2 years; Sham-50.8±12.2 years); AHI 10-15: N=113	Hypopneas identified using nasal pressure and oral thermistor; Defined using arousal and/or 3% desaturation	Active CPAP vs. Sham CPAP for 6 months	ESS and MWT sleep latency: P=NS between groups *Primary neurocognitive outcomes:* Pathfinder Test-Total Time, Buschke Selective Reminding Test-Sum Recall, Sustained Working Memory Test-Overall Mid-Day index: All P=NS between groups *Secondary neurocognitive outcomes:* Pathfinder Number-Reaction Time, Shifting Attention Test Discovery Condition – Number of Rule Changes (Dichotomized), BSRT Delayed Recall – Total Recall, SWMT – Mid-day Behavioral Index, SWMT – Mid-day Activation Index, PVT – Median Reaction Time, PVT – Mean Slowest 10% of Reaction Times: All P=NS between groups

Lettieri, 2011(47)	Observational, Retrospective analysis	Adult Military clinic patients requesting OA therapy; mild OSA N=274, mean age: 41.3±9.2 years	AASM 2007 Criteria: Hypopneas identified using nasal pressure catheter and thermistor; Defined using arousal and/or 3% /4% desaturation	Adjustable OA or Fixed OA, duration not specified No control group	ESS: baseline=14.4±4.4 to 9.8±3.9 on adjustable OA baseline = 14.2±5.6 to 10.8±4.4 on fixed OA
Tuomilehto, 2009(48)	Randomized Clinical Trial	Adults 18-65 years from outpatient clinics of ENT and Respiratory medicine, AHI 5 to <15 ;intervention group, N=35 (Mean age: 50.9±8.6 years), control group N=37 (Mean age: 51.8±9.0 years)	Hypopneas identified by nasal pressure; defined using 4% oxygen desaturation	Very low calorie diet+ Lifestyle modification vs. Lifestyle modification alone for 12 months	Weight Change (kg) Intervention= -10.7±6.5 vs. control = -2.4±5.6, p<0.001 ESS: P=NS between groups; 15D Questionnaire for QoL at 3 months: sleeping (p=0.016) and elimination (p=.017) at 3 months
Tuomilehto, 2010(49)	2 year follow up of participants reported in Tuomilheto, 2009	Intervention group, N=35, mean age: 51.8±9.0 years, control group N=36, mean age: 51.7±8.8 years; Same cohort as in Tuomilheto, 2009	Hypopneas identified by nasal pressure; defined using 4% oxygen desaturation	Very low calorie diet+ Lifestyle modification vs. Lifestyle modification alone, 24 month follow up after *1 year of active intervention*	Weight Change (kg) Intervention= -7.3±6.5 vs. control = -2.9±7.5, p=0.01 No significant change in ESS: between intervention and control groups: 0.6 (95% C.I.:-1.3, 2.5).

Tuomilheto, 2014(50)	5 year follow up of participants reported in Tuomilheto, 2009	N=28 intervention group, N=29 control group, group Same cohort as in Tuomilheto, 2009	Hypopneas identified by nasal pressure; defined using 4% oxygen desaturation	Very low calorie diet+ Lifestyle modification vs. Lifestyle modification alone, 60 month follow up after *1 year of active intervention* Successful weight loss (≥ 5% of baseline) regardless of group assigned to. Comparator Unsuccessful weight loss regardless of group assigned to.	No significant difference in ESS at baseline between intervention and control groups, 10.1±5 vs. 9.9±5. No significant difference in ESS between successful weight loss and unsuccessful weight loss groups: -1.1, p=ns.
Yaremchuk, 2011(51)	Observational, retrospective	ENT surgery clinic population (Mean age: 45.0±9.6 years); AHI 5 to 15: N=6	Not provided	6 weeks post surgery (UPPP, tonsillectomy, tonsillectomy or radiofrequency ablation of base of tongue) vs. baseline No control group	ESS: Change from pre to post = 7.3±3.5, p=0.0001

*Data provided as Mean±SD unless otherwise indicated.

AASM American academy of sleep medicine; AHI Apnea-hypopnea index; BSRT Buschke Selective Reminding Test-Sum Recall; BVRT Benton visual retention test; CI Confidence interval; CPAP Continuous positive airway pressure; ENT Ear-nose-throat; ESS Epworth sleepiness scale; FOSQ Functional outcomes of sleep questionnaire; GHQ-28 General health questionnaire-28; HADS Hospital anxiety and depression

scales; IQ Intelligence quotient; MSLT Mean sleep latency test; MWT Maintenance of wakefulness test; N sample size; NHP Nottingham health profile; NS Not significant; SaO2 oxygen saturation; OA Oral appliance; OSA Obstructive Sleep Apnea; PASAT Paced auditory serial addition test; PVT Psychomotor vigilance testing; QOL Quality of life; RCT Randomized controlled trial; RVIPT Rapid visual information processing test; SD Standard deviation; SE Standard error; SAQLI Sleep apnea quality of life index; SF-36 Short Form;Medical Outcomes Survey; SOL Sleep onset latency; SE Standard error; SWMT Sustained working memory test; UMACL UWIST mood adjective checklist; UPPP Uvolopharyngopalatoplasty

Table E5. Studies pertinent to the question: *Does mild OSA in comparison to the absence of OSA contribute to adverse long-term cardiovascular outcomes such as hypertension, coronary artery disease, cerebrovascular events, arrhythmias, and cardiovascular and all-cause mortality?*

Author Year	Study Type/Analysis & Source of study population	Participants*	Event Identification Methodology	Major Results
Hypertension				
Prospective Cohort Studies				
Cano Pumarega, 2011(52)	Prospective cohort; mean follow-up 7.5 years	Age 30-70 years, RDI 3–6.9, N= 417; RDI 7–13.9, N=247; population sample (Vittoria cohort)	Respiratory polygraphy using MESAM IV Sitting BP using standard methodology.	Hypertension defined as a BP ≥140/90 mm Hg or the use of antihypertensive medications. OR for incident hypertension-RDI 3–6.9: 1.08 (0.77–1.52); RDI 7–13.9: 0.90 (0.61–1.34). There were no significant sex differences.
Hla, 2008(53)	Prospective cohort, followed over 7.2 years	Age 52 (8) years, AHI 5-15, mild OSA sample size not noted; population sample; (this is the same population as in Peppard, 2000 (54) with additional analysis for nondipping BP)	Hypopneas identified using nasal pressure catheter and oral and nasal thermistor and RIP; defined as decrease in respiratory effort with > 4% desaturation. Measured 24-hour ambulatory BP.	OR of incident nondipping-(Systolic BP nondipping was defined as mean systolic sleep BP/mean systolic wake BP ratio greater than 0.9. Diastolic BP nondipping was defined similarly using mean diastolic sleep and wake BP). Systolic nondipping-baseline AHI 5 to < 15 vs. <5: 3.1 (1.3-7.7), n=39; Diastolic nondipping-baseline AHI 5 to < 15 vs. <5: 2.0 (0.7, 5.6), n=43 Adjusted for relevant covariates.

Marin, 2012(55)	Prospective cohort; median follow up 12.2 years	Mild OSA: Non-eligible for CPAP, age 49.2±10.8 years, N= 276; declined CPAP N= 11; clinic sample	Hypopnea identified using airflow by nasal and oral pressure sensor and RIP; defined as discernible reduction in airflow or thoracoabdominal excursion and with 4% desaturation. BP measured using standard methodology	Hypertension defined as a BP ≥140/90 mm Hg or treatment with antihypertensive medications. Crude incidence rate, number per 100 person-years: 3.02 in patients ineligible for CPAP, 2.88 in patients who declined CPAP, 4.05 in patients non-adherent to CPAP, and 2.12 in patients treated with CPAP, p=ns comparing the rate of incident hypertension in CPAP therapy group with the remaining groups. Adjusted for relevant covariates. Adjusted OR for incident hypertension in patients ineligible for CPAP, AHI 5–14.9 vs. <5 and ESS <11: 1.24 (0.89 - 1.73), N=218; AHI 5–14.9 vs. <5 and ESS >11: 0.76 (0.39 - 1.56), N=58
O'Connor, 2009(56)	Prospective cohort; mean follow-up 5.2 years	Age>40 years, mild OSA N=355, 23.4% men and 26.8% women with mild OSA had hypertension at 2nd follow-up; population sample; multicenter (Sleep Heart Health Study)	Hypopnea identified using nasal-oral thermocouple and RIP; defined as 70% reduction in amplitude of the thermocouple or thorax/abdominal inductance band signals and ≥ 4% desaturation. BP: average of 2nd and 3rd measurements.	Hypertension defined as a BP ≥140/90 mm Hg or the use of antihypertensive medications. OR for incident hypertension among subjects who were normotensive at baseline: Males with AHI 5 to < 15 vs. <0-4.9: 0.96 (0.68–1.36); females with AHI 5 to < 15 vs. <0-4.9: 0.83 (0.59–1.18). Results were not altered

				when stratified by BMI, age, sleepiness or in subjects without baseline hypertension. Regression adjusted for relevant covariates.
Peppard, 2000(54)	Prospective cohort; followed over 4-8 years	Age at baseline 50±8 years, mild OSA N=132; population sample; (Wisconsin Sleep Cohort)	Hypopneas identified using nasal pressure catheter and oral and nasal thermistor and RIP; defined as an discernible reduction in the sum amplitude of the rib-cage plus the abdominal excursions on respiratory inductance plethysmography and with 4 percent desaturation. BP-2-3 readings using standard methodology	OR for incident hypertension (defined as a BP at least 140/90 mm Hg or the use of antihypertensive medications):AHI 5-14.9 vs. 0: 2.03 (1.29-3.17) BP 160/100 mm Hg or the use of antihypertensive medications: AHI 5-14.9 vs. 0: 1.92 (1.09 to 3.39) Regression adjusted for relevant covariates.
Cross-sectional studies				
Abe, 2010(57)	Cross-sectional	Age 50.0±18.4 years, mild OSA N=17; clinic/hospital sample	Hypopneas identified using nasal pressure transducer and airflow sensor thermocouple; defined as discernible 50% decrease in the amplitude of a valid measure of breathing. BP measurement	Hypertension defined as BP ≥130/85 mmHg or use of antihypertensive medications. Percent with hypertension: AHI >5-<15 vs. <5: 18.8% vs. 13.6%, p=ns BP was not the primary outcome.

			method not specified.	
Bixler, 2000(58)	Cross-sectional	Age 20-88 years, mild OSA, AHI 0.1-14.9, N=164; population sample	Hypopnea identified by nasal and oral thermistors; defined using 50% decline in oral or nasal thermistor flow and 4% oxygen desaturation Evening supine BP, 3 readings	OR for hypertension (defined as BP ≥ 140/90 or use of anti-HTN medications) AHI 0.1-14.9 vs. 0.0: 2.29 (1.43-3.61); Mild SDB, BMI and age interaction: OR 1.3 (1.05-1.63); mild SDB and age interaction: OR 0.93 (0.90-.96) OR in snorers: 1.56 (1.09-2.20). The association with hypertension was stronger in young individuals, especially in those who were normal weight.
Cui, 2008(5)	Cross-sectional	Adult females, age 56±0.4 years, mild OSA ODI 5-9, N=492; population sample, multicenter	No measurement of flow. Oxygen desaturation index (ODI) defined as ≥3% drops in *S*pO2 during sleep. Sitting BP between 8:00 AM and 4:00 PM	OR for hypertension (defined as BP ≥ 140/90 or use of anti-hypertensive medications), ODI 5-9 vs. <5: 1.1 (0.9–1.4). Excluded patients with stroke and coronary artery disease. Pulse oximetry may underestimate the respiratory events during sleep compared with PSG.
Duran, 2001(6)	Cross-sectional	Age 30 to 70 years, white, mild OSA N=115; population sample	Hypopnea identified by nasal and oral thermistor; defined as 50% reduction in airflow and >4% desaturation	OR for hypertension (defined as BP ≥ 140/90 or use of anti-HTN medications) AHI 5-14.9 vs. 0.0: 1.30 (0.54 to 4.14)

			and/or an arousal. Sitting BP measured using standard methodology.	
Grote, 1999(59)	Cross-sectional	Age 49.7±6.9 years, mild OSA AHI 5 to <10, N=68 with prior HTN, N=101 without prior HTN; clinic sample	Hypopneas identified using MESAM 4; defined using 4% desaturation. Morning sitting on two consecutive days	OR for hypertension (defined as BP ≥ 140/90) RDI 5 to 10 vs. <5: 1.25 (0.8-2.0) OR for hypertension (defined as BP ≥ 160/95) RDI 5 to 10 vs. <5: 1.52 (1-2.3), p=0.054 OR for younger (< 50 yr) was 2.95 vs. 0.81 for older (> 50 yr) patients with mild OSA. Risk of hypertension was increased in younger compared with older patients.
Haas, 2005(60)	Cross-sectional	Mild OSA, age category 40-59 years: N= 557, ≥60 years: N=1180; population sample (SHHS), multicenter	Airflow by airflow measured by oronasal thermocouples, hypopnea as a 30% reduction in airflow or thoracoabdominal excursion and 4% oxygen desaturation. BP was average of 2nd and 3rd readings	Systolic/diastolic hypertension (SBP≥140 and DBP≥ 90 mm Hg) or ISH (SBP ≥140 and DBP<90 mm Hg. Age ≥60 y: No association between AHI and either systolic/diastolic hypertension, AHI 5-14.9 vs. 0.0 to <0: OR 0.93 (0.55–1.55) or ISH OR: 1.14 (0.75–1.75) Age 40-59 y: the odds of systolic/diastolic hypertension increased significantly with AHI for systolic/diastolic hypertension, AHI 5-14.9 vs. 0.0 to <1.5: OR 1.78 (1.09–2.92) but not for ISH OR: 1.14 (0.75–1.75)

				Regression adjusted for gender, race, age, BP medication use, diabetes, BMI, waist:hip ratio, smoking, and alcohol consumption.
Kapur, 2008(61)	Cross-sectional	All adults, population sample, multicenter. Mild OSA AHI 5-14.9 and frequently sleepy (≥5 days/mo), N=244 vs. Not frequently sleepy (<5 days/mo.), N=1491: 31.0 vs. 28.4 %, p<0.001. AHI 5-14.9 and ESS >10, N=463 vs. ≤10, N=1272: 51.5 vs. 21.1%, p<0.001	Hypopnea identified using nasal-oral thermocouple and RIP; defined as 70% reduction in amplitude of the thermocouple or thorax/abdominal inductance band signals and ≥ 4% desaturation. BP: average of 2nd and 3rd measurements.	OR for hypertension (defined as BP ≥ 140/90 or current antihypertensive medications):AHI 5-14.9 vs. <1.5 and frequently sleepy: 1.26 (0.77–2.07); AHI 5-14.9 vs. <1.5 and not frequently sleepy: 1.16 (0.97–1.40) OR for hypertension-AHI 5-14.9 vs. <1.5 and ESS>10: 1.15 (0.80–1.65); AHI 5-14.9 vs. <1.5 and ESS<10: 1.20 (0.99-1.46) Regression models were adjusted for relevant covariates. Overall, frequently sleepy subjects showed an increase in risk for hypertension with increase in AHI severity in contrast to not frequently sleepy subjects but the effect was not significant in patients with mild OSA.
Mason, 2011(19)	Cross-sectional	Adults age 18-75 years with abdominal aortic aneurysm, mild OSA AHI 6-15,	Hypopneas identified using nasal pressure canula (limited channel study);	HTN (defined as BP ≥ 140/90 or current antihypertensive medications)-

		N=43 BP: average of 3 readings at study visit; clinic sample, multicenter	defined as 50% reduction in airflow with ≥ 4% desaturation. Three consecutive BP measurements.	AHI 6-15 vs. 0-5: Systolic BP: 140.7 (125.7-149.3) vs. 137.7 (120.7-152), p=ns Diastolic BP: (72.7-89) vs. 80.5 (74-88.2), p=ns Percent with hypertension:88.4 vs. 82.9, p=ns BP was not the primary outcome.
Minoguchi, 2007(21)	Cross-sectional	Males, age 47.6±1.9 years, mild OSA N=26, clinic sample	Hypopnea identified by nasal and oral thermistors; defined as a reduction in airflow with ≥4% desaturation or an EEG arousal from sleep. BP measurement methodology not specified	HTN defined as BP ≥ 140/90 or current use of anti-HTN medications AHI 5 to <15 vs. obese controls: Systolic BP: 127.9±2.5 vs. 130.4±2.8, Diastolic BP: 76.2±2.1 vs. 77.6±2.3, respectively, p=ns. BP was a secondary outcome.
Nazzaro, 2008(23)	Cross-sectional	Age 52±8 years; mild OSA N=33; clinic sample	Hypopnea identified by nasal and oral thermistor; defined as 2/3 reduction in airflow with ≥3% desaturation or awakening. Office BP at rest, average of 3 readings; ambulatory blood pressure monitoring every 20 minutes	No significant difference in systolic or diastolic BP between mild and no OSA groups. There was absence of dipping of diastolic BP in mild OSA vs. non OSA group (night diastolic BP: non OSA vs. mild OSA 69 ± 8 vs.. 74 ± 8 mmHg, p<0.05)
Nieto, 2000(62)	Cross-sectional	Age≥40 years, 54% ≥65 years,	Hypopnea identified using	OR for HTN (defined as BP ≥ 140/90) AHI 5-15 vs.

		mild OSA N=1751; population sample, multicenter	oronasal thermocouple or RIP; defined as 30% or more decline in airflow or thoracoabdominal excursion and 4% oxygen desaturation; Resting home BP, average of 2nd and 3rd readings	<1.5: 1.2 (1.01-1.42), participants taking anti-hypertensive medications were excluded from the analyses. AHI 5-15 vs. <1.5: 1.57 (1.35-1.81) when adjusted only for age, sex and ethnicity
Rola, 2007(63)	Cross-sectional	Patients with stroke or TIA, mild OSA AHI 5-10, number of patient with mild OSA not available; hospital sample	Hypopnea defined "per AASM criteria", details not provided; BP measurement methodology not specified	In patients with stroke or TIA, percentage with hypertension: AHI 5-10 vs. ≤5: 68.4% vs. 72.9%, p=ns. Demographic data were provided graphically. BP was not the primary outcome.
Samson, 2012(28)	Cross-sectional retrospective chart review	All veterans, age 55.6±11.9 years; mild OSA N=136; clinic sample	Hypopneas identified by nasal/ oral thermocouple; defined as 30% reduction in airflow and 4% desaturation; BP from chart review	Percent of patients with HTN: AHI 5-14 vs. <5: 77.9% vs. 61.8%, p=ns
Sert Kuniyoshi, 2013(64)	Cross-sectional	Patients with recent myocardial infarction with brachial measurement of flow mediated dilation, age 57±9 years mild OSA N=19; clinic	Hypopneas identified by thermistor and transduced nasal pressure; defined as >30% reduction in nasal pressure signal and ≥ 4% desaturation;	AHI ≥5-<15 vs. <5 Systolic BP: 115(104,130) vs. 118(104,130); Diastolic BP: 64(57,69) vs. 66(60,73), p=ns Percent with HTN: 58 vs. 45%, p=ns

		sample	Morning BP measured after PSG.	BP was not the primary outcome. Excluded previous diagnosis of OSA, continuous positive airway pressure treatment and 50% of events central apnea and/or Cheyne-Stokes respiration
Theorell-Haglow, 2008(65)	Cross-sectional	Females, age 50.9±9.9 years; mild OSA N=131; population sample	Hypopnea identified by oronasal thermistor and nasal flow pressure sensor; defined as ≥50% reduction in airflow amplitude compared with baseline with ≥3% desaturation or an EEG arousal. Morning supine BP	HTN defined as ≥130/90 mmHg or known hypertension or medication for hypertension; AHI 5 to <15 vs. <5: Percent with HTN: 51.9% vs. 26.9%, p<0.001
Utriainen, 2013(34)	Cross-sectional	Age 64±10 years, patients scheduled for lower limb revascularization surgery; mild OSA N=23; clinic sample	Hypopneas identified by nasal pressure transducer; defined as >50% reduction in flow with 4% desaturation. BP measurement methodology not specified.	Percent of patients with HTN, defined BP ≥130/85 or on drug treatment, AHI 5-14 vs. <5: 61 vs. 67%, p=ns
Wachter, 2013(36)	Cross-sectional	Age 67±6 years, mild OSA N=140 in patients with risk for diastolic dysfunction; clinic sample	Hypopneas identified by nasal pressure; defined as ≥50% reduction in tidal volume and ≥3% desaturation. BP measurement method not specified.	Hypertension in AHI 5-14 vs. <5: 85 vs. 87.5, p=ns

Young, 1997(66)	Cross-sectional	Age 30-60 years, AHI<2: 44.0(7.3)y N=642; AHI 2 to 5: 47.1(7.9)y, N=191; AHI 5 to 15: 47.2(7.7)y N=141; population sample	Hypopnea identified by nasal end-tidal carbon dioxide detection and oral thermistor and RIP; defined as reduction in effort and 4% desaturation Evening sitting BP, 3 readings	OR for systolic hypertension (defined as systolic BP≥ 140 or use of anti-HTN medications) AHI 5 vs. 0: 1.21 (1.1-1.34); OR for systolic hypertension (defined diastolic BP ≥ 90 or use of anti-HTN medications) AHI 5 vs. 0: 1.18 (1.07-1.30); [Young et al, 1996, OR: 3.3 (1-14)]
Coronary Artery Disease				
Prospective studies				
Gottlieb, 2010(67)	Prospective cohort; 8.7 years follow-up	Middle aged and older adults; AHI 0.1–4.9 N=829M/1605F; AHI 5.0–14.9 N=644M/610F; population sample	Hypopneas identified using thermistor; Defined as decrease in airflow or chest or abdominal plethysmography with ≥4% desaturation. CHD was defined as the first occurrence of myocardial infarction, CHD death, or coronary revascularization procedure.	OSA was associated with a modest increase in CHD risk in middle-aged men. However, all covariates in the models for mild OSA were smaller than 1.0, (no significant difference). Adjusted for age, race, BMI, smoking, total and HDL cholesterol, lipid-lowering medications, diabetes mellitus, BP, use of antihypertensive medications
Hla, 2015, (68)	Prospective cohort; 24 years follow-up	Mild OSA 5-<15/hour, N=182, age 49±8 years; population sample	Hypopneas identified using nasal and oral airflow; defined as discernible reduction in breathing (sum of chest and abdominal excursions) and	Incident rate of CHD or heart failure in mild OSA was 18.9 per 1000 person years. Adjusted risk for incident CHD or heart failure was increased in mild OSA vs. no OSA; HR, 95% CI: 1.9, 1.05-3.5 (excluded patients on

			>4% desaturation	CPAP); risk was higher in women vs. men (HR:4.6 vs. 1.1); adjusted risk for only untreated CHD, HR, 95% CI: 1.79, 0.96, 3.35
Cross-sectional studies				
Shahar, 2001(69)	Cross-sectional	Mild OSA AHI 4.5–11.0, N=, 1606 (quartile III) mean age 65 years; population cohort, multicenter	Unattended polysomnography; hypopnea identified by oronasal thermocouple; defined as 30% reduction in airflow and ≥4% desaturation	Odds of coronary artery disease in the quartile with AHI 4.4-11 vs. quartile with AHI 0-1.3 were not significantly elevated.
Samson, 2012 (28)	Cross-sectional retrospective chart review	All veterans, age 55.6±11.9 years; mild OSA N=136; clinic sample	Hypopneas identified by nasal/ oral thermocouple; defined as 30% reduction in airflow and 4% desaturation	No significant difference in the percent of patients with coronary artery disease in the mild OSA vs. no OSA groups
Utriainen, 2013(34)	Cross-sectional	Age 64±10 years, patients scheduled for lower limb revascularization surgery; mild OSA N=23; clinic sample	Hypopneas identified by nasal pressure transducer; defined as >50% reduction in flow with 4% desaturation.	No significant difference in percentage of patients with CAD in mild OSA vs. no OSA group.
Heart Failure				
Prospective studies				
Gottlieb, 2010(67)	Prospective cohort; 8.7 years follow-up	Middle aged and older adults AHI 0.1–4.9 N=829M/1605F; AHI 5.0–14.9 N=644M/610F; population	Hypopneas identified using thermistor; Defined as decrease in airflow or chest or abdominal plethysmography with ≥4%	OSA was significant associated with increase in the risk of incident heart failure in community-dwelling middle-aged and older men. However, all covariates in the models

		sample	desaturation. The occurrence of heart failure was based on medical history, including clinical symptoms and therapy and supportive findings from chest radiographs or cardiac functional imaging.	for mild OSA were smaller than 1.0, (no significant difference). Adjusted for relevant covariates.
Hla, 2015(68)	Prospective cohort; 24 years follow-up	Age 30-60 years, Mild OSA N=182, excluded patients on CPAP; population sample	Hypopneas identified using nasal and oral airflow; defined as discernible reduction in breathing (sum of chest and abdominal excursions) and >4% desaturation	Adjusted risk for incident heart failure was increased in mild OSA vs. no OSA; HR, 95% CI: 1.81, 1.02-3.22
Cross-sectional studies				
Abe, 2010(57)	Cross-sectional	Age 50.0±18.4 years, mild OSA N=17; clinic/hospital sample	Hypopneas identified using nasal pressure transducer and airflow sensor thermocouple; defined as discernible 50% decrease in the amplitude of a valid measure of breathing.	No difference in percentage of patients with heart failure in mild vs. no OSA groups.
Shahar, 2001(69)	Cross-sectional analysis	Mild OSA AHI 4.5–11.0, N=1606 (quartile III) mean age 65; population sample	Unattended polysomnography; hypopnea identified by oronasal thermocouple; defined as 70% airflow and ≥4%	Odds of heart failure in the quartile with AHI 4.4-11 vs. quartile with AHI 0-1.3 were not significantly elevated.

			desaturation	
Samson, 2012(28)	Cross-sectional retrospective chart review	All veterans, age 55.6±11.9 years; mild OSA N=136; clinic sample	Hypopneas identified by nasal/ oral thermocouple; defined as 30% reduction in airflow and 4% desaturation	No significant difference in the percent of patients with heart failure in the mild OSA vs. no OSA groups
Wachter, 2013(36)	Cross-sectional	Age 67±6 years, mild OSA N=140 in patients with risk for diastolic dysfunction; clinic sample	Hypopneas identified by nasal pressure; defined as ≥50% reduction in tidal volume and ≥3% desaturation.	No significant difference in ejection fraction between normal and mild OSA groups.
Combined Cardiovascular Endpoints				
Prospective studies				
Korostovtseva, 2011(70)	Prospective cohort study, 46.4 months follow-up	Total 234 hypertensive patients, mild OSA N=27, median age for the cohort 54.0 years; clinic sample	Hypopneas identified using nasal canula. Defined >50% reduction in flow and ≥4% oxygen desaturation. The primary endpoint was a composite of cardiovascular death, fatal/non-fatal myocardial infarction and stroke.	Presence of mild and moderate (separated) did not affect survival. OR for mild OSA was 8.59 (0.999–73.82, p=0.5) although similar to severe OR 9.2 (1.176–72.002; p=0.034), for mild it was not significant (high variability). Adjusted for sex, age, BMI, duration of hypertension, smoking, alcohol use, physical activity level, family history of cardiovascular diseases, current coronary heart disease, glucose metabolism.
Marshall, 2014(71)	Prospective cohort study; 20-year follow-up	400 residents of the Western Australian town of Busselton, N=81 patients with mild OSA,	Respiratory disturbances were defined as oxygen desaturations ≥ 3% from the preceding baseline level that	Mild OSA was not associated with increased cardiovascular events Adjusted HR, 95% CI for CV Events: 1.0, 0.60-1.7; Strokes: 1.0, 0.39-2.7;

		age 54.3±7.3 years; population sample	were accompanied by either (a) an increased heart rate ≥ 10 beats/min and/or (b) a burst of snoring associated with commencement and termination of the desaturation event . Composite cardiovascular outcome: coronary heart disease, stroke, congestive heart failure, peripheral arterial disease or death from cardiovascular disease	Coronary Heart Disease: 0.99, 0.24-4.6 Adjusted for age, gender, BMI, smoking status, total cholesterol, high density lipoprotein cholesterol, mean arterial pressure, diabetes, doctor-diagnosed angina (yes/no), mortality, stroke, and CHD models a history of cardiovascular disease (via record linkage yes/no).
Shah, 2010(72)	Prospective cohort; 2.9 years follow-up	1,436 patients ≥ 50 years of age; N=342 with mild OSA, clinic sample	Hypopneas identified using nasal and oral airflow using pressure transducer and thermistor; defined as 30% reduction in airflow for at and ≥4% Combined coronary events (myocardial infarction, coro-nary artery revascularization) or cardiovascular death.	Mild OSA was independently associated with coronary events or death from cardiovascular causes (combined endpoint), HR, 95% CI: 2.22, 1.10–4.45. Adjusted for age, sex, race, smoking status, alcohol consumption status, BMI, diabetes mellitus, atrial fibrillation, hyperlipidemia, and hypertension.
Yaggi, 2005(73)	Prospective cohort study; 48 months of follow-up	N=1022, mean age 60 years; 697 had OSA, N=258 with mild OSA AHI 4–12; age for mild group not given;	Hypopnea was defined by a decrease in airflow by 30% for at least 10 sec, and associated with	The risk of stroke or death in patients in the most severe quartile of sleep apnea was three times that in the controls. Mild OSA (AHI

		clinic sample	oxygen desaturation of 4% or more	4-12) was not associated with the aforementioned combined events: (hazard ratio 1.75; 0.88–3.49). Age, sex, race, smoking status, alcohol-consumption status, BMI and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation.
Retrospective cohorts				
Hudgel, 2012(74)	Retrospective review of sleep center data linked with hospital EMR; 8 years of follow-up	Age 50.1 ± 12.0 years; mild OSA N=371 and non-apneic snorers N=494; clinic sample	Hypopneas identified using nasal canula and nasal/oral thermistor; Defined as 50% to 80% reduction in flow and >3% desaturation or an arousal. Combined endpoints: all-cause mortality, myocardial infarction, cerebral vascular accident, and pulmonary embolus	No significant correlations were seen between any level of OSA severity and any outcome. For all cause mortality: Hazard ratio for mild OSA: 0.96 (0.52- 1.74). For myocardial infarction: 0.66 (0.33- 1.30). Cerebrovascular accident: 0.93 (0.48- 1.79). Of note, several OSA patients were using CPAP. Adjusted for age, African American race, male gender, BMI, history of specific risk factors, and prior history of cardiopulmonary disease.
Kendzerska, 2014(75)	Retrospective review of cohort with data from sleep clinical database and health administrative data;; 68 months follow-up	Middle aged, 62% men, age 49. 9 ±41 years for the cohort Mild OSA N= 2703 (26.6%), clinic sample	Hypopneas identification method not provided. Hypopnea was defined by: (i) a decrease of more than 50% of the baseline amplitude of breathing lasting 10 seconds or longer; or (ii) a clear but smaller	The authors found that 1,172 (11.5%) of 10,149 participants experienced the composite outcome (hospitalization due to myocardial infarction, stroke, or exacerbation of congestive heart failure; a revascularization procedure (percutaneous coronary intervention, coronary artery bypass

			decrease in amplitude lasting for at least 10 seconds that is associated with either an SaO2 drop of >3% or an arousal	graft surgery); or all-cause death. No association of mild OSA (with composite endpoint compared to those without OSA. Adjusted for age, sex, smoking status, BMI, AHI, TST, and daytime somnolence, prior HTN, diabetes, MI, stroke, and CHF.
Cerebrovascular Events				
Prospective studies				
Redline, 2010(76)	Prospective cohort study; 8.7 months of follow-up	N=5422 total participants Age, median/ interquartile range 72 (68–77) years for entire cohort; population sample	Hypopneas identified using thermistor; Defined as a clear decrease in flow with ≥3% desaturation.	Mild OSA (II quartile – AHI 4.05 to <9.5) was not associated with stroke in both sex (hazard ratio 1.86; 0.67–5.12). Adjusted for age, body mass index, smoking status, systolic blood pressure, use of antihypertensive medications, diabetes status, and race.
Marshall, 2014(71)	Prospective cohort study; 20-year follow-up	400 residents of the Western Australian town of Busselton, N=81 patients with mild OSA, age 54.3±7.3 years; population sample	Respiratory disturbances were defined as oxygen desaturations ≥ 3% from the preceding baseline level that were accompanied by either (a) an increased heart rate ≥ 10 beats/min and/or (b) a burst of snoring associated with commencement and termination of the desaturation	Mild OSA was not independently associated with incident stroke after a 20-year follow-up of 397 residents (HR 1.0, 95%CI: 0.39-2.7) Adjusted for age, gender, BMI, smoking status, total cholesterol, high density lipoprotein cholesterol, mean arterial pressure, diabetes, doctor-diagnosed angina (yes/no), mortality, stroke, and CHD models a

			event .	history of cardiovascular disease (via record linkage yes/no).
Valham, 2008 (77)	Prospective cohort; 10 years of follow-up	Total of 392,subjects with coronary heart disease referred for coronary angiography, age 60.7±7.0 years; number with mild AHI not provided; clinic sample	Hypopnea identified with oronasal airflow; Defined as a 50% reduction in air flow and ≥3% desaturation.	Mild sleep apnea is an independent risk factor for stroke among patients with coronary artery disease (hazard ratio 2.44; 1.08–5.52). Adjusted for age, body mass index, gender, left ventricular function, coronary artery intervention, diabetes mellitus, hypertension, previous stroke/transient ischemic attack, atrial fibrillation, and current smoking.
Cross-sectional studies				
Abe, 2010(57)	Cross-sectional	Age 50.0±18.4 years, mild OSA N=17; clinic/hospital sample	Hypopneas identified using nasal pressure transducer and airflow sensor thermocouple; defined as discernible 50% decrease in the amplitude of a valid measure of breathing. BP measurement method not specified.	No significant difference in percentage of patients with stroke in mild OSA vs. no OSA group.
Samson, 2012(28)	Cross-sectional retrospective chart review	All veterans, age 55.6±11.9 years; mild OSA N=136; clinic sample	Hypopneas identified by nasal/ oral thermocouple; defined as 30% reduction in airflow and 4%	No significant difference in the percent of patients with cerebrovascular events in the mild OSA vs. no OSA groups

			desaturation	
Shahar, 2001(69)	Cross-sectional	Mild OSA AHI 4.5–11.0, N=1606 (quartiles) , mean age 65 years; population sample	Unattended polysomnography; hypopnea identified by oronasal thermocouple; defined as 70% reduction in airflow and ≥4% desaturation	Odds of stroke in the quartile with AHI 4.4-11 vs. quartile with AHI 0-1.3 were not significantly elevated.
Utriainen2013, (34)	Cross-sectional	Age 64±10 years, patients scheduled for lower limb revascularization surgery; mild OSA N=23; clinic sample	Hypopneas identified by nasal pressure transducer; defined as >50% reduction in flow with 4% desaturation.	No significant difference in percentage of patients with stroke in mild OSA vs. no OSA group.
Arrhythmia				
Cross-sectional studies/analyses				
Abe 2010(57)	Cross-sectional	Age 50.0± 18.4 years Japanese, mild OSA N=197; clinic sample	Hypopneas identified using nasal canula and thermistor; defined as 50% reduction in flow	Trend analysis showed association of arrhythmias found on PSG with increasing severity of OSA but there was no direct comparison of mild OSA with non-OSA group.
Mehra, 2009 (78)	Cross-sectional analysis of a prospective longitudinal cohort of elderly men (MrOS Sleep Study)	Age 76.1±5.6 years; mild OSA N=728; population sample	Hypopneas identified using nasal canula and nasal-oral thermocouple pressure; defined as reduction of more than 30 and associated with a 3% or more oxygen desaturation	Trend analysis showed an association of complex ventricular ectopy with OSA severity. However, AHI between 6.5 ≤ OAHI < 12.7 was not associated with higher arrhythmia burden compared to the lowest AHI quartile (<2.9), OR: 1.21 (0.66–2.21) for atrial fibrillation and OR: 1.18 (0.93–1.50) for complex ectopic

				events.
Samson, 2012(28)	Cross-sectional retrospective chart review	All veterans, age 55.6±11.9 years; mild OSA N=136; clinic sample	Hypopneas identified by nasal/ oral thermocouple; defined as 30% reduction in airflow and 4% desaturation	No significant difference in the percent of patients with atrial fibrillation in the mild OSA vs. no OSA groups
Mortality				
Prospective studies				
Lee, 2013(79)	Prospective cohort; 61.4 months of follow-up	Korean cohort, mean age 56 years; mild OSA N=550; clinic sample	Hypopneas identified using nasal airflow, mouth airflow (thermistor); Defined as reduction in flow with oxygen saturation ≥ 4%.	No increase in CV mortality in patients with mild OSA, adjusted HR 95% CI:0.32, 0.03-3.57 No increase in all-cause mortality in mild OSA vs. no-OSA, adjusted HR, 95% C.I.: (0.91, 0.36-2.28) Adjusted for age, sex, BMI, hypertension, diabetes, cardiovascular disease, previous history of stroke, and treatment.
Marshall, 2014(71)	Prospective cohort (Busselton Cohort) mean follow-up 13.4 years 20 years follow-up	Mild OSA N=81 of 393 participants with, age 54.3±7.3 years, population sample	MESAM IV device, RDI defined as oxygen desaturations of ≥ 3% accompanied by either a) an increased heart rate ≥ 10 beats/min and/or b) a burst of snoring associated with commencement and termination of the desaturation event	No increase in all-cause mortality for mild OSA vs. no OSA, adjusted HR, 95% CI: 0.51; 0.27-0.99.
Punjabi, 2009(80)	Prospective cohort; 8.2 years of follow-	Mild OSA N= 1,797; age 64.8 (10.6) years;	Hypopneas identified using oronasal	No increase in all-cause mortality for mild OSA vs. no OSA, adjusted HR,

	up	population sample (SHHS)	thermistor; Defined as 30% reduction in airflow or thoracoabdominal movement	95% CI: 0.93 (0.80–1.08
Young, 2008(81)	Prospective cohort; 18 years of follow-up	Mild OSA N=220 participants; age 50±8 years; popu-lation sample (Wisconsin Sleep Cohort)	Hypopneas identified using oronasal thermistor; Defined as discernible reduction in breathing (sum of chest and abdominal excursions) with ≥ 4% desaturation.	No increase in increase CV mortality, HR 1.8, 95% CI 0.7, 4.9 or all-cause mortality, adjusted HR, 95% C.I.: 1.6, 0.9-2.8. Adjusted for age, age2, sex, body mass index, and body mass index.

*Data provided as Mean±SD unless otherwise indicated

AHI Apnea-hypopnea index; BP Blood pressure; BMI Body mass index; HTN hypertension; CAD Coronary artery disease; CHD Coronary heart disease; CHF Congestive heart failure; CI Confidence interval; CV Cardiovascular; CPAP Continuous positive airway pressure; EEG Electro encephalogram; ESS Epworth sleepiness scale; HDL High density lipid; HR Hazard ratio; ISH Isolated systolic hypertension, MI Myocardial infarction; N sample size; ODI: Oxygen desaturation index; OR: Odd ratio; OSA Obstructive sleep apnea; RDI Respiratory disturbance index, RIP Respiratory inductance plethysmography; SD Standard deviation, SDB Sleep disordered breathing; SHHS Sleep heart health study; TIA Transient ischemic activity; TST Total sleep time; Y Years

Table E6. Studies pertinent to the question: *Does treatment of mild OSA in comparison to no treatment prevent or reduce adverse cardiovascular outcomes, including hypertension, coronary artery disease, cerebrovascular events, arrhythmias, and cardiovascular and all-cause mortality?*

Author Year	Study Type	Participants*	Event Identification Methodology	Intervention and Comparator	Major Results*
Jaimchariyatam, 2010(82)	Retrospective cohort, single center	N=255 Patients with mild OSA without pre-existing cardiovascular or cerebrovascular disease, diabetes, or hyperlipidemia, age 44.74 years no CPAP group, 45.46 years CPAP group	Flow measurement: using a thermistor, nasal pressure transducer Hypopnea defined: 50% reduction and 3% desaturation or followed by an arousal Mean blood pressure (MBP) was the mean of at least two MBP values obtained within a 3 month period prior to the day of the diagnosis of OSA or CPAP use and at least two MBP values within 3 months prior to the day of the last visit.	Intervention CPAP treatment Comparator No CPAP treatment Follow up after 2 years	Change in mean arterial blood pressure: On CPAP vs. No CPAP (-1.97 vs. +9.61 mm Hg; p < 0.001) With propensity matched groups: Net change in mean blood pressure in CPAP. No CPAP group: -11.97 mm Hg (95% CI: -14.02 to -9.92; p < 0.0001)
Hudgel, 2012(74)	Retrospective cohort, single center	N=1519 entire cohort, mild OSA N=372, age 50.1±12.0 years Patients with primary snoring or sleep apnea	Hypopnea identified using airflow by nasal and oral thermistor and nasal pressure sensor (type not specified); defined as 50% reduction in flow and 3% desaturation or an arousal.	Intervention CPAP treatment≥4 hours/night Comparator No CPAP treatment (refused CPAP or < 4 hours	All Cause Mortality: HR 1.61 (0.48 - 5.44) for CPAP ≥ 4 h/night compared to CPAP < 4h/night.

				therapy/night)	
Marin, 2012(55)	Prospective observational cohort; median follow up 12.2 years	AHI 5–14.9, adherent to CPAP, N= 57; non-adherent to CPAP N= 11; clinic sample	Hypopnea identified using airflow by nasal and oral pressure sensor and RIP; defined as discernible reduction in airflow or thoracoabdominal excursion and with 4% desaturation. BP measured using standard methodology	Intervention: CPAP therapy in patients with mild OSA and coexisting daytime sleepiness that interfered with daily activities	No significant differences (p=0.15) in crude incident rates of incident hypertension in patients ineligible for CPAP, declined CPAP or non-adherent to CPAP or treated with CPAP. Adjusted risk for incident HTN in CPAP-adherent mild OSA group alone was not provided.
Tuomilheto, 2009(48)	Randomized trial, single center	N=81 (72 completed study) Participants with mild OSA age 50.9 (8.6) years control group, 51.8 (9.0) years intervention group	Hypopnea identified using airflow by nasal and oral sensor (type not specified); defined as 30% reduction in flow and 4% desaturation. 24 hr BP measurement described	Intervention Very low calorie diet (VLCD) for 12 weeks followed by lifestyle modifications for 1 year, mean weight reduction within 1 year was 11 kg, Comparator/control Usual care arm/counselin	After 1 year, weight -2.4 (5.6) in control group and -10.47 (6.5) kg in intervention group, adjusted p<0.001 After 1 year, AHI 0.3 (8.0) control group and -4.0 (5.6)in intervention group, p=0.017 Systolic BP (mean change

				g by physician and nurse	± SD) Intervention (-1.1±19.6 mm Hg) vs. Control (-1.7 ± 14.7 mm Hg). Adjusted p-value 0.47. Diastolic BP (mean change ± SD) Intervention (-0.4±12.6 mm Hg) vs. Control (-1.9±10.6 mm Hg). Adjusted p-value 0.87. Adjusted for age, sex, waist circumference, and baseline value.
Tuomilheto, 2010(49)	Randomized trial, follow up after 2 years of the subjects reported in Tuomilheto, 2009	N=81 (71 completed study) Same cohort in Tuomilheto, 2009	Same cohort as in Tuomilheto, 2009 (84)	Intervention Very low calorie diet for 12 weeks followed by lifestyle modifications for 2 years Comparator/control Usual care arm	Systolic BP (mean change ± SD) Intervention (-3.0±11.3 mm Hg) vs. Control (+0.6±8.5 mm Hg). Adjusted p-value 0.041. Diastolic BP (mean change ± SD) Intervention (-1.7±6.9 mm Hg) vs. Control (-0.03±5.4 mm Hg). Adjusted

					p-value 0.12. Adjusted for age, sex, waist circumference, and baseline value.
Tuomilheto,2014(50)	Prospective cohort 5 year follow up of the subjects reported in Tuomilheto, 2009	N=57 with mild OSA	Same cohort as in Tuomilheto, 2009 (84)	Intervention Successful weight loss (≥ 5% of baseline) regardless of group assigned to. Comparator Unsuccessful weight loss regardless of group assigned to.	Systolic BP (mean change ± SD) Successful group (+0.7±14.1 mm Hg) vs. Unsuccessful group (0.3±25.7 mm Hg). Adjusted p-value 0.74. Diastolic BP (mean change ± SD) Successful group (+0.0±9.0 mm Hg) vs. Unsuccessful group (-.3±9.7 mm Hg). Adjusted p-value 0.81.
Wang, 2012(83)	Non-randomized before/after surgery; single center	N=180 Patients with a mild OSA and diagnosis of essential hypertension, age 51.0 ±10 years	Hypopnea identified using specified); defined as 50% reduction in flow and 3% airflow by nasal and oral sensor (type not desaturation. 24 hr BP measurement described	Intervention Upper airway surgery by indication (UPPP, HPS, RFTBA with tongue-base or hyoid suspension)	Mean 24h Pre-operative vs. Post-operative Systolic BP (160±5 mm Hg vs. 144±1 mm Hg; p< 0.05).

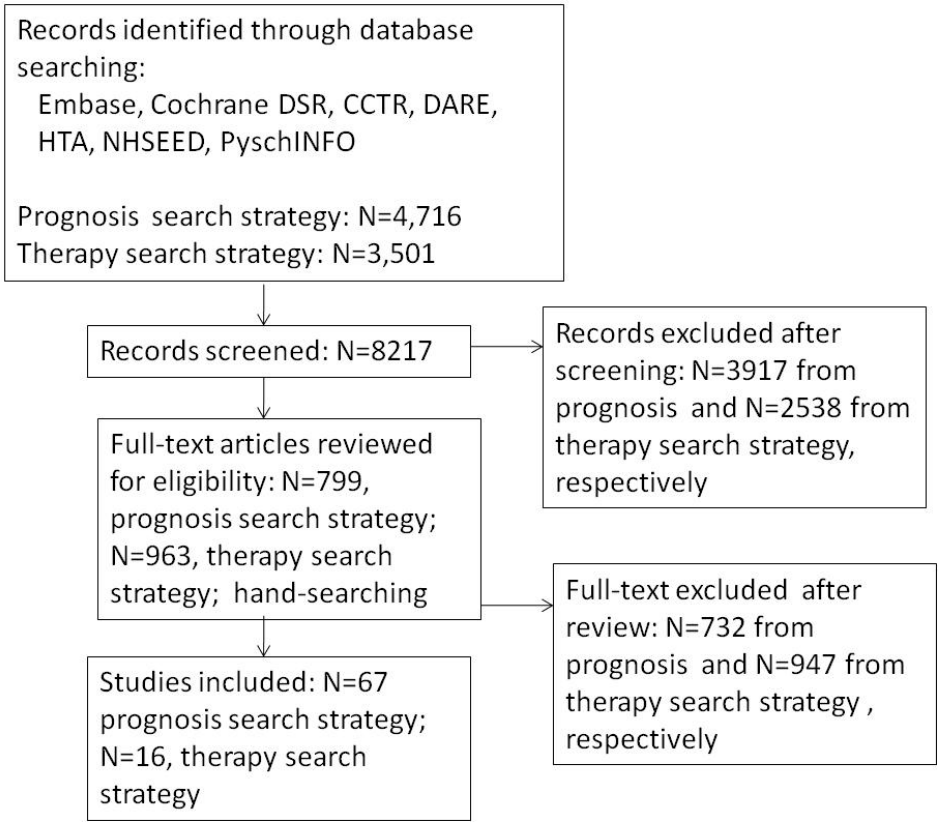
				Comparator Prior to surgery and no OSA group	Diastolic BP (92±8 mm Hg vs. 90±12 mm Hg; p > ns) Systolic BP mild OSA vs. no OSA: 160±5 vs. 152±6 vs. mm HG, p<0.05 Daytime Pre-operative vs. Post-operative Systolic BP (165±11 mm Hg vs. 148±10 mm Hg; p < 0.05). Diastolic BP (98±15 mm Hg vs. 94±10 mm Hg; p < 0.05) Nocturnal Pre-operative vs. Post-operative Systolic BP (148±13 mm Hg vs. 139±14 mm Hg; p < 0.05). Diastolic BP (88 ± 8 mm Hg vs. 86±11 mm Hg; p ns Systolic BP mild OSA vs. no OSA:

					148±13 vs. 138±11 mmHg, p<0.05Diastolic BP mild OSA vs. no OSA: 88±8 mm Hg vs. 82±10 mm Hg; Dipping status Pre-operative vs. Post-operative Dipper profile: 48.3% vs. 61.7% (p < 0.05)

*Data provided as Mean±SD unless otherwise indicated

AHI Apnea-hypopnea index; BP Blood pressure; CI Confidence interval; CPAP Continuous positive airway pressure; HPS Hard palate shortening; HR Hazard ratio; HTN hypertension; MBP Mean blood pressure; N sample size; OSA Obstructive sleep apnea; RFTBA radiofrequency tongue base ablation ; UPPP uvulopalatopharyngoplasty; VLCD Very low calorie diet

Figure 1. Flow chart of results



DSR Database of Systematic Reviews; Cochrane Central Register of Controlled Trials (CCTR); Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) and National Health Service Economic Evaluation Database (NHSEED)

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