



CLINICAL REVIEW

Nasal continuous positive airway pressure (nCPAP) treatment for obstructive sleep apnea, road traffic accidents and driving simulator performance: A meta-analysis

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ARTICLE INFO

Article history:

Received 29 July 2010

Received in revised form

27 October 2010

Accepted 28 October 2010

Available online 30 December 2010

Keywords:

Obstructive sleep apnea

Nasal continuous positive airway pressure

nCPAP

Road traffic accidents

Driving simulator

Meta-analysis

SUMMARY

We used meta-analysis to synthesize current evidence regarding the effect of nasal continuous positive airway pressure (nCPAP) on road traffic accidents in patients with obstructive sleep apnea (OSA) as well as on their performance in driving simulator. The primary outcomes were real accidents, near miss accidents, and accident-related events in the driving simulator. Pooled odds ratios (ORs), incidence rate ratios (IRRs) and standardized mean differences (SMDs) were appropriately calculated through fixed or random effects models after assessing between-study heterogeneity. Furthermore, risk differences (RDs) and numbers needed to treat (NNTs) were estimated for real and near miss accidents. Meta-regression analysis was performed to examine the effect of moderator variables and publication bias was also evaluated. **Ten studies on real accidents (1221 patients),** five studies on near miss accidents (769 patients) and six studies on the performance in driving simulator (110 patients) were included. **A statistically significant reduction in real accidents (OR = 0.21, 95% CI = 0.12–0.35, random effects model; IRR = 0.45, 95% CI = 0.34–0.59, fixed effects model)** and near miss accidents (OR = 0.09, 95% CI = 0.04–0.21, random effects model; IRR = 0.23, 95% CI = 0.08–0.67, random effects model) was observed. Likewise, a significant reduction in accident-related events was observed in the driving simulator (SMD = –1.20, 95% CI = –1.75 to –0.64, random effects). **The RD for real accidents was –0.22 (95% CI = –0.32 to –0.13, random effects), with NNT equal to five patients (95% CI = 3–8),** whereas for near miss accidents the RD was –0.47 (95% CI = –0.69 to –0.25, random effects), with NNT equal to two patients (95% CI = 1–4). For near miss accidents, meta-regression analysis suggested that nCPAP seemed more effective among patients entering the studies with higher baseline accident rates. **In conclusion, all three meta-analyses demonstrated a sizeable protective effect of nCPAP on road traffic accidents, both in real life and virtual environment.**

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Introduction

Obstructive sleep apnea (OSA) is a common chronic disorder that affects approximately 20% of the general population if defined as an apnoea hypopnea index (AHI) ≥ 5 events/h, or 2–9% if defined as an AHI ≥ 5 events/h accompanied by at least one symptom that is known to respond to treatment, such as daytime sleepiness.^{1–3} The high prevalence rates are disturbing taking under consideration

that OSA patients have an increased risk of morbidity and mortality, particularly due to cardiovascular disease or involvement in road traffic accidents. Indeed, OSA patients are often sleepy during daytime causing traffic accidents and work injuries.^{4,5} If left untreated, OSA leads to excessive daytime sleepiness, cognitive dysfunction, impaired work performance, and decrements in quality of life.⁶

Many treatment modalities have been proposed for the treatment of OSA including dietary and lifestyle management, pharmacological agents, oral appliance devices and surgical interventions (nasal reconstruction, various uvulopalatopharyngoglossoplasty techniques, maxillomandibular manipulations, and tracheotomy). Despite the variety of alternative choices, nasal

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Abbreviations

AHI	apnea–hypopnea index
BMI	body mass index
CI	confidence interval
ESS	Epworth sleepiness scale
FP	full polysomnography
ICER	incremental cost-effectiveness ratio
IR	incidence rate
IRR	incidence rate ratio
MSLT	multiple sleep latency test
nCPAP	nasal continuous positive airway pressure
NNT	number needed to treat
OR	odds ratio
OSA	obstructive sleep apnea
PRISMA	preferred reporting items for systematic reviews and meta-analyses
QALY	quality-adjusted life-year
RD	risk difference
RDI	respiratory disturbance index
RP	respiratory polygraphy
SMD	standardized mean difference
SSS	Stanford sleepiness scale

continuous positive airway pressure (nCPAP) device remains the gold standard of treatment.^{1,7} It is indicated for mild to severe OSA patients, and it has proved to be efficient in improving symptoms and reducing the severity of a pleiad of medical conditions related to upper airway obstruction during sleep.⁸

The purpose of this meta-analysis is to estimate the extent to which nCPAP treatment affects real and near miss road traffic accident rates in OSA patients, as well as the extent to which nCPAP affects their performance in driving simulator. We also sought to estimate the number needed to treat (NNT) to avoid road traffic accidents.

Materials and methods

Data collection

The present meta-analysis was conducted in accordance to the “preferred reporting items for systematic reviews and meta-analyses” (PRISMA) guidelines.⁹ A combined computerized and manual systematic database search of medical literature was performed and the respective publications were retrieved from electronic search engines (Medline, Embase, Scopus, Google Scholar, Ovid and the Cochrane Library). “Bibliosleep”, a subject specific electronic database including sleep and sleep-related publications, as well as a series of nine peer-reviewed journals focused on sleep medicine and eight on pulmonary medicine with interest in sleep were also searched. Reference lists were thereafter systematically examined for relevant articles.

Types of studies, search terms, eligibility and exclusion criteria

Publications of interest included randomized and non-randomized studies, editorials, systematic reviews, meta-analyses, short papers, case reports, case series, letters to the editor, personal views, special communications and unpublished data. Mesh terminology used for search purposes were “CPAP”[All Fields] AND (“accident”[All Fields] OR “injury”[All Fields] OR “crash”[All Fields] OR “automobile”[All Fields] OR “motor vehicle” [All Fields]), “sleep apnea”[All Fields] AND (“accident”[All Fields] OR “injury”[All Fields] OR “crash”[All Fields] OR “automobile”[All Fields] OR “motor

vehicle” [All Fields]), “ sleep apnea”[All Fields] AND “driving”[All Fields] and “simulator”[All Fields] and “CPAP”[All Fields] AND “driving”[All Fields] and “simulator”[All Fields]. We identified all studies that evaluated the effect of nCPAP on OSA patients with respect to real and/or near miss road traffic accidents or performance in the driving simulator. Given that CPAP was first introduced in 1981,¹⁰ scientific papers published between April 1981 and July 2010 were examined and no restriction of publication language or participants’ sex or age was applied.

The studies that did not refer to OSA patients or did not report road traffic accident-related or simulated driving-related outcomes before and after use of nCPAP and studies in which OSA patients only intermittently used nCPAP were excluded. When multiple publications on the same study population were identified or study populations overlapped, only the study of larger size was included, unless the reported outcomes were mutually exclusive. Data were independently extracted and analyzed and individual study quality was assessed by two of the authors (CNA, TNS) and final decision was reached by consensus.

Data extraction

Data extracted from eligible studies included authors, study year, journal, type of study, study quality¹¹ and characteristics for nCPAP users/non-users among OSA patients, including: 1) Study descriptives; namely sample size, time period of road traffic accidents monitoring before and after nCPAP treatment, 2) Demographic variables; namely age, sex, male to female ratio and anthropometrics such as weight or body mass index (BMI), 3) Sleep apnea related variables; namely AHI and respiratory disturbance index (RDI), defined as the total number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing occurring per hour of sleep, nCPAP usage (number of hours used per night), sleep apnea diagnostic tools used for patient recruitment and sleepiness scores,¹² 4) Driving-related variables; namely number of patients with real and near miss road traffic accidents, 5) Driving simulator-related variables: number of accident-related events, tracking error (standard deviation from the center of the road) and vigilance reaction time, defined as average time needed to respond to visual stimulus for both before and after nCPAP treatment and 6) method used for data collection (self-report, state records or performance on driving simulator). The corresponding authors were contacted if the required data were not readily available in the published article and feedback was given by the authors of two studies.^{13,14}

Statistical analyses

Data synthesis and treatment effects

Three separate meta-analyses were performed according to the outcome measures under investigation. Particularly, the effect of nCPAP on the occurrence of a) real road traffic accidents, b) near miss road traffic accidents and c) accident-related events in the driving simulator was tested.

With respect to real and near miss accidents, the pooled estimate of crude odds ratios (ORs) with corresponding confidence intervals (95% CIs) was initially calculated simply based on the number of patients reporting accidents in the individual studies. Consequently, an effort was made to take into account the observation period during which the reported accidents occurred before and after nCPAP treatment. To this end, the incidence rates (IR) of real or near miss accidents before and after nCPAP were calculated, by dividing the number of patients reporting road traffic accidents by the respective person-years; thereafter, the incidence rate ratios (IRRs) for real and near miss accidents were estimated in each study

by dividing the IR after nCPAP by the IR before nCPAP. Lastly, the risk differences (RDs) were estimated and the respective NNTs were derived as the inverse of the RDs.¹⁵ In our case, NNT indicates the number of OSA patients that would have to receive nCPAP treatment in order to prevent one OSA patient to report at least one road traffic accident.

The fixed effects model or the random effects model was used for non-heterogeneous or heterogeneous data, as appropriate. An OR or IRR < 1 favored nCPAP treatment when compared with no treatment. The Z test was applied for the overall effect and the statistical significance level was set at $p < 0.05$. Data were graphically presented as forest plots.

With respect to performance in driving simulator, accident-related events before and after nCPAP use were extracted. Standardized mean differences (SMDs) and 95% CIs were then calculated as principal measures of effect size and the statistical significance level was again set at $p < 0.05$. An issue of concern in the meta-analysis of small trials with continuous outcomes is the alternative reporting of either mean or median values of the effect outcomes, a fact that forbids computation of the overall effect estimate. In order to overcome this difficulty when median values were reported as outcomes in small eligible studies (sample size < 25), a simple formula ($x = a + 2m + b/4$) was used to derive an estimate of the mean (x) on the basis of the available median (m) value, as well as the low and high end of the range of variation (a and b , respectively).¹⁶ For larger sample size studies, namely those exceeding 25 patients, the median itself was considered as reasonably approximating the mean value.¹⁶

Heterogeneity – meta-regression analysis

Heterogeneity among studies was estimated by chi-square test and Cochran Q score (reported as I^2) with corresponding p values and the level of significance set at $p = 0.10$.¹⁷ When heterogeneity was present, meta-regression analysis was undertaken to explore the association between predictor variables and the effect size; a Q model statistic was used to estimate this association.

Publication bias

Publication bias was assessed by Egger's regression,¹⁷ Duval and Tweedie's Trim and Fill test, Kendall's rank correlation coefficient¹⁷ and visual inspection of the funnel plots. Specifically, the Duval and Tweedie's Trim and Fill test estimates the number of theoretically missing studies and computes the combined effect estimate, if the meta-analysis had captured all the relevant studies and these studies were also included in the analysis.¹⁸ Furthermore, Rosenthal's "fail-safe N test" was performed for every comparison group in order to compute the number of missing studies (with mean effect of zero) that would theoretically need to be added in the analysis to yield a statistically non-significant overall effect.¹⁹

Sensitivity analysis

Sensitivity analysis was primarily performed, when heterogeneity was observed; in this instance, one-by-one exclusion of studies was performed to assess their effect on the pooled effect estimate and on heterogeneity overall. Secondly, sensitivity analysis was performed in studies reporting accident rates rather than patient experiencing accident rates by excluding the respective studies and examining their impact on the effect estimates. Pooling of individual studies through fixed or random effects models, assessment of publication bias, sensitivity and meta-regression analysis were performed using the Comprehensive Meta-analysis v2.2, (Biostat, Englewood, NJ, USA).

Results

As shown in the flow diagram (Fig. 1), after extraction and review of the abstracts, 19 articles were eventually deemed eligible out of a total of 549 potentially relevant articles of interest; out of these, in the subsequent detailed evaluation, three were found to have been performed on mutually overlapping populations^{20–22} and were therefore, also excluded. A fourth article was by necessity excluded, as no distinction was made between real and near miss accidents and the corresponding author did not provide the requested information.²³ Finally, 15 articles pertaining to a total of 21 investigations were included in the analyses.^{13,14,24–36} Specifically, ten studies including a total of 1221 patients evaluated the effect of nCPAP on reducing real accidents,^{13,14,24–30,36} five of which assessed the effect of nCPAP treatment on reducing near miss accidents among 769 OSA patients.^{14,25,28–30} Lastly, six studies examined the effect of nCPAP on the performance of 110 OSA patients in the driving simulator.^{29,31–35}

Characteristics of eligible studies

Real and near miss accidents

Among the nine eligible studies (Table 1), eight were published as original articles,^{13,14,24–27,30,36} whereas two were published as abstracts in peer-reviewed journals.^{28,29} Full polysomnography (FP) was used as the method for OSA diagnosis in eight studies,^{13,14,24–27,30,36} whereas respiratory polygraphy (RP) was alternatively used in one study.¹⁴ A pre-coded questionnaire was used and data were self-reported in all but two^{13,26} of the eligible studies. Measures of daytime sleepiness were the Epworth sleepiness scale (ESS),^{25,27,30,36} the Stanford sleepiness scale (SSS)^{14,28} and the multiple sleep latency test (MSLT)²⁴ and the vast majority of subjects pertained to male gender (83.3–100%). Details on study quality, patients' age, body mass index (BMI), AHI, use of nCPAP, definition of accidents and OSA, accident record, duration of reporting accidents before and after nCPAP are also provided in Table 1.

Performance in driving simulator

All six eligible studies (Table 2) were published as full papers, apart from one study that was published as an abstract in a peer-review journal.²⁹ The ESS was used in half of them.^{33–35} Duration of nCPAP treatment ranged among the six studies (7–276 days). Median values were reported in three studies.^{33–35}

Meta-analyses

Effect of nCPAP on real accidents

A statistically significant and sizeable reduction of real accidents among OSA patients was observed after treatment with nCPAP (OR = 0.21, 95% CI = 0.12–0.35, random effects model). Due to the observed heterogeneity ($I^2 = 48\%$, $p = 0.04$), one study, in which almost half of the subjects (49.1%) reported real accidents before nCPAP treatment,²⁴ was excluded. This led to a non-statistically significant heterogeneity ($I^2 = 21\%$, $p = 0.26$) but no significant change in the initially observed effect of nCPAP treatment (OR = 0.30, 95% CI = 0.22–0.41, fixed effects model). Regarding the assessment of publication bias, Egger's regression test was statistically significant (intercept $b = -2.03$, $p < 0.01$), whereas the rank correlation test was not significant (Kendall's tau = -0.40 ; $p = 0.11$). Furthermore, Duval and Tweedie's Trim and Fill test did not show significant modification of the pooled OR. The Trim and Fill test suggested that four studies were theoretically missing and estimated a new, imputed OR, which did not significantly differ from the original effect estimate (OR = 0.29,

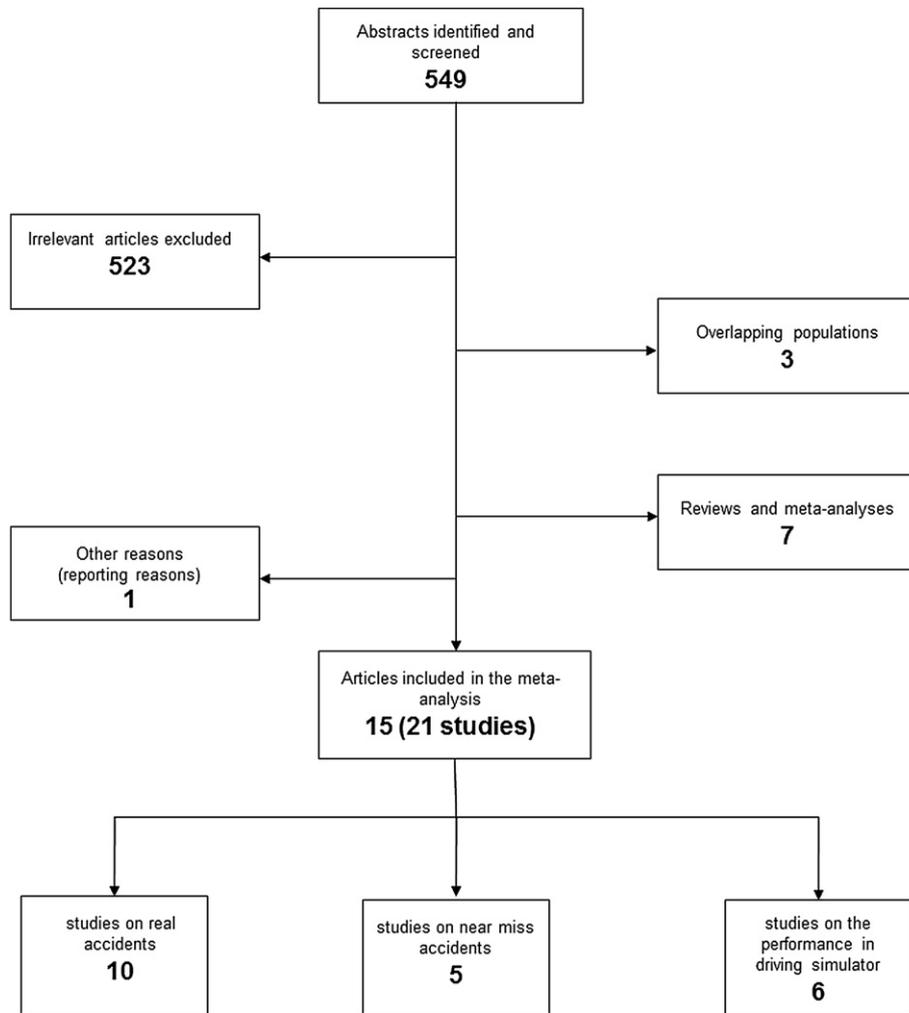


Fig. 1. Flow chart graphically presenting the selection of the eligible studies.

95% CI = 0.16–0.53, random effects model). The “fail-safe N” was equal to 195, which means that 195 theoretical null studies need to be located in order for the overall effect to be nullified. Thus, publication bias seemed to be of no major significance in the present study as the computed effect estimate seemed fairly robust. In the sensitivity analysis, the results remained practically unchanged (OR = 0.17, 95% CI = 0.09–0.31, random effects model) after the exclusion of one study¹⁴ which reported number of accidents rather than number of patients who encountered accidents.

When IRR was used, which takes into account the observed period of reporting accidents (before and after nCPAP treatment), a statistically significant but of smaller size reduction in real accidents was again noted (IRR = 0.45, 95% CI = 0.34–0.59) (Fig. 2). Fixed effects model was used in this case as no between-studies heterogeneity was found ($I^2 = 26\%$, $p = 0.20$). Again the Egger’s regression test for publication bias was nominally statistically significant (intercept $b = -1.25$, $p = 0.05$), whereas the rank correlation test was statistically significant (Kendall’s tau was -0.49 , $p = 0.04$). Duval and Tweedie’s Trim and Fill test showed that five studies were theoretically missing (new, imputed IRR = 0.49, 95% CI = 0.38–0.65), whereas the “fail-safe N” was equal to 84. The pooled RD was -0.22 (95% CI = -0.32 to -0.13 , random effects model), which corresponded to a NNT equal to five (95% CI = 3–8) OSA patients.

Effect of nCPAP on near miss accidents

A significant reduction in near miss accidents was observed after treatment with nCPAP (OR = 0.09, 95% CI = 0.04–0.21, random effects model). Again, when one study³⁰ was excluded due to the marked heterogeneity ($I^2 = 67\%$, $p = 0.02$), no between-studies heterogeneity was observed ($I^2 = 38\%$, $p = 0.19$), whereas the effect estimate remained practically unchanged (OR = 0.16, 95% CI = 0.12–0.24, fixed effects model). Worthy of note, the excluded study was characterized by a strikingly high percentage of patients reporting road traffic accidents prior to nCPAP treatment (32 out of 39 patients). In line with this observation, meta-regression analysis with the percentage of patients reporting near miss accidents prior to treatment revealed that part of the observed heterogeneity ($Q = 4.5$, $p = 0.03$) could be explained. Specifically, a larger decrease in the rate of patients reporting near miss accidents (lower OR) was observed along with a higher proportion of patients reporting near miss accidents prior to treatment (i.e., 2% decrease of the OR when the proportion of patients reporting near miss accidents prior to treatment increased by 1%; $p = 0.03$). Interestingly enough, a significant variability in the percentage of patients reporting near miss accidents prior to treatment was observed (range: 20.7–82.1%, Pearson chi-square⁴ = 105.8, $p < 0.001$, Table 1). On the other hand, duration of nCPAP treatment did not contribute to the explanation of the observed heterogeneity ($Q = 0.7$, $p = 0.4$). The Egger’s

Table 1
Characteristics of studies examining the effect of nCPAP on real and near miss accidents.

First author, Year, (level of evidence)	Diagnostic tool	No of patients	Mean age	Males (%)	BMI (kg/m ²)	AHI before treatment (events/h)	Use of nCPAP (h/night)	Sleepiness Score (pre/post)	Accident definition	Accident record	Data collection method	Sleep apnea definition	Additional reporting of near miss accidents	Percentage of patients reporting near miss accidents (pre nCPAP)	Duration of reporting accidents before nCPAP treatment (months)	Duration of reporting accidents after nCPAP treatment (months)
Barbé, 2007 (2+)	FP	76	49 ± 1 SE	97.5	33 ± 0.7 SE	60 ± 2 SE	5.9 ± 0.3 SE	ESS: 12 ± 1 SE/ 3 ± 0.5 SE	automobile accident (>\$500 property damage and/or personal injury)	DR	Q/re	AHI > 20 events/h	No	–	24	24
Cassel, 1996 (3)	FP	59	49 ± 1 SE	100	31.7 ± 0.7 SE	38.9 ± 3.4 SE	7.2 ± 0.13 SE	MSLT: 12 ± 0.7 SE/ 16.8 ± 0.7 SE	motor vehicle accident	SR	Q/re	na	No	–	60	12
Engleman, 1996 (3)	FP	147	53 ± 10 SD	91.7	na	47 ± 38 SD	5.8 ± 2 SD	ESS: 15 ± 6 SD/ 7 ± 5 SD	road traffic incident	SR	Q/re	AHI ≥ 5 events/h	Yes	45.6	60	6
Findley, 2000 (2+)	FP	36	54 ± 2 SE	83.3	na	37.9 ± 5 SE	7.2 ± 0.3 SE	nm	automobile accident (>\$500 property damage or personal injury and drivers conviction)	DR	tel int	AHI ≥ 5 events/h	No	–	24	24
George, 2001 (2+)	FP	210	52 ± 11 SD	90.0	35.5 ± 10 SD	54 ± 9 SD	5.9 ± 0.9 SD	nm	motor vehicle crash	DR	tel/ mail int	AHI ≥ 10 events/h	No	–	36	36
Horstmann, 2000 (3)	FP	71	56.5 ± 10 SD	90.0	na	na	na	ESS: 13.3 ± 6.2 SD/ 6.7 ± 4.8 SD	motor vehicle accident	SR	Q/re	AHI ≥ 10 events/h	No	–	36	15.4
Krieger, 1997 (3)	FP & RP	547	57 ± 11 SD	87.0	33.9 ± 6.9 SD	61.3 ± 25.4 SD	6.1 ± 2 SD	SS by authors: 2.2 ± 0.7 SD/na	car accident	SR	Q/re	symptoms of OSA	Yes	20.7	12	12
Minemura, 1993 (3)	na	14	46 ± 7 SD	100	na	na	na	SSS: 4.7 ± 1 SD/ 2 ± 0.8 SD	traffic accident	SR	Q/re	na	Yes	64.3	36	11
Suratt, 1992 (2–)	na	22	na	na	na	na	na	nm	automobile accident	SR	Q/re	na	Yes	59.1	24	24
Yamamoto, 2000 (3)	FP	39	48.3 ± 11 SD	100	29.5 ± 5.1 SD	55.7 ± 18.6 SD	na	ESS: 12.8 ± 4.8 SD/ 3.6 ± 2.7 SD	traffic car accident	SR	Q/re	symptoms of OSA	Yes	82.1	24	24

AHI = Apnea–hypopnea index.
DR = Driving record.
ESS = Epworth sleepiness scale.
FP = Full polysomnography.
int = Interview.
MSLT = Multiple sleep latency test.
na = Not available.
nm = Not measured.
nm = Not measured.
Q/re = Questionnaire.
RP = Respiratory polygraphy.
SD = Standard deviation.
SE = Standard error.
SR = Self-report.
SSS = Stanford sleepiness scale.
tel = Telephone.

Table 2
Characteristics of studies reporting the effect of nCPAP on the performance in driving simulator.

Author, year (level of evidence)	Diagnostic Tool	No of patients	Age (years)	Males (%)	Type of accident-related measures	Sleep apnea definition (events/h)	BMI (kg/m ²)	Apnea index before treatment (events/h) ^a		ESS		Tracking error		Reaction time (s)		Type of simulator	Duration of simulator test (min)	Duration of nCPAP treatment (days)
								pre	post	pre	post	pre	post	pre	post			
Findley, 1989 (2–)	na	6	53 ± 11 ^a	50	road obstacles hitted	RDI > 50	na	61 ± 33 (AHI)	nm	nm	nm	nm	nm	nm	D.F.S.	30	120	
George, 1997 (2+)	FP	17	49.3 ± 5.1 ^a	100	off road events	AHI ≥ 15	na	73 ± 28.9 (AHI)	nm	nm	0.23 ± 17.2 ^a	0.11 ± 9.5 ^a	3.2 ± 0.1 ^a	2.8 ± 0.1 ^a	SP	20	276	
Hack, 2000 (1+)	FP	26	50 [38–68] ^b	100	off road events	AHI ≥ 10	32.2 [26.3–42.8] ^b	na	15 [10–19.8] ^b	5.5 [1–13.5] ^b	0.36 [0.15–1.12] ^b	0.21 [0.14–0.63] ^b	2.8 [1.8–4.9] ^b	2.3 [1.5–3.5] ^b	SP	30	30	
Orth, 2005 (2+)	FP	31	55.3 ± 10.2 ^a	100	off road events and road crashes	AHI ≥ 5	29.9 ± 2.2 ^a	24.8 ± 21.5 (AHI)	10.1 ± 4.2 ^a	6.1 ± 3.3 ^a	na	na	0.51 ± 0.9 ^a	0.48 ± 1.0 ^a	C.A.R.S.	60	42	
Suratt, 1992 (2–)	na	12	na	na	road obstacles hitted	na	na	na	nm	nm	nm	nm	nm	nm	“Steer Clear”SP	na	120	
Turkington, 2004 (2+)	FP	18	49.9 ± 10 ^a	94	off road events	RDI > 50	39 ± 7.7 ^a	59.8 ± 16.9 (RDI)	15.5 [12.75–19] ^b	6 [2–8.75] ^b	0.29 [0.22–0.48] ^b	na	2.25 [1.84–3.44] ^b	na	S.D.A.D.S.	20	7	

AHI = Apnea–hypopnea index.

C.A.R.S. = Computer aided risk simulator.

D.F.S. = Doron film simulator.

ESS = Epworth sleepiness scale.

FP = Full polysomnography.

na = Not available.

nm = Not measured.

RDI = Respiratory disturbance index.

S.D.A.D.S. = Simdrive divided attention driving simulator.

SP = Software program.

^a Mean ± standard deviation.

^b Median [range].

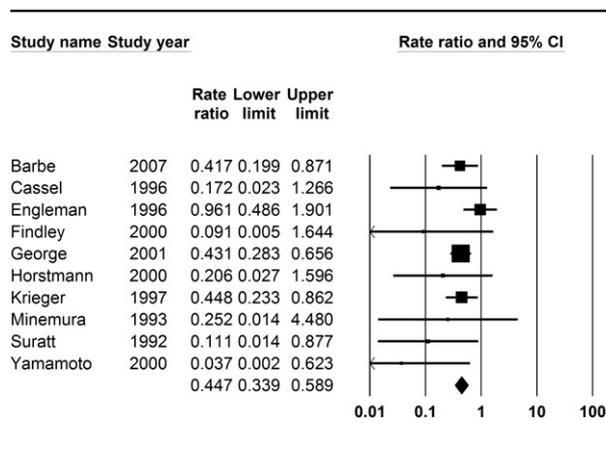


Fig. 2. Forest plot presenting the meta-analysis based on IRRs for real accidents (after vs before nCPAP treatment). IRRs in the individual studies are presented as squares with 95% CIs presented as extending lines. The pooled IRR with its 95% CI is depicted as a diamond.

regression test revealed a borderline publication bias (intercept $b = -2.34$, $p = 0.06$), whereas the correlation rank test was statistically non-significant (Kendall's tau: -0.1 ; $p = 0.8$). Duval and Tweedie's Trim and Fill test suggested that two studies were theoretically missing. Under the random effects model the new, imputed point estimate for near miss accidents was $OR = 0.12$, 95% CI = $0.05-0.25$ (random effects model), i.e., no substantial modification of the pooled estimate was observed. Furthermore, "fail-safe N" was equal to 145. Under the light of the above, publication bias was not an issue of concern in the current meta-analysis.

Likewise, regarding the IRR, when the observed period of reporting accidents before and after nCPAP treatment was taken into account, the reduction in near miss accidents was shown to be statistically significant (IRR = 0.23 , 95% CI = $0.08-0.67$, random effects model) (Fig. 3). Although between-studies heterogeneity was noted ($I^2 = 85\%$, $p < 0.001$), sensitivity analysis showed that only one study²⁵ was the source of this heterogeneity, probably due to the relatively long study period of reporting accidents before nCPAP treatment (5 years). When this study was excluded the new estimated IRR was also significant (IRR = 0.18 , 95% CI = $0.12-0.26$, fixed effects model). Moreover, no publication bias was observed with either Egger's regression test (intercept $b = -1.58$, $p = 0.5$) or rank correlation test (Kendall's tau was 0.3 , $p = 0.46$) and "fail-safe N" was equal to 53. Duval and Tweedie's Trim and Fill test suggested that two studies were theoretically missing. Under the random effects model the new, imputed point estimate for near miss accidents was IRR = 0.37 , 95% CI = $0.15-0.92$. The pooled RD

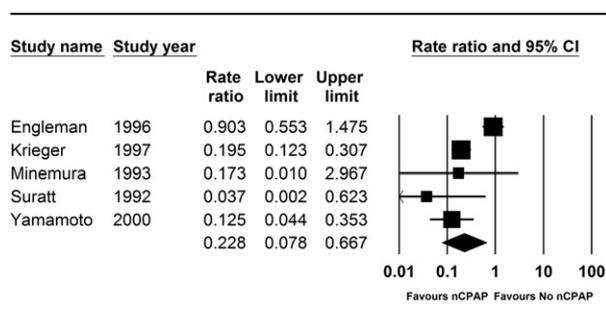


Fig. 3. Forest plot presenting the meta-analysis based on IRRs for near miss accidents (after vs before nCPAP treatment). IRRs in the individual studies are presented as squares with 95% CIs presented as extending lines. The pooled IRR with its 95% CI is depicted as a diamond.

estimate was sizeable and statistically significant (RD = -0.47 ; 95% CI = -0.69 to -0.25 , random effects), corresponding to a NNT equal to 2 (95% CI = $1-4$) OSA patients.

Effect of nCPAP on driving simulator's performance

A significant reduction in accident-related events was observed, as noted by the significant improvement in driving simulator performance following nCPAP treatment (SMD = -1.20 , 95% CI = -1.75 to -0.64 , random effects model) (Fig. 4). Due to the marked between-study heterogeneity ($I^2 = 69\%$, $p < 0.01$), meta-regression analysis was performed. Duration of nCPAP treatment did not seem, however, to explain this heterogeneity ($Q = 0.98$, $p = 0.32$). In contrast, exclusion of two studies with marginal SMDs^{33,35} (one at a time) minimized the observed heterogeneity ($I^2 = 24\%$, $p = 0.26$ and $I^2 = 49\%$, $p = 0.1$ respectively) with no substantial change in the effect of nCPAP on performance in the driving simulator (SMD = -1.39 , 95% CI = -1.74 to -1.04 and SMD = -0.9 , 95% CI = -1.22 to -0.59 , respectively). Both Egger's regression test and the rank correlation test did not reveal publication bias (intercept $b = -3.9$, $p = 0.2$; and Kendall's tau was -0.3 , $p = 0.5$, respectively) and the funnel plot was symmetrical. Duval and Tweedie's Trim and Fill test suggested that two studies were theoretically missing. Under the random effects model the new, imputed point estimate for accident-related events was SMD = -0.89 , 95% CI = -1.44 to -0.34 , whereas the "fail-safe N" was equal to 81.

Discussion

In the current meta-analysis comprising of 1221 OSA subjects, the application of nCPAP treatment was associated with an estimated statistically significant 55% reduction of the reporting involvement in real accidents within a specified time period (IRR = 0.45). A comparable, sizeable finding emerged for the reduction of near miss accidents (IRR = 0.23). More importantly, it has been estimated for the first time that five and two OSA patients should be treated with nCPAP to prevent one patient reporting real and near miss road traffic accidents, respectively. These findings entail special public health, financial and insurance implications and advocate the potential for prevention when a relatively easily applicable intervention, such as nCPAP is used.

The estimation of IRR as measure of the impact of nCPAP treatment for the prevention of road traffic accidents among OSA patients seems to be the most appropriate index for the effect, given the uneven observation time periods during which accidents were reported before and after nCPAP treatment and the variability of this time period among the individual studies under consideration. Taken into account that the observation time tended to be longer before nCPAP than after nCPAP (Table 1), the calculation of crude ORs inevitably overestimates the protective effect of nCPAP upon road traffic accidents as more accidents accumulate during a longer observation period. Thus, adjustment for observation time seems an indispensable tool when assessing the true magnitude of nCPAP efficacy regarding road traffic accidents.

NNT was first described, almost 20 years ago. Since then, NNT calculation has been established as an intuitive and simple way to summarize the investment of time, energy and public health resources towards achieving a specific therapeutic goal.³⁷ There has been an increasing demand for health care policy makers and physicians to comprehensively illustrate the potential impact of a therapy when discussing treatment options, which has led to the calculation of NNT for various medical interventions.³⁸ Specifically, a meta-analysis of randomized studies, aiming to assess the impact of treatment with aspirin showed that the NNT was equal to 73 for total myocardial infarction, 278 for fatal myocardial infarction and

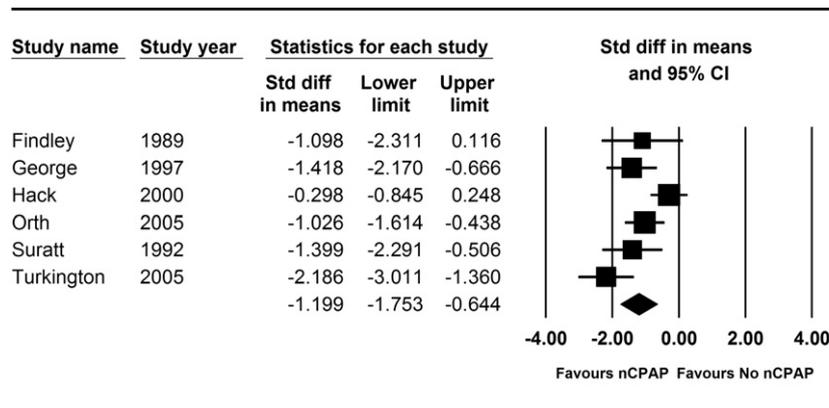


Fig. 4. Forest plot presenting the meta-analysis based on SMDs for accident-related events (after vs before nCPAP treatment). SMDs in the individual studies are presented as squares with 95% CIs presented as extending lines. The pooled SMD with its 95% CI is depicted as a diamond.

256 for ischemic stroke.³⁹ With respect to lipid lowering drug treatment, a calculated NNT of 44 for major coronary event and 66 for stroke has been evidenced.⁴⁰ Consequently, the substantially smaller NNT of five and two patients to prevent one real and near miss road traffic accident, respectively, estimated in the current meta-analysis, indicates the significant public health benefit of CPAP use for OSA patients.

The proportion of patients reporting a road traffic accident prior to nCPAP treatment seemed to be a significant factor affecting the risk reduction in near miss accidents. In this sense, it can be hypothesized that nCPAP seemed more effective in patients entering the studies with higher baseline near miss accident rates, namely on the most vulnerable patients.

When patients were tested on the driving simulator, a significant reduction in accident-related events was observed (SMD = -1.20). This finding may be of special clinical importance as it points to the therapeutic effect of nCPAP and may also portray the driving simulator as a useful tool for assessing the improvement in driving before an OSA patient is involved in real driving situations.

Effectiveness of nCPAP in OSA

The findings of the present meta-analysis concerning reduction in accident rates after nCPAP treatment may be inscribed as an additional merit of the already known beneficial effects mediated by nCPAP in OSA patients, which have been summarized by a recent Cochrane Review. The latter highlighted the significant improvements in medical conditions such as in systolic/diastolic blood pressure measurements, cognitive function, as well as measures of quality of life. When compared to oral devices, nCPAP treatment exhibited higher efficacy in terms of AHI, sleep efficiency and oxygen saturation.⁴¹ As a result, nCPAP is currently recommended in OSA patients with AHI or RDI > 15 episodes/h. If AHI or RDI is between 5 and 14 episodes/h, nCPAP should be used in patients with history of hypertension, stroke, excessive sleepiness, ischemic heart disease, insomnia or mood disorders.⁸

The studies that have been included in the present meta-analysis were essentially performed in OSA patients who have been involved in road traffic accidents as drivers. Despite the fact that OSA affects about 5% of the population, when it comes to drivers, a potentially dangerous context can be detected. Howard et al., have estimated that 60% of a random sample of 3268 Australian commercial vehicle drivers had sleep-disordered breathing, whereas 16% actually had OSA, compared respectively with 24% and 4% of working men in the general community.⁴² This has been attributed to the higher rate of obesity among the commercial drivers, as also confirmed in other

studies, which also identified AHI and severity of hypoxemia as significant factors associated with increased risk for motor vehicle accidents.^{4,43} A meta-analysis which investigated the association of OSA and the risk of motor vehicle accident, has estimated a crash risk of 0.08 crashes per person-year for a healthy driver, which is about half of the risk of a driver with OSA.⁴

Cost-effectiveness of nCPAP treatment

Although nCPAP has been shown as offering great benefits in reducing accident rates, it has not been fully clarified whether such an intervention may prove cost-effective for the health care delivery system.^{44,45} The cost of OSA-related collisions has been estimated to \$15.9 billion in the year 2000, whereas, treating all OSA drivers in the United States would cost \$3.18 billion.⁴⁶ A cost-effectiveness analysis in the U.S. population has suggested that when both direct and indirect costs were considered, nCPAP presented with an incremental cost-effectiveness ratio (ICER) of \$134 per quality-adjusted life-year (QALY) gained. When third-party payer was taken into consideration, the ICER was \$3354 per QALY.⁴⁴ These results were very comparable with those deriving from well-established cost-effective interventions in public health, such as cholesterol-lowering therapy for the prevention of cardiovascular events.⁴⁴ Application of this model to the Canadian population yielded an ICER of Can \$3626 per QALY gained.⁴⁵ Similarly, an earlier economical evaluation by Tousignant et al. in Canada⁴⁷ reported an ICER of Can \$4214 to Can \$12,146. When nCPAP was compared to dental devices or conservative management, nCPAP was an effective and cost-effective treatment for OSA in populations with moderate to severe daytime sleepiness; there may also be benefits when the disease is mild.^{6,8} These observations indicate that nCPAP use for sleep apnea treatment represents an efficient use of health care resources and thus a requisite discussion point for policy makers' agenda.

Limitations – uncertainties

Over and beyond the advantages of this meta-analysis which are related to the estimation of measurable effect estimates and the NNTs on account of nCPAP, this study has several limitations, which actually reflect the ones of the included individual studies. Indeed, a rather wide variety of non-compliance rates were reported (9–36%) for real and near miss accidents; this may have led to potential selection bias, as patients who finally participated in the studies might represent those with higher compliance and therefore, more likely to benefit from nCPAP treatment. The subjective

reporting of nCPAP usage in the rather older studies is an issue of concern; nowadays the use of smart card technologies and convert monitors for compliance surveillance allows a rather accurate estimation of exact nCPAP usage.^{13,26}

As expected, the design of these preliminary studies regarding the effect of nCPAP treatment on the prevention of road traffic accidents is variable with some studies not availing untreated groups that could be used for comparisons. Moreover, even in studies which used the case-control design, the proportion of professional drivers and drivers engaging in dangerous driving practices was not taken into consideration,²⁷ whereas in others the control group was not randomly selected from the general population and was not screened for OSA.²⁷ To account for these concerns we opted for a before versus after comparison. Additionally, recall and telescopic bias⁴⁸ could not be excluded in retrospective studies including recalls of the number of accidents.²⁵ Furthermore, under-reporting of accidents may have also occurred due to the reluctance and fear of drivers for the consequences and possible banning from driving after accident admission.^{14,24–26} On the other hand, obtaining personal information and making objective nCPAP usage evaluation for each study participant may violate anonymity.²⁷ Nevertheless, even in the case of underestimation, the treatment effect in both real and near miss accidents was strongly in favor of nCPAP, indicating the unquestionable efficacy of such intervention in OSA drivers.²⁴

Additional uncertainties arise from the small number of patients included in several studies and the unavailability of raw data, which could allow the estimation of age adjusted accident rates,²⁴ as well as the lack of information on kilometers driven per patient (mile-adjusted accident rates), which could allow adjustment for risk exposure.¹⁴ In fact, only three out of the ten eligible studies presented with availed mile-adjusted accident rates,^{24,25,27} which deprived us from a more profound examination of this aspect due to the limited statistical power.

An additional limitation of the individual studies, as well as of the present meta-analysis, pertains to the modifying effects of time upon the efficacy of nCPAP. The analysis on IRRs, as well as the crude analyses, presented in the individual studies assumes an underlying constant incidence rate. Nevertheless, this assumption may, at a certain extent, miss a part of the phenomenon, as efficacy of nCPAP may vary along with time. Consequently, this meta-analysis confers the additional message that future longitudinal studies should focus on this interesting topic.

Many studies have reported both reduction in accident rates and major improvement in sleepiness and daytime vigilance. It is possible that the decrease in accidents is caused by amelioration of OSA symptoms in general, thus indicating an indirect association with nCPAP treatment. Regardless of the mechanism of improvement, however, the benefits of nCPAP treatment seem indisputable.¹⁴ In light of these results, physicians should be more alert to identify OSA, a well under-diagnosed medical condition and encourage the use of nCPAP as appropriate. Likewise, from a public health perspective, policy makers should be informed in order to consider this highly cost-effective intervention that reduces road traffic accidents and saves lives as a priority in their agendas.

Conclusion

In conclusion, this meta-analysis provides support to nCPAP treatment as a highly effective and cost-effective intervention for the prevention of road traffic accidents among OSA patients, whereas it also portrays the driving simulator as a useful tool for assessing the improvement in driving before an OSA patient is involved in real driving situations.

Practice points

- 1) A growing body of evidence supports the efficacy of nCPAP treatment in a) reducing real and near miss accidents and b) improving the performance in the driving simulator among OSA patients.
- 2) It is estimated that for every five patients being treated with nCPAP, one patient avoids a real road traffic accident, whereas for every two patients being treated with nCPAP one patient avoids a near miss road traffic accident. This is of great significance concerning public health, financial and insurance policies.
- 3) nCPAP use for sleep apnea treatment represents an efficient use of health care resources and thus a requisite discussion point for policy makers' agenda.

Research agenda

- 1) Adjustment for observation time seems an indispensable tool when assessing the true magnitude of nCPAP efficacy regarding road traffic accidents.
- 2) Future studies should take into account the duration of nCPAP treatment and distance driven per patient.
- 3) Future studies should routinely use smart card technologies and convert monitors for objective compliance surveillance. Sleepiness and daytime vigilance tests seem valuable in all OSA patients.
- 4) Comprehensive studies assessing simultaneously the effect of nCPAP on the driving simulator and in real life (real and near miss accidents) may be of special interest.

Acknowledgment

The study was partially supported by the National and Kapodistrian University of Athens. The authors would like to thank Nick Dessypris for the statistical comments and remarks on the manuscript. We would also like to thank Theodoros Michelakos for his remarks on the text.

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