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SCIENTIFIC INVESTIGATIONS

Effect of CPAP Treatment for Obstructive Sleep Apnea Hypopnea Syndrome on Lipid Profile: A Meta-Regression Analysis

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Study Objective: Patients with obstructive sleep apnea (OSA) frequently exhibit higher rates of dyslipidemia, a risk factor for cardiovascular and cerebrovascular disorders. Treatment for OSA by CPAP may improve cholesterol metabolism. This meta-regression analysis (MA) estimates the effect of CPAP treatment on dyslipidemia.

Methods: PubMed and Cochrane libraries were searched by utilizing different combinations of keywords: CPAP, obstructive sleep apnea, serum lipids, dyslipidemia, cholesterol, total cholesterol (TC), low density lipoprotein, LDL, high density lipoprotein, HDL, triglyceride, and TG. Inclusion criteria were: (1) English articles and (2) studies with an adult population with the diagnosis of OSA who were treated with CPAP. The OSA group must have cholesterol profile including TC, LDLc, HDLc, and TG, without and with CPAP treatment. Fifty-four studies were reviewed, while 29 studies pooled for MA.

Results: Thirty-four datasets from 29 studies with 1,958 subjects pooled. Treatment duration range was from 2 days to 1 year. TC standardized mean differences (SMD) ranged from -41.5 to -0.077, pooled mean difference (PMD) was -5.660 (LL -6.715 to UL -4.606, $p < 0.001$). SMD in LDL ranged from -3.7 to 0; PMD was -0.488 (LL -0.715 to UL -0.261, $p < 0.001$). HDL SMD ranged from -0.498 to 1.94. The PMD was 0.207 (LL 0.05 to UL 0.364, $p < 0.01$). TG SMD ranged from -9.327 to 1.98; PMD was -0.054 (LL -0.124 to UL 0.016, $p < 0.129$).

Conclusions: CPAP treatment for OSA seems to improve dyslipidemia (decrease in total cholesterol and LDL, and increase in HDL). It does not appear to affect TG levels.

Keywords: obstructive sleep apnea, dyslipidemia, CPAP, cholesterol, sleep disordered breathing

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Obstructive sleep apnea (OSA) is a common disorder that is often asymptomatic; the prevalence of patients with OSA who do not present clinical syndrome, might be as high as 20% to 30% in the middle-aged.[1] OSA is a significant source of morbidity and mortality, as OSA has been increasingly linked to cardiovascular and cerebrovascular disease, and many studies have shown that OSA is associated with increased cardiovascular and cerebrovascular morbidity.[2-9] OSA is associated with obesity and metabolic syndrome, most likely from associated endocrine abnormalities, especially reduced androgens.[10] Subjects with OSA manifest increased dyslipidemia.[11] CPAP—the main modality of treatment—serves as a pneumatic splint device and reduces upper airway collapse, which results in reduction of arousals and improvement in oxyhemoglobin saturation. This may result in improvement in hormonal regulation and metabolic abnormalities: blood glucose levels, inflammation, and dyslipidemia. Multiple studies document this effect of OSA treatment by CPAP on dyslipidemia. We performed meta-analysis (MA) and meta-regression (MR) to specifically detect treatment effect by CPAP on dyslipidemia.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with obstructive sleep apnea (OSA) frequently exhibit higher rates of dyslipidemia, a risk factors for cardiovascular and cerebrovascular disorders. Multiple studies with small sample size documented the improvement in dyslipidemia by treatment for OSA by CPAP therapy, hence the meta-regression analysis aim to estimates the effect of CPAP treatment on dyslipidemia.

Study Impact: CPAP treatment for OSA seems to improve dyslipidemia (decrease in total cholesterol and LDL, and increase in HDL). Study suggests that improvement in dyslipidemia may be the mechanism for improvement of cardiovascular and cerebrovascular disorders in patients, treated for sleep apnea by pressure therapy.

METHODS

We performed this review in accordance with PRISMA guidelines for performing meta-analysis. A protocol was prospectively developed, detailing the objectives, criteria for study selection, and approach to assessing the study quality, primary outcome, and methodology.

Data Source and Study Selection

Studies for review were found searching the PubMed, Cochrane, and EMBASE databases from January 1, 1960, to December 31, 2013. Unpublished data from scientific meetings were not searched, since most abstracts do not provide detail data needed for meta-analysis. Searches were conducted using the keywords: sleep apnea, obstructive sleep apnea, CPAP, APAP, AutoPAP, pressure therapy, serum lipids, dyslipidemia, cholesterol, total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride. Each target outcome was also searched in its abbreviated forms (Chol T, HDL, LDL, TG) to ensure that no relevant source is left out. Additionally, each target and its abbreviated forms were searched in combination with obstructive sleep apnea and CPAP. Multiple authors individually searched for and scored manuscripts for inclusion. If a manuscript was scored differently by 2 authors, then it was reviewed by third author to finalize its inclusion.

Studies and Endpoint Definitions

Lipid profile includes total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol HDL, and triglyceride (TG). Inclusion criteria defined for subsequent study selection were as follows: (1) the study must be in English, (2) studies with adult population only, (3) full text manuscripts had to be available, (4) the study must have reported values for at least one of the outcomes of interest, (5) OSA was diagnosed by sleep study and OSA defined as AHI of ≥ 5/h, (6) the study must have included individuals with obstructive sleep apnea treated with PAP device, and (7) the study must have reported values in mean and standard deviation or median with range.

Data Extraction

Study selection, data extraction, and statistical analysis were all done in accordance to previously published methodology for meta-analyses. Studies identified for inclusion then underwent data extraction. Data was extracted at a study level by a single author and then reviewed by a second author to ensure no errors were made. Levels of serum lipids were extracted from studies as mean with standard deviation. Measurement unit of lipid profile was mmol/L. If any of these values were in mg/dl they were converted into mmol/L by dividing them by their molar weight. For studies with data reported in median and range, mean and standard deviation were calculated utilizing methods outlined by Hozo et al.[12] Target variables (TC, HDL, LDL, TG) were recorded, as well as reported demographics (age, gender, BMI), confounding factors (AHI, blood glucose, insulin level), and Epworth Sleepiness Scale (ESS) score (when available) to evaluate the effect of these parameters on the target by employing subgroup analysis or meta-regression.

Statistical Analysis

The statistical analysis was performed by the Comprehensive Meta-Analysis software package (version CM 2.2, Biostat, Englewood, NJ). Heterogeneity analysis by the Cochran's Q statistics for individual end points across all studies was performed. An I^2 of 25% to 49% was considered to represent a low level of heterogeneity, 50% to 74% a moderate level, and 75% to 100% a high level. A 2-sided α error of less than 0.05 was considered to be statistically significant.

RESULTS

The literature was ranked according to the hierarchy of evidence of Sackett et al.[13] Total citations identified from electronic search by using key words without duplication were N = 367; sleep apnea and cholesterol N = 287; sleep apnea and dyslipidemia N = 334; CPAP and lipids N = 59; additional studies found by other combinations N = 57. A total of 313 citations were excluded after screening titles and abstracts; therefore, 54 articles were retrieved for detailed evaluation. Twenty-five studies were excluded for different reasons (full text not available N = 4, non-English manuscript N = 4, inappropriate population N = 4, data not extractable N = 4, missing relevant information N = 2, and data not reported N = 7). Therefore, 29 studies (with 34 datasets) (**Table 1**) met inclusion criteria and were pooled for meta-analysis including total 1,958 subjects (without CPAP [N = 1,554] and with CPAP treatment [N = 1,260]). Few studies (Borgel 2006, Coughlin 2007, Marin 2005, and Sharma 2011) compare the lipid profile between untreated (N = 698) and treated OSA (N = 404) patients, while majority of studies compared lipid profile on subjects (N = 856) before CPAP usage and after CPAP usage for a specified amount of time. CPAP treatment duration ranged from 2 days to 1 year. Data from all of studies were pooled for analysis. Data regarding compliance was not reported by all studies. Available compliance data was variable across included studies. Another meta-analysis can be performed by including only studies with compliant subjects (when enough studies are available) to address the issue of effect of optimal pressure therapy on lipid profile, although it will not be applicable as compliance rates are not very high in general.

Total Cholesterol

A total of 24 studies with 33 datasets including 1,929 subjects were pooled for TC. Standardized mean differences ranged from -41.5 to -0.077, pooled mean difference was calculated to be -5.660 (LL -6.715 to UL -4.606, I^2 for this analysis was 97.37, $p < 0.001$; **Figure 1**).

LDL Cholesterol

For LDL, 18 studies with 25 datasets including 676 subjects were pooled. Standardized mean difference in LDL ranged from -3.7 to 0; pooled mean difference was calculated to be -0.488 (LL -0.715 to UL -0.26, I^2 for this analysis was 78.37, $p < 0.001$; **Figure 2**)

HDL Cholesterol

For HDL, 23 studies with 32 datasets including 806 subjects were pooled. Standardized mean difference ranged from -0.498 to 1.94. The pooled mean difference was calculated to be 0.207 (LL 0.05 to UL 0.364, I^2 for this analysis was 59.11, $p < 0.01$; **Figure 3**).

Triglyceride

For TG, 25 studies with 35 datasets including 1,926 subjects were pooled and analyzed. Standardized mean difference ranged from -9.327 to 1.98; pooled mean difference was calculated to be -0.054 (LL -0.124 to UL 0.016, I^2 for this analysis was 0, $p < 0.129$; **Figure 4**).

Table 1—Characteristics of included studies.

Author, year	Study Design	Without CPAP (N)	After CPAP (N)	Duration	Outcome Measured
Barcelo 2004 A	before and after CPAP	16	16	3 months	HDL, CRP
Barcelo 2008	before and after CPAP	20	20	3 months	lipids, insulin resistan
Borgel 2006	before and after CPAP	127	127	6 months	lipids profile
Buechner 2001	before and after CPAP	69	69	6 months	lipids profile
Chihara 2012	before and after CPAP	20	20	2 days	lipids, prostaglandin D synthase
Chin 1999	before and after CPAP	13	13	8 months	lipids, fats, leptins
Chin 2000	before and after CPAP	23	23	1 month	lipids, cell adhesion molecule
Cholidou 2013	cases versus controls	33	13	6 months	lipids profile, calprotectin
Chung 2011	before and after CPAP	24	24	3 months	lipids profile, vascular functions
Coughlin 2007	before and after CPAP	23	23	6 weeks	lipids profile, metabolic syndrome
Cuhadaroglu 2009	before and after CPAP	31	31	8 weeks	lipids profile, insulin resistance, leptins
Davies 1994	before and after CPAP	10	10	3 months	lipids profile, insulin
Dorkova 2008	before and after CPAP	16	16	8 weeks	lipids profile, cardivascular risk profile
Drager 2007	before and after CPAP	12	12	4 months	lipids profile, catechoamines, BP
Iguchi 2013	before and after CPAP	19	19	3 months	lipids profile, arterial stiffness
IP 2000	before and after CPAP	9	9	6 months	lipids profile, leptins, vascular risk factors
Kawano 2012	before and after CPAP	30	30	6 months	lipids profile, LDL/HDL ratio
Kitahara 2006	before and after CPAP	13	13	2 months	lipids, brachial-ankle pulse wave velocity
Kumor 2009	before and after CPAP	24	24	3 months	lipids profile, homocysteine, leptins
Lattimore 2006	before and after CPAP	10	10	3 months	lipids profile, endothelial functions
Li 2009	before and after CPAP	20	20	3 months	lipids profile, interleukin 18, CIMT
Marin 2005	cases versus controls	403	372	6 months	lipids profile, death, MI, CVA
Nena 2010	before and after CPAP	47	47	6 months	lipids, retinol binding protein-4
Oktay 2009	before and after CPAP	20	20	1 year	lipids, glucose BP
Paracha 2010	before and after CPAP	41	41	3 months	lipids, insulin sensitivity, CV risk factors
Phillip 2011	before and after CPAP	16	16	8 weeks	post prandial lipidemia.
Robinson 2004	before and after CPAP	106	106	1 month	lipids, FXIIa, FVIIa, s-Psel, TAT
Sharma 2011	before and after CPAP	43	43	3 months	lipids, visceral Fat, metabolic syndrome
Steiropolus 2007	before and after CPAP	20	20	6 months	lipids, CRP, glucose, homocysteine

Table 2—Meta-regression statistics.

	Age			BMI			AHI		
	Slope	Intercept	p value	Slope	Intercept	p value	Slope	Intercept	p value
TC	0.307	-17.63	0.00	0.013	-1.546	0.71	-0.083	2.21	0.001
LDL	-0.006	-0.03	0.55	0.09	-3.37	0.001	-0.002	-0.231	0.50
HDL	0.009	-0.334	0.36	-0.046	1.636	0.03	0.0018	0.096	0.65
TG	-0.001	0.0027	0.92	-0.005	0.125	0.51	-0.0029	0.069	0.27

Meta-Regression to Evaluate the Effect of Age, BMI, and AHI on Lipid Levels after CPAP Treatment

Only age was found to have modest but significant effect on improvement of total cholesterol levels after treatment with CPAP (Beta 0.307, p = 0.0001). There was no effect for age on LDL (p = 0.55), HDL (p = 0.36), or TG (p = 0.92). BMI was found to have modest but significant effect on LDL (Beta 0.09, p = 0.001) and HDL (Beta -0.046, p = 0.03) while there was no significant effect on TC (p = 0.71) or TG (p = 0.511). AHI was found to be a significant but modest confounder for effect on only TC after CPAP treatment (Beta -0.083, p = 0.001). AHI had no effect on LDL (p = 0.50), HDL (p = 0.65), or TG (p = 0.27) (**Figure 5**, **Table 2**).

DISCUSSION

There is strong positive association between LDL and the risk of coronary heart disease.[14,15] Randomized trials have demonstrated that lowering LDL cholesterol with medications reduces the risk of cardiac death, nonfatal myocardial infarction, ischemic stroke, and the need for revascularization procedures.[16-18]

The present meta-regression analysis (MR) showed that there is an improvement in the levels of cholesterol in subjects with OSA treated with pressure therapy (decrease in total cholesterol and low density lipoprotein, and an increase in high density lipoprotein) although it did not show any improvement in triglyceride.

Figure 1—Total cholesterol, standard difference in means, before treatment versus after CPAP treatment.

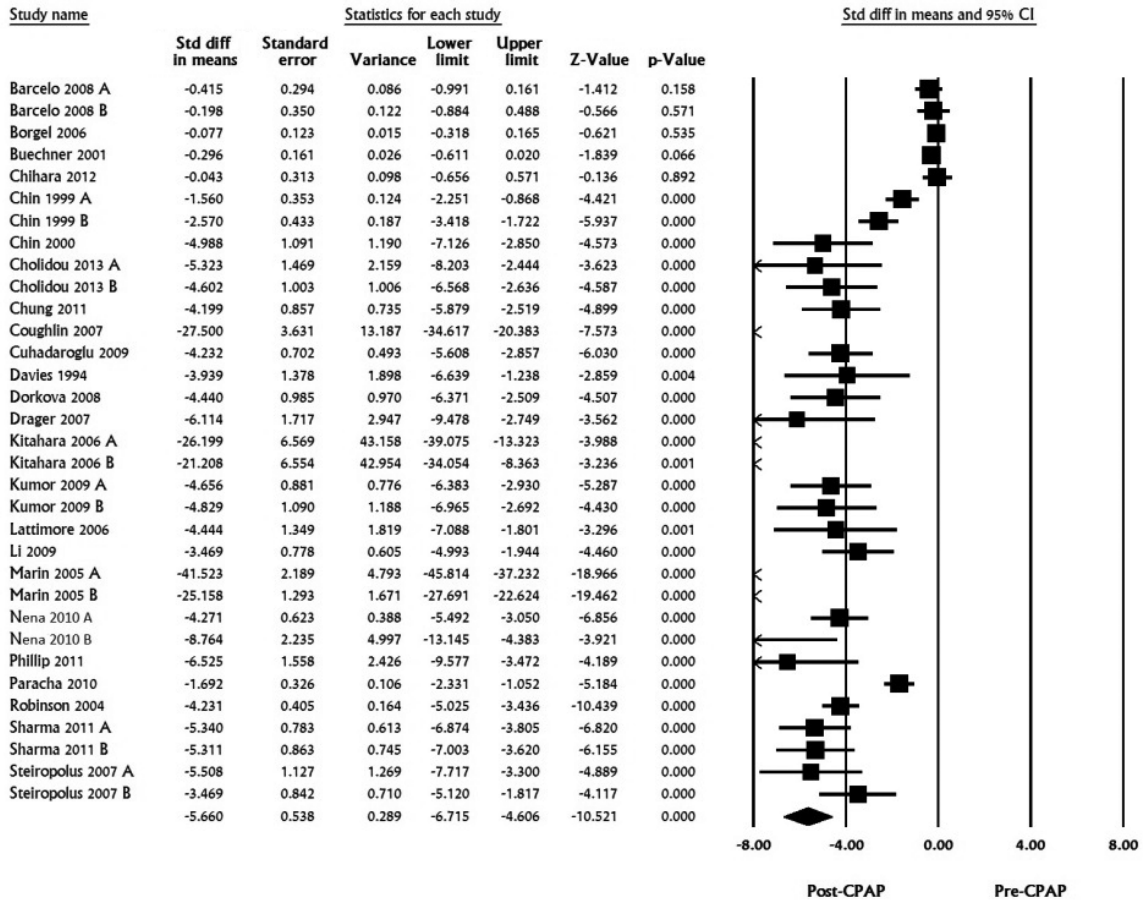


Figure 2—LDL, standard difference in means, before treatment versus after CPAP treatment.

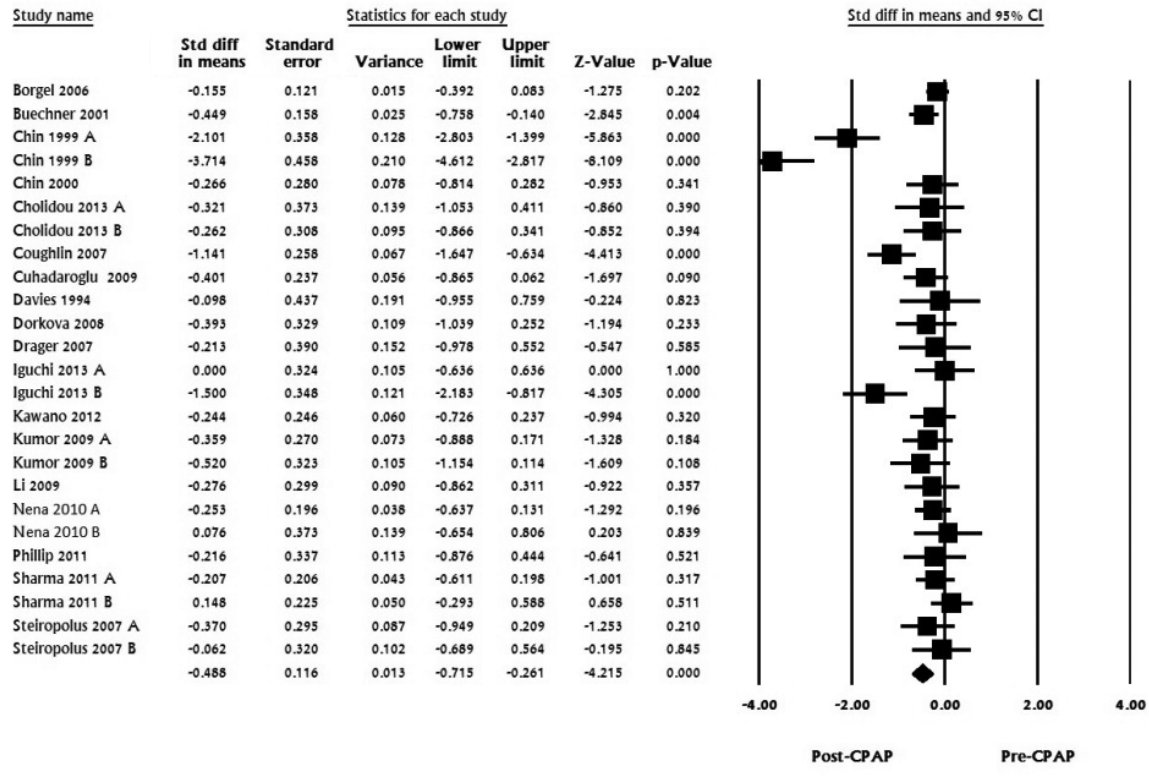
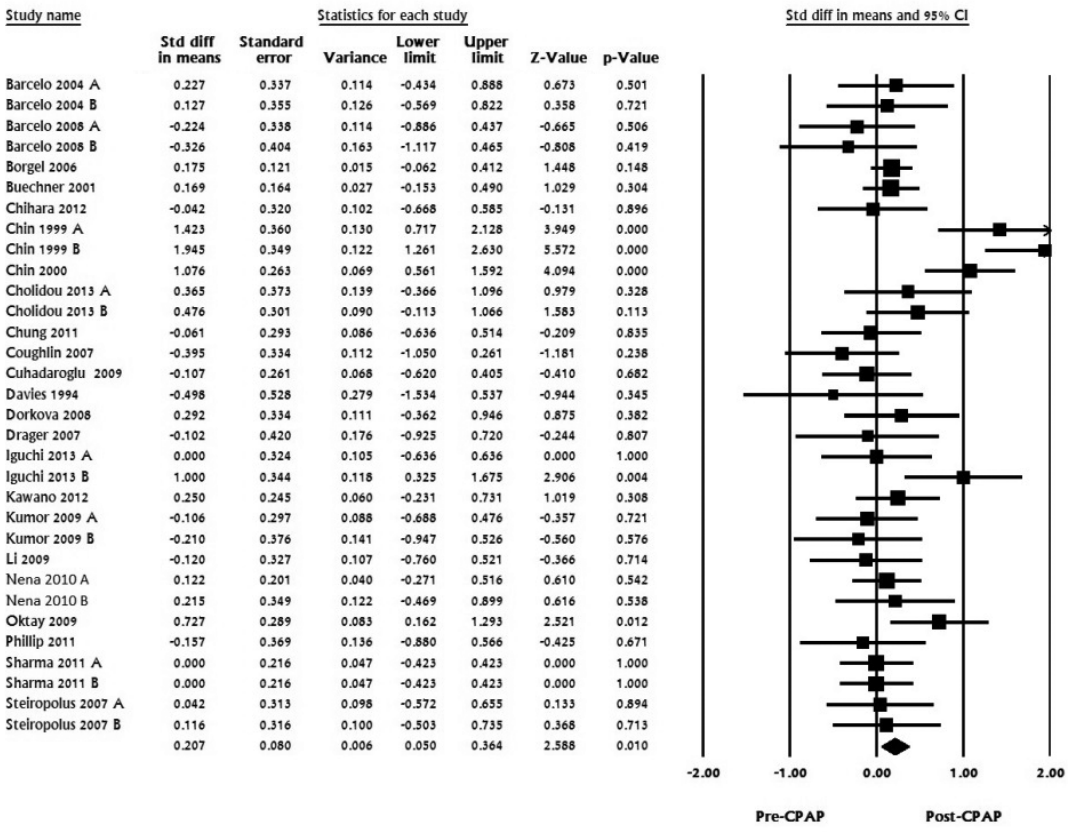
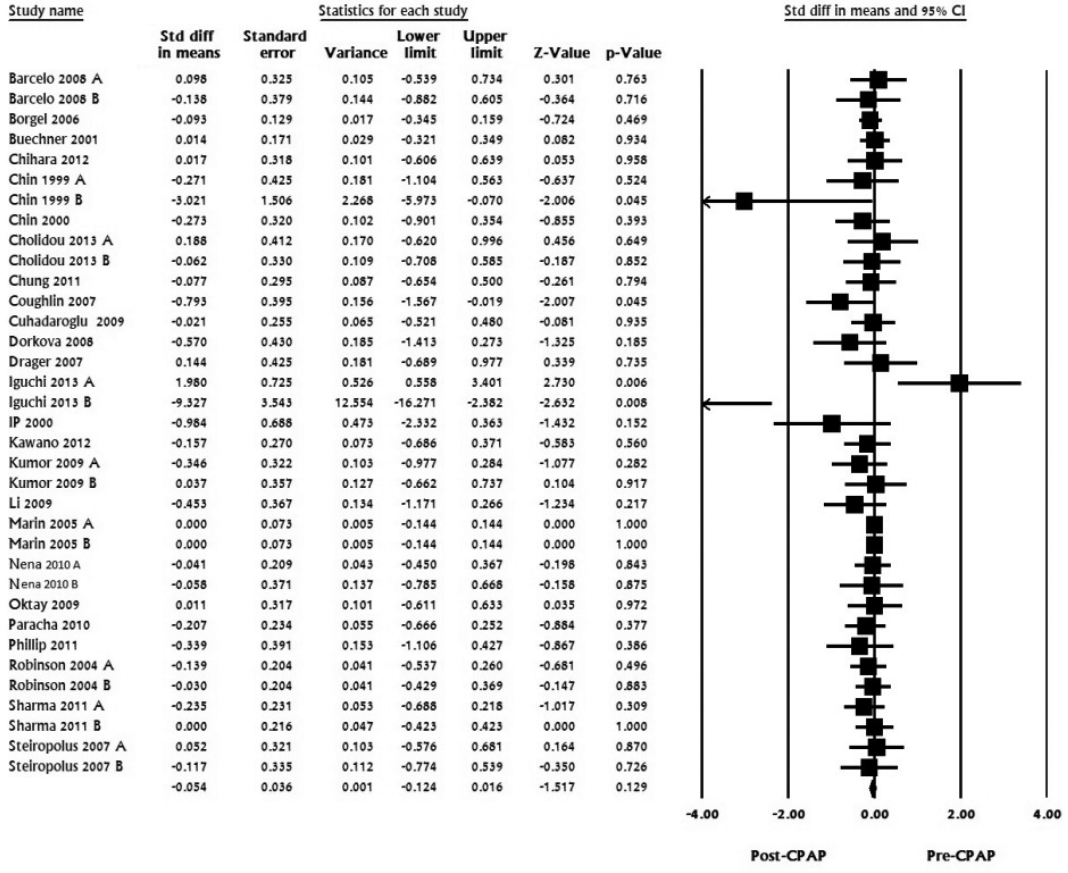


Figure 3—HDL, standard difference in means, before treatment versus after CPAP treatment.



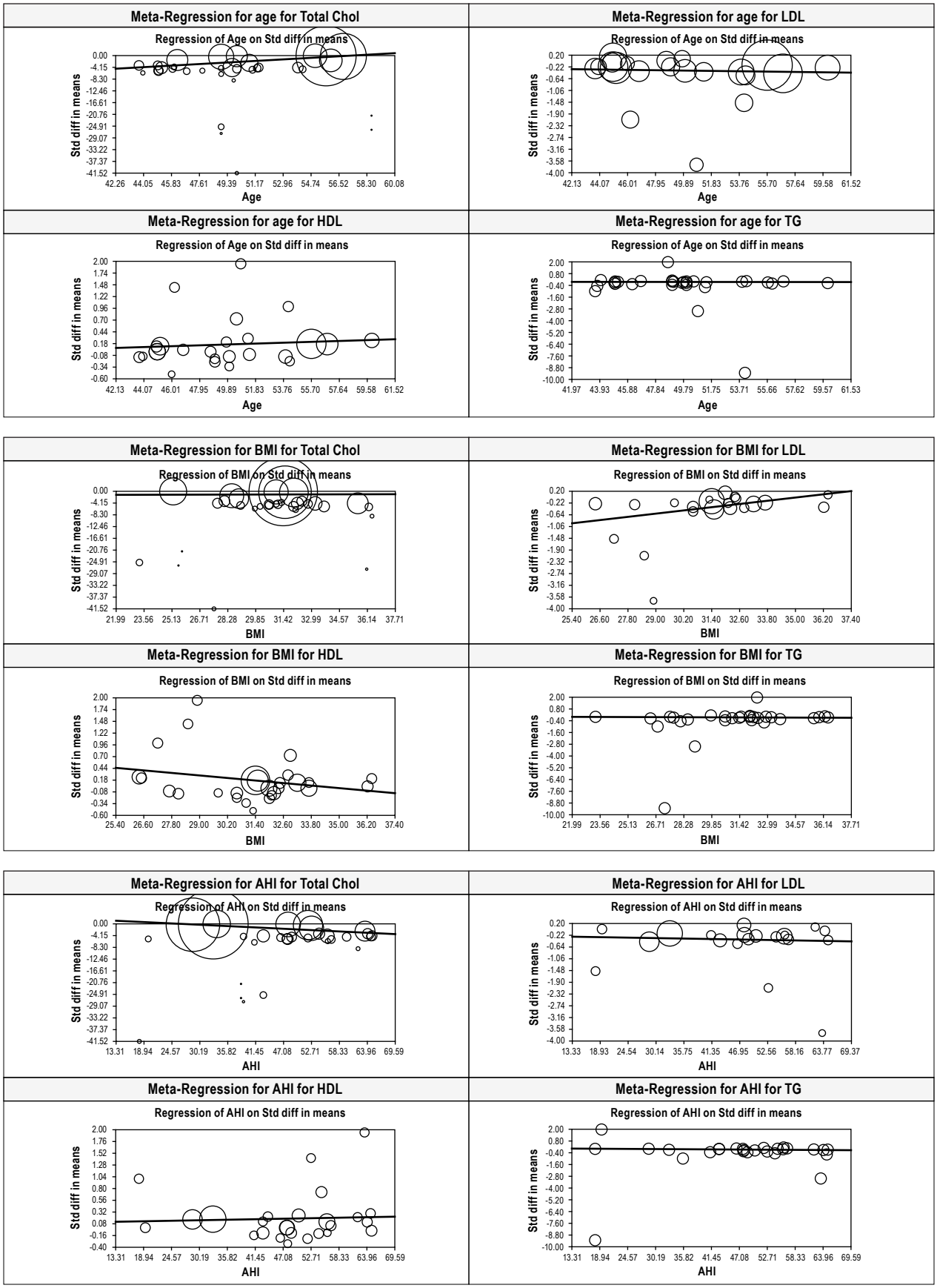
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Barcelo 2004 A	0.227	0.337	0.114	-0.434	0.888	0.673	0.501
Barcelo 2004 B	0.127	0.355	0.126	-0.569	0.822	0.358	0.721
Barcelo 2008 A	-0.224	0.338	0.114	-0.886	0.437	-0.665	0.506
Barcelo 2008 B	-0.326	0.404	0.163	-1.117	0.465	-0.808	0.419
Borgel 2006	0.175	0.121	0.015	-0.062	0.412	1.448	0.148
Buechner 2001	0.169	0.164	0.027	-0.153	0.490	1.029	0.304
Chihara 2012	-0.042	0.320	0.102	-0.668	0.585	-0.131	0.896
Chin 1999 A	1.423	0.360	0.130	0.717	2.128	3.949	0.000
Chin 1999 B	1.945	0.349	0.122	1.261	2.630	5.572	0.000
Chin 2000	1.076	0.263	0.069	0.561	1.592	4.094	0.000
Cholidou 2013 A	0.365	0.373	0.139	-0.366	1.096	0.979	0.328
Cholidou 2013 B	0.476	0.301	0.090	-0.113	1.066	1.583	0.113
Chung 2011	-0.061	0.293	0.086	-0.636	0.514	-0.209	0.835
Coughlin 2007	-0.395	0.334	0.112	-1.050	0.261	-1.181	0.238
Cuhadaroglu 2009	-0.107	0.261	0.068	-0.620	0.405	-0.410	0.682
Davies 1994	-0.498	0.528	0.279	-1.534	0.537	-0.944	0.345
Dorkova 2008	0.292	0.334	0.111	-0.362	0.946	0.875	0.382
Drager 2007	-0.102	0.420	0.176	-0.925	0.720	-0.244	0.807
Iguchi 2013 A	0.000	0.324	0.105	-0.636	0.636	0.000	1.000
Iguchi 2013 B	1.000	0.344	0.118	0.325	1.675	2.906	0.004
Kawano 2012	0.250	0.245	0.060	-0.231	0.731	1.019	0.308
Kumor 2009 A	-0.106	0.297	0.088	-0.688	0.476	-0.357	0.721
Kumor 2009 B	-0.210	0.376	0.141	-0.947	0.526	-0.560	0.576
Li 2009	-0.120	0.327	0.107	-0.760	0.521	-0.366	0.714
Nena 2010 A	0.122	0.201	0.040	-0.271	0.516	0.610	0.542
Nena 2010 B	0.215	0.349	0.122	-0.469	0.899	0.616	0.538
Oktay 2009	0.727	0.289	0.083	0.162	1.293	2.521	0.012
Phillip 2011	-0.157	0.369	0.136	-0.880	0.566	-0.425	0.671
Sharma 2011 A	0.000	0.216	0.047	-0.423	0.423	0.000	1.000
Sharma 2011 B	0.000	0.216	0.047	-0.423	0.423	0.000	1.000
Steiropolus 2007 A	0.042	0.313	0.098	-0.572	0.655	0.133	0.894
Steiropolus 2007 B	0.116	0.316	0.100	-0.503	0.735	0.368	0.713
	0.207	0.080	0.006	0.050	0.364	2.588	0.010

Figure 4—Triglycerides, standard difference in means, before treatment versus after CPAP treatment.



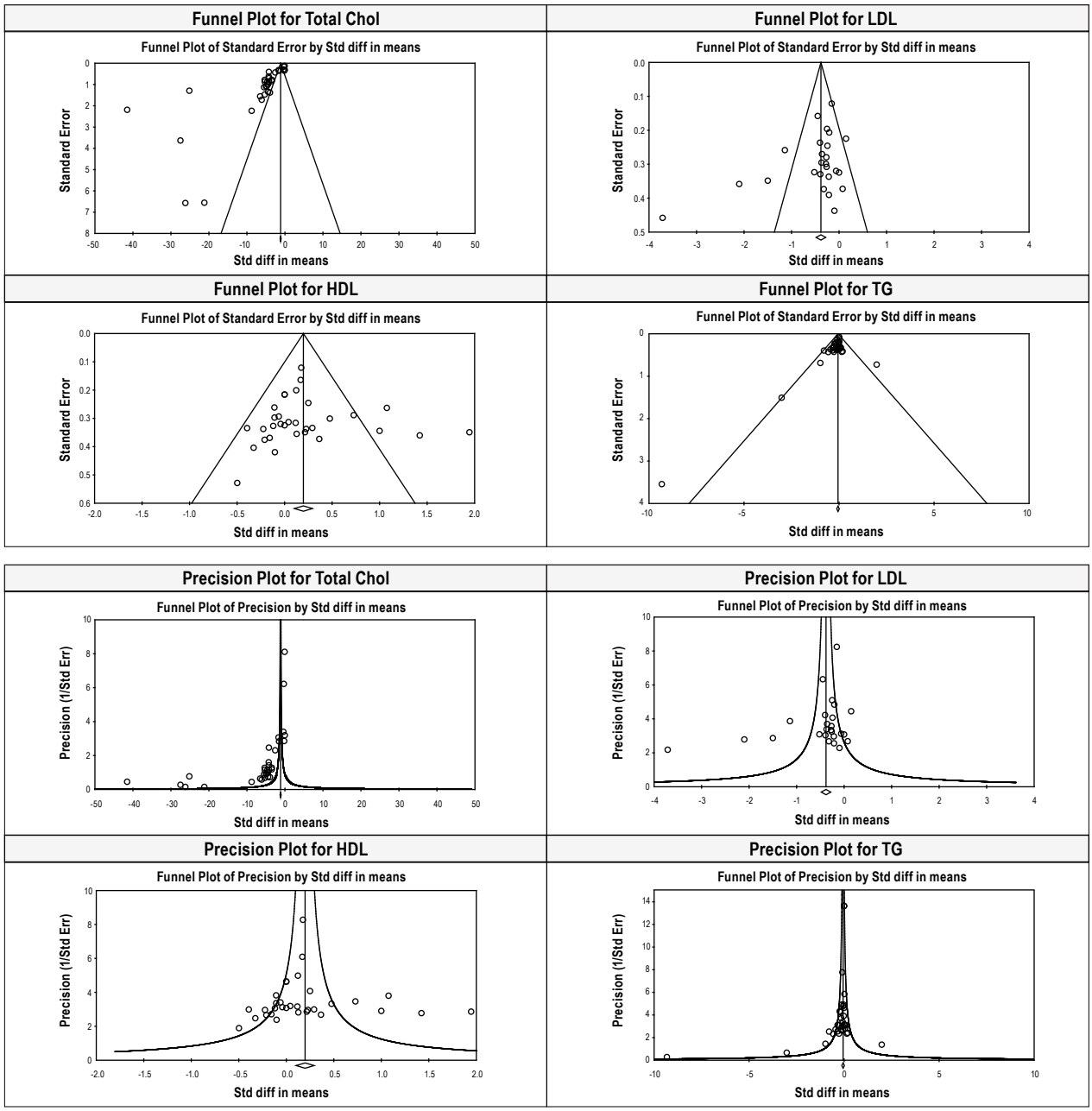
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Barcelo 2008 A	0.098	0.325	0.105	-0.539	0.734	0.301	0.763
Barcelo 2008 B	-0.138	0.379	0.144	-0.882	0.605	-0.364	0.716
Borgel 2006	-0.093	0.129	0.017	-0.345	0.159	-0.724	0.469
Buechner 2001	0.014	0.171	0.029	-0.321	0.349	0.082	0.934
Chihara 2012	0.017	0.318	0.101	-0.606	0.639	0.053	0.958
Chin 1999 A	-0.271	0.425	0.181	-1.104	0.563	-0.637	0.524
Chin 1999 B	-3.021	1.506	2.268	-5.973	-0.070	-2.006	0.045
Chin 2000	-0.273	0.320	0.102	-0.901	0.354	-0.855	0.393
Cholidou 2013 A	0.188	0.412	0.170	-0.620	0.996	0.456	0.649
Cholidou 2013 B	-0.062	0.330	0.109	-0.708	0.585	-0.187	0.852
Chung 2011	-0.077	0.295	0.087	-0.654	0.500	-0.261	0.794
Coughlin 2007	-0.793	0.395	0.156	-1.567	-0.019	-2.007	0.045
Cuhadaroglu 2009	-0.021	0.255	0.065	-0.521	0.480	-0.081	0.935
Dorkova 2008	-0.570	0.430	0.185	-1.413	0.273	-1.325	0.185
Drager 2007	0.144	0.425	0.181	-0.689	0.977	0.339	0.735
Iguchi 2013 A	1.980	0.725	0.526	0.558	3.401	2.730	0.006
Iguchi 2013 B	-9.327	3.543	12.554	-16.271	-2.382	-2.632	0.008
IP 2000	-0.984	0.688	0.473	-2.332	0.363	-1.432	0.152
Kawano 2012	-0.157	0.270	0.073	-0.686	0.371	-0.583	0.560
Kumor 2009 A	-0.346	0.322	0.103	-0.977	0.284	-1.077	0.282
Kumor 2009 B	0.037	0.357	0.127	-0.662	0.737	0.104	0.917
Li 2009	-0.453	0.367	0.134	-1.171	0.266	-1.234	0.217
Marin 2005 A	0.000	0.073	0.005	-0.144	0.144	0.000	1.000
Marin 2005 B	0.000	0.073	0.005	-0.144	0.144	0.000	1.000
Nena 2010 A	-0.041	0.209	0.043	-0.450	0.367	-0.198	0.843
Nena 2010 B	-0.058	0.371	0.137	-0.785	0.668	-0.158	0.875
Oktay 2009	0.011	0.317	0.101	-0.611	0.633	0.035	0.972
Paracha 2010	-0.207	0.234	0.055	-0.666	0.252	-0.884	0.377
Phillip 2011	-0.339	0.391	0.153	-1.106	0.427	-0.867	0.386
Robinson 2004 A	-0.139	0.204	0.041	-0.537	0.260	-0.681	0.496
Robinson 2004 B	-0.030	0.204	0.041	-0.429	0.369	-0.147	0.883
Sharma 2011 A	-0.235	0.231	0.053	-0.688	0.218	-1.017	0.309
Sharma 2011 B	0.000	0.216	0.047	-0.423	0.423	0.000	1.000
Steiropolus 2007 A	0.052	0.321	0.103	-0.576	0.681	0.164	0.870
Steiropolus 2007 B	-0.117	0.335	0.112	-0.774	0.539	-0.350	0.726
	-0.054	0.036	0.001	-0.124	0.016	-1.517	0.129

Figure 5—All MR plots for age, BMI, and AHI for TC, LDL, HDL, and TG before versus after CPAP treatment.



Size of the bubbles is proportional to the study sample size.

Figure 6—Funnel plots and precision plot for TC, LDL, HDL, and TG levels before and after CPAP treatment.



This finding of heightened dyslipidemia in patients with obstructive sleep apnea suggest that treatment of sleep apnea may improve this risk factors for heart disease directly or indirectly by affecting other confounding factors—obesity, hypertension, diabetes mellitus, and metabolic syndrome—as CPAP treatment for sleep apnea has been shown to positively impact management of these confounding variables.

The mechanism for lipid metabolism modulation by CPAP is unknown. Chronic intermittent hypoxia (CIH) associated with OSA may adversely affect dyslipidemia, as suggested by animal studies that CIH up-regulates lipoprotein secretion,[19] increases free fatty acid flux to the liver,[20] may induce sympathetic activity,[21] which could induce lipolysis.[22] CPAP may improve dyslipidemia by improving hypoxia.[23] Another mechanism may be from improvement in insulin resistance, which may increase total cholesterol and LDL cholesterol by decreasing the catabolism of LDL, by down-regulation of LDL receptors.[24] CPAP may improve lipids by affecting inflammatory markers.[23,25] Another possibility is reduction of hypersomnolence during the day with increase in activity.[26] Alternatively, exercise may increase the desire for foods that are high in carbohydrates and reduce the desire for foods that are high in fat.[27]

Several limitations of this meta-analysis should be emphasized. Available literature is largely low level evidence. Few of the relevant studies regarding the improvement with CPAP therapy were cross-sectional in nature, so the temporal relationships between these two factors were unclear. There was significant heterogeneity among studies, and funnel plots and

precision plots also suggest publication bias in TC, LDL, and HDL analysis (**Figure 6**). We could not perform the meta-regression for other confounding factors—sleepiness, presence of hypertension or hyperglycemia, or insulin levels—since we have data on these variables only in few studies. These factors have been found to be associated with elevated dyslipidemia.

Another weakness of our meta-analysis is that all papers written in languages other than English were excluded, and we used only published studies, raising the possibility of publication bias.

In summary, there appears to be some evidence indicating improvement in degree of hypercholesterolemia in patients with OSA treated by pressure therapy. These findings suggest that mechanism of improvement in cardiovascular disorders in patients treated for OSA may be by reducing atherosclerosis by improving cholesterol profile. Prospective studies are needed to asses if this improvement is related to compliance with pressure therapy and if such improvement is only specific to pressure therapy or if it holds true for other modalities, such as oral devices and surgical treatment, as well.

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