NEW RESEARCH

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

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SCIENTIFIC INVESTIGATIONS

Background: Obstructive sleep apnea (OSA) is associated with obesity, metabolic syndrome, and dyslipidemia, which may be related to decrease androgen levels found in OSA patients. Dyslipidemia may contribute to atherosclerosis leading to increasing risk of heart disease.

Methods: Systematic review was conducted using PubMed and Cochrane library by utilizing different combinations of key words; sleep apnea, obstructive sleep apnea, serum lipids, dyslipidemia, cholesterol, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG). Inclusion criteria were: English articles, and studies with adult population in 2 groups of patients (patients with OSA and without OSA). A total 96 studies were reviewed for inclusion, with 25 studies pooled for analysis.

Results: Sixty-four studies were pooled for analysis; since some studies have more than one dataset, there were 107 datasets with 18,116 patients pooled for meta-analysis. All studies measured serum lipids. Total cholesterol pooled standardized difference in means was 0.267 (p = 0.001). LDL cholesterol pooled standardized difference in means was 0.296 (p = 0.001). HDL cholesterol pooled standardized difference in means was -0.433 (p = 0.001). Triglyceride pooled standardized difference in means was 0.603 (p = 0.001). Meta-regression for age, BMI, and AHI showed that age has significant effect for TC, LDL, and HDL. BMI had significant effect for LDL and HDL, while AHI had significant effect for LDL and TG.

Conclusion: Patients with OSA appear to have increased dyslipidemia (high total cholesterol, LDL, TG, and low HDL).

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

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Obstructive sleep apnea (OSA) is a common disorder affecting about 4% of middle-aged males and 2% of middle-aged women in the developed world and is a significant source of morbidity and mortality.[1,2] OSA is characterized by recurrent episodes of upper airway collapses during sleep. These recurrent episodes of upper airway collapse usually are accompanied by oxyhemoglobin desaturation and terminated by brief arousals which result in marked sleep fragmentation and chronic excessive daytime sleepiness (EDS).[1,2]

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.[3-9] OSA is associated with obesity and metabolic syndrome.[10] Multiple studies addressing this interesting and complex issue are available where lipid profile was measured in subjects with OSA.[11-35] We performed meta-analysis (MA) and meta-regression (MR) to specifically detect if OSA adversely affects degree of dyslipidemia; elevation of total cholesterol (TC), low density lipoprotein cholesterol (LDL), triglyceride (TG), and reduces level of high density lipoprotein cholesterol (HDL).

BRIEF SUMMARY

Current Knowledge/Study Rationale: Dyslipidemia (increase in total cholesterol, LDL, and triglycerides, and decrease in HDL) and obstructive sleep apnea (OSA) are risk factors for cardiovascular and cerebrovascular disorders. This meta-regression analysis estimates the adverse effect of OSA on dyslipidemia as many studies have measured dyslipidemia in subjects with OSA.

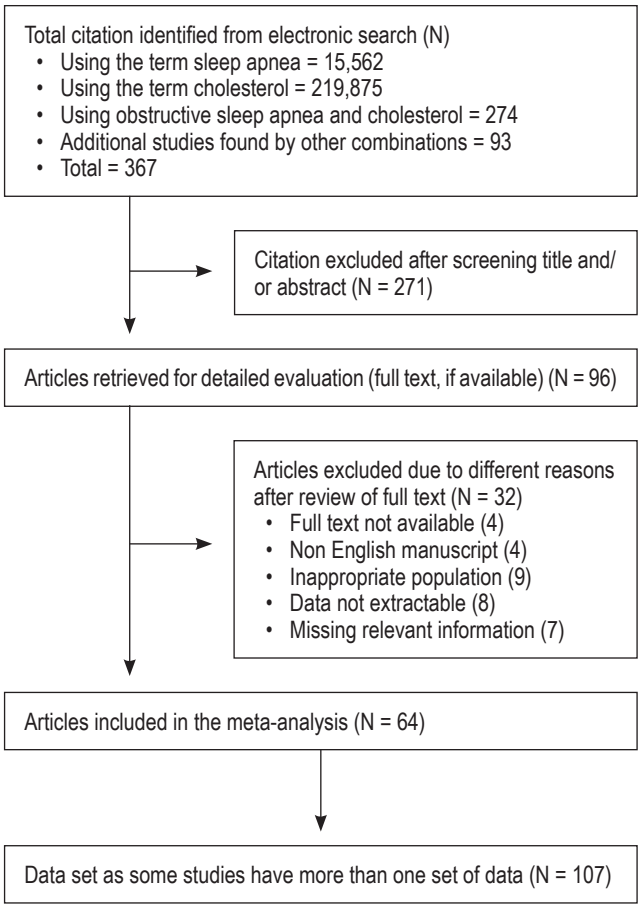
Study Impact: Study suggests dyslipidemia may be the mechanism of atherosclerosis in subjects with OSA. It also suggests OSA as potential target for treatment to improve dyslipidemia for prevention and treatment for cardiovascular and cerebrovascular disease.

METHODS

Data Source and Study Selection

Studies for review were found searching the PubMed, Cochrane, and EMBASE databases from January 01, 1968, to November 30th, 2013. Unpublished data from scientific meetings were not searched, since most abstract do not provide detail raw data needed for meta-analysis. Searches were

Figure 1—Flow diagram for search and inclusion and exclusion of studies



conducted using the keywords; sleep apnea, obstructive sleep apnea, 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, and TG) to ensure that no relevant source was left out. Additionally, each target and its abbreviated forms were searched in combination with obstructive sleep apnea. Multiple authors individually searched for and scored manuscripts for inclusion. If manuscripts 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 outcome of interest, (5) the study must have included ≥ 2 separate groups with one being a group consisting of individuals with obstructive sleep apnea and the other consisting of individuals without obstructive sleep apnea, (6) OSA was defined as AHI ≥ 5/h, (7) the study must have reported values in mean and standard deviation or median with range, and (8) patient number for all groups must have been reported.

Data Extraction and Statistical Analysis

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. For studies with data reported in median and range, mean and standard deviation were calculated utilizing methods outlined by Hozo et al.[36]

For studies in which OSA patients were compared with more than one group of control patients (e.g., obese and lean control), each set of data in the study was included in the meta-analysis as a separate data set. For example, Barcelo et al. compared lipid profiles of obese OSA patients and non-obese OSA to healthy controls.[11] We used standardized differences in means method for analyzing extracted data from studies.

Study selection, data extraction, and statistical analysis were all done in accordance to previously published methodology for meta-analyses. All statistical analysis was done using Comprehensive Meta-Analysis Version 2.

Heterogeneity was assessed by calculating the Cochrane Q statistic. Additionally I^2 statistics was also calculated to assess heterogeneity. An I^2 of 25% to 49% was considered to represent a low level of heterogeneity, 50% to 60% a moderate level, and 60% to 100% a high level. Standardized differences in mean were calculated using a random effects model for all outcomes with > 60% heterogeneity ($I^2 > 60$) and fixed effect model for $I^2 < 60$. 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. Publication bias analysis was done using four different methods to provide robust results. The methods included funnel plot analysis, Eggers reg intercept, Duval and Tweedie trim and fill, and Kendall tau with and without continuity correction.

RESULTS

The literature was ranked according to the hierarchy of evidence of Sackett et al.[37] A total of 96 studies were reviewed for inclusion. Sixty-four studies (with 107 datasets) met inclusion criteria and pooled for meta-analysis including total subjects 18,116 (controls [N = 10,145] and OSA subjects [N = 7,971]) for analysis (**Figure 1**).

Total Cholesterol

A total of 63 studies with 107 datasets including 18,111 subjects were pooled for TC. Standardized differences in means ranged from −2.05 to 5.0; pooled mean difference was calculated to be 0.267 (lower limit [LL] 0.146 to upper limit [UL] 0.389, p value = 0.001; see appendix following references, **Figure A1**).

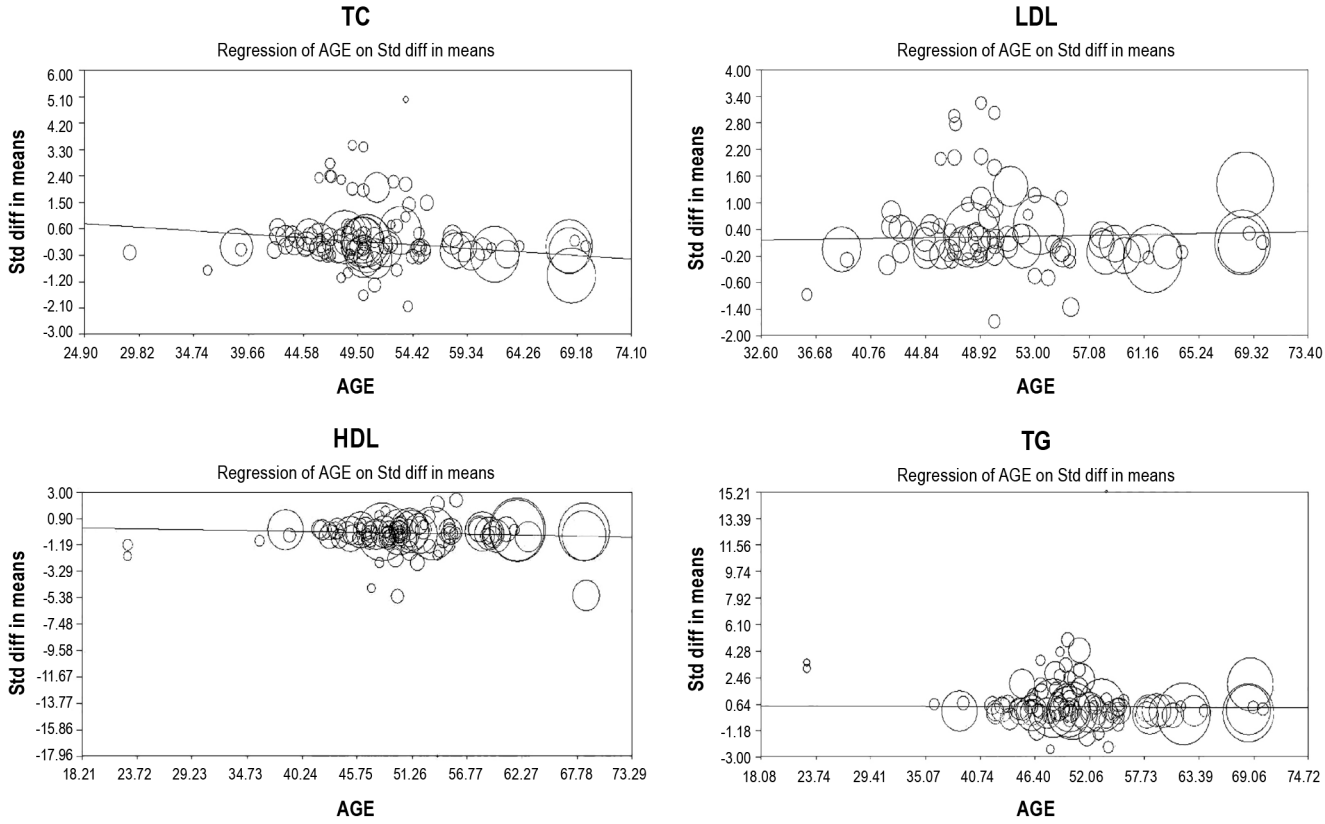
LDL Cholesterol

For LDL, 50 studies with 82 datasets including 13,894 subjects were pooled. Standardized mean difference in LDL ranged from −1.679 to 3.243, pooled mean difference was calculated to be 0.296 (LL 0.156 to UL 0.436, p = 0.001; **Figure A2**)

Table 1—Meta Regression statistics for Lipids (TC, LDL, HDL, TG) for Age, BMI, and AHI

	Age			BMI			AHI		
	slope	intercept	p	slope	intercept	p	slope	intercept	p
TC	-0.02	1.37	0.001	-0.0052	0.23	0.12	-0.0005	0.04	0.65
LDL	0.004	0.011	0.04	0.02	0.85	0.001	0.0006	0.22	0.67
HDL	-0.01	0.39	0.001	0.02	-1.18	0.001	-0.005	-0.24	0.001
TG	-0.002	0.55	0.34	-0.002	0.51	0.51	0.007	0.18	0.001

Figure 2—Meta-regression plots for age on TC, LDL, HDL, and TG



HDL Cholesterol

For HDL, 64 studies with 107 datasets including 18,116 subjects were pooled. Standardized mean difference ranged from −17.96 to 2.364. The pooled mean difference was calculated to be −0.433 (LL −0.604 to UL −0.262, $p < 0.001$; **Figure A3**).

Triglyceride

For TG, 62 studies with 104 datasets including 17,831 subjects were pooled and analyzed. Standardized mean difference ranged from −2.476 to 15.206, pooled mean difference was calculated to be 0.603 (LL 0.431 to UL 0.775, $p < 0.001$; **Figure A4**).

Meta-Regression to evaluate the effect of Age, BMI, and AHI on Lipid Levels

Data was also analyzed by meta-regression for effect of age, BMI, and AHI on all 4 variables of interest. Results of this analysis are given in **Table 1**. Age had significant effect for TC, LDL, and HDL. BMI had significant effect for LDL and HDL, while AHI had significant effect for HDL and TG (**Figures 2-4**). Only AHI had significant effect for TG.

Publication Bias Analysis

Publication bias analysis was done using four different methods to provide robust results. The methods included funnel plot analysis (**Figure 5**), Eggers reg intercept, Duval and Tweedie trim and fill, and Kendall tau with and without continuity correction. Overall, there was no significant publication bias in combined analysis. We also performed this analysis for individual lipid components and this analysis showed that there is low likelihood of publication bias for TC, TG, and LDL-c. HDL-c analysis showed likelihood of publication bias. We also performed precision plots (**Figure 6**).

Sensitivity Analysis

We also performed sensitivity analysis by removing one study at each step that did not change results, and it makes our results more robust (**Figures A5-A8**).

Figure 3—Meta-regression plots for BMI on TC, LDL, HDL, and TG

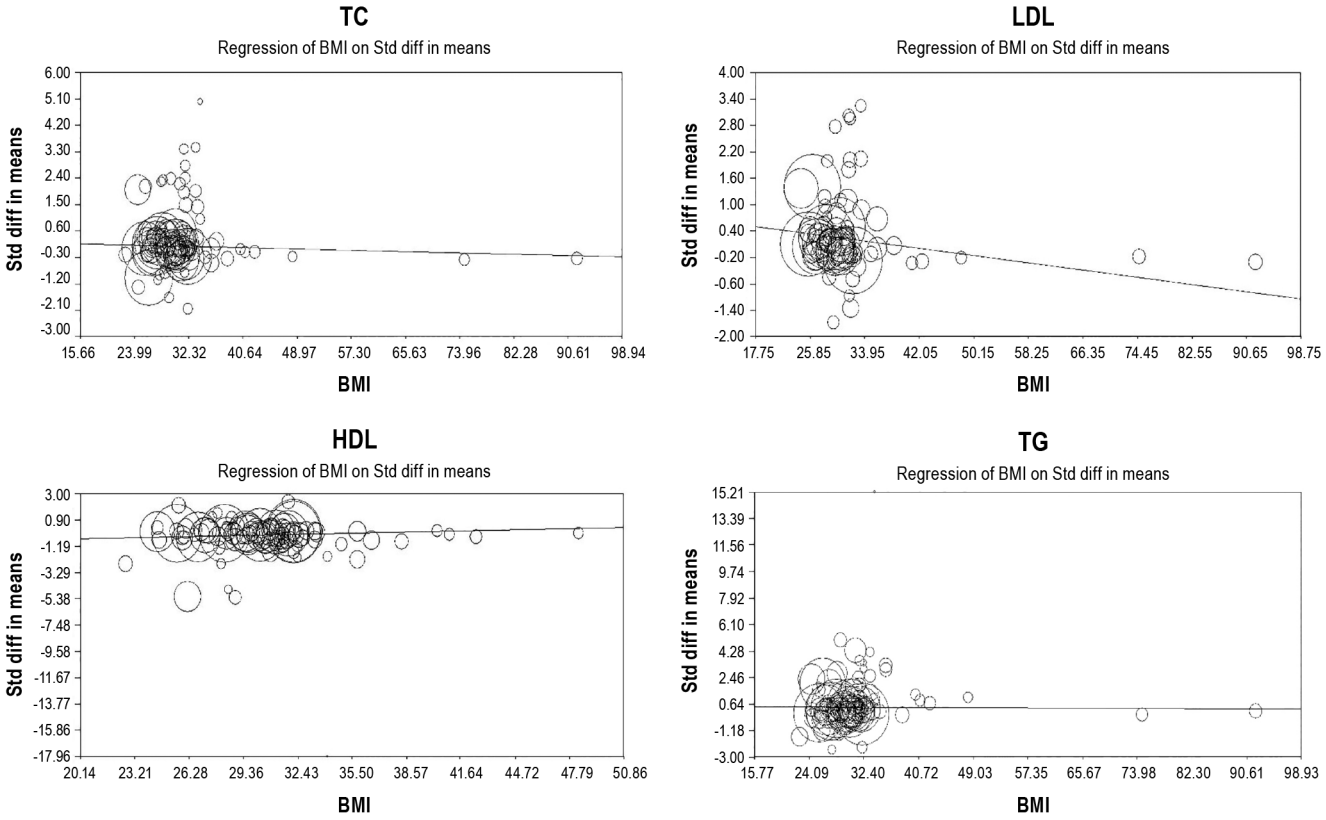


Figure 4—Meta-regression plots for AHI on TC, LDL, HDL, and TG

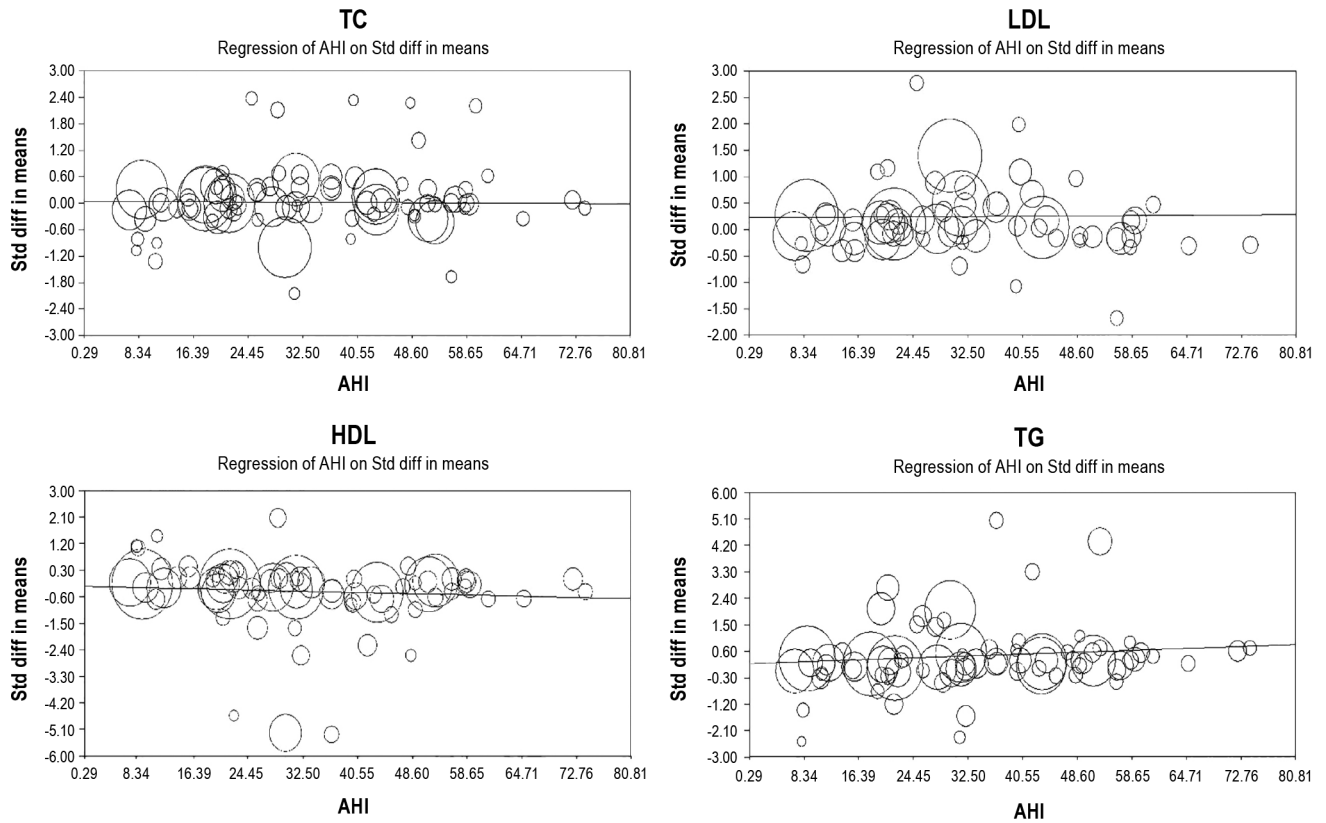


Figure 5—Publication bias estimation, Funnel plots for TC, LDL, HDL, and TG

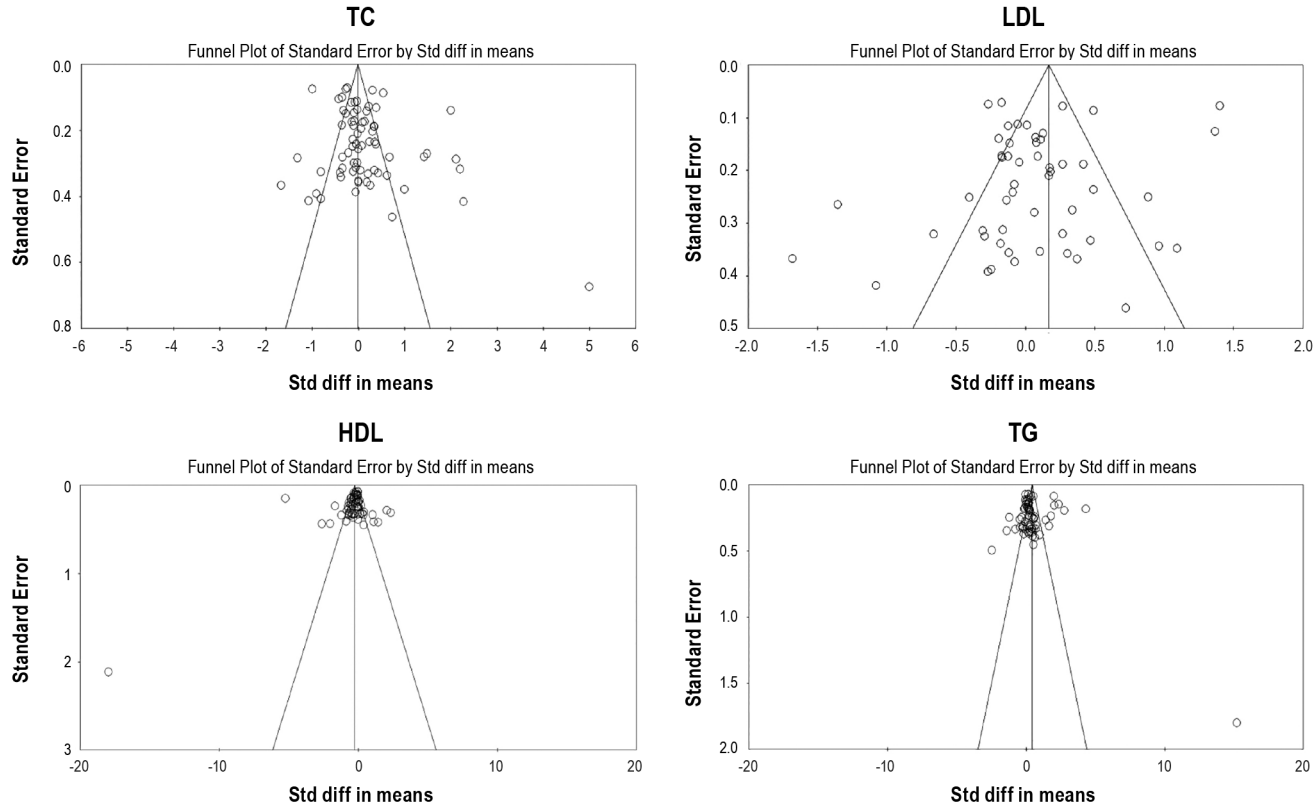
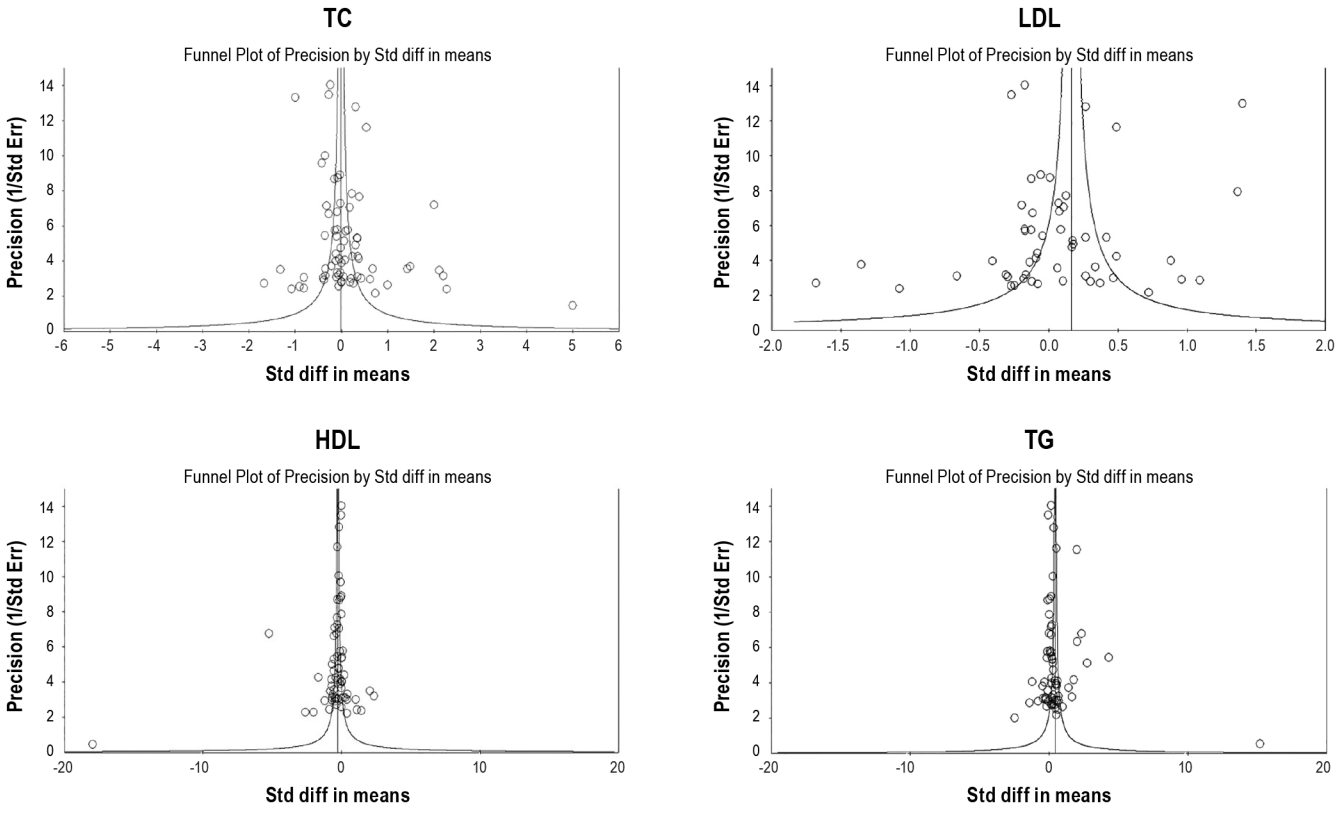


Figure 6—Precision plot analyses



DISCUSSION

There is strong positive associations between low-density lipoprotein (LDL) particles, which carry cholesterol, and the risk of coronary heart disease (CHD).[38,39] Randomized trials have demonstrated that lowering LDL cholesterol with medications reduces the risk of cardiac death, nonfatal myocardial infarction (MI), ischemic stroke, and the need for revascularization procedures.[40-42]

Although a clear causal relationship of OSA and dyslipidemia is yet to be demonstrated, there is increasing evidence that chronic intermittent hypoxia, a major component of OSA, is independently associated and possibly the root cause of the dyslipidemia via the generation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species, peroxidation of lipids, and sympathetic system dysfunction.[43] Intermittent hypoxia associated with sleep apnea promotes oxidative, and immune-inflammatory alterations.[44] Systemic inflammatory markers are higher in OSA patients than control subjects.[45] Cytokines, specifically IL-1, may alter LDL metabolism by human vascular endothelial cells and alter endothelial cell cholesterol metabolism. These changes in endothelial cell metabolism provide evidence supporting the critical role of cytokines in atherogenesis.[46]

The present meta-analysis (MA) showed that there is an increase in levels of dyslipidemia in subjects with OSA including total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride. An obvious majority of studies[11-26,31-35] showed this effect, while few did not.[27,30,31] Ozol et al. found less dyslipidemia in patients with moderate OSA than controls, most likely because their controls have high insulin resistance measured by HOMA and higher insulin levels than moderate OSA patients.[27] Moreover they found a high degree of dyslipidemia in their mild and severe OSA groups, which suggest that confounding factors may have played a role in their subjects' lipid levels (hypertension, obesity, and frequency of metabolic syndrome) in their sample. Another study which did not show significant dyslipidemia in OSA was by Salord et al. Their small sample (OSA, n = 15 and control n = 12) had unique characteristics: all controls without OSA were significantly obese (BMI 46.9) undergoing bariatric surgery.[31] Moreover their OSA patients were being treated with CPAP, which may explain the different findings of the study.

These findings highlight the adverse role of OSA as risk factor for cardiovascular diseases. These finding also suggest that increasing dyslipidemia may also be the mechanism of atherosclerosis in patients with OSA. It provides a potential target for treatment of dyslipidemia. Conceivably there is data suggesting that treatment of OSA by CPAP improves dyslipidemia, atherosclerosis and cardiovascular disease.[47]

Meta-regression Analysis for Confounding Variables

These MR plots show that dyslipidemia (HDL and TG) is correlated by severity of OSA, higher the AHI the higher the dyslipidemia. Gasa et al.[19] show that level of dyslipidemia correlates well with the severity of OSA; gradual worsening with worst numbers found in severe OSA group. Their regression analysis showed beta of 0.007 for TG. Likewise, Peled et al. found dyslipidemia in their sample as follow; control < mild OSA < severe OSA < moderate OSA[30]. Their Beta coefficient was 0.332 for AHI, which suggests that this relationship is probably confounded by multiple factors including weight, BMI, and comorbid conditions.

These MR plots also showed the modest but significant effect of BMI on dyslipidemia (LDL and HDL). This is in agreement with many other studies. Sharma et al. showed that BMI had an independent association with OSA.

This finding of heightened dyslipidemia in patients with obstructive sleep apnea suggest that treatment of sleep apnea should 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 affect management of these confounding variables.[48-51]

Several limitations of this meta-analysis should be emphasized. Available literature is low level evidence. Many of the relevant studies regarding the association between OSA and level of dyslipidemia were cross-sectional in nature, so the temporal relationships between these two factors were unclear. Funnel plots suggest heterogeneity and publication bias (**Figure 5**). We could not perform the meta-regression for other confounding factors—sleepiness, presence of hypertension, or measures of visceral adipose tissue—since we have data on these variables only in few studies. These factors have been found to be associated with elevated dyslipidemia.

One weakness of our meta-analysis is that all papers written in languages other than English were excluded. Another weakness is that studies not yet published were also excluded (publication bias).

In summary, there appears to be some evidence indicating higher degree of dyslipidemia in patients with OSA, these levels may be correlated to the level of severity of disease as suggested by meta-regression plot for AHI. These findings may explain, at least in part, the mechanism for atherosclerosis leading to cardiovascular disorder in patients with OSA and the common occurrence of systemic complications among these patients. Future studies are needed to further explore the correlation between the level of dyslipidemia and severity of OSA and to determine whether levels of dyslipidemia can be modified by therapeutic interventions in these patients.

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DISCLOSURE STATEMENT

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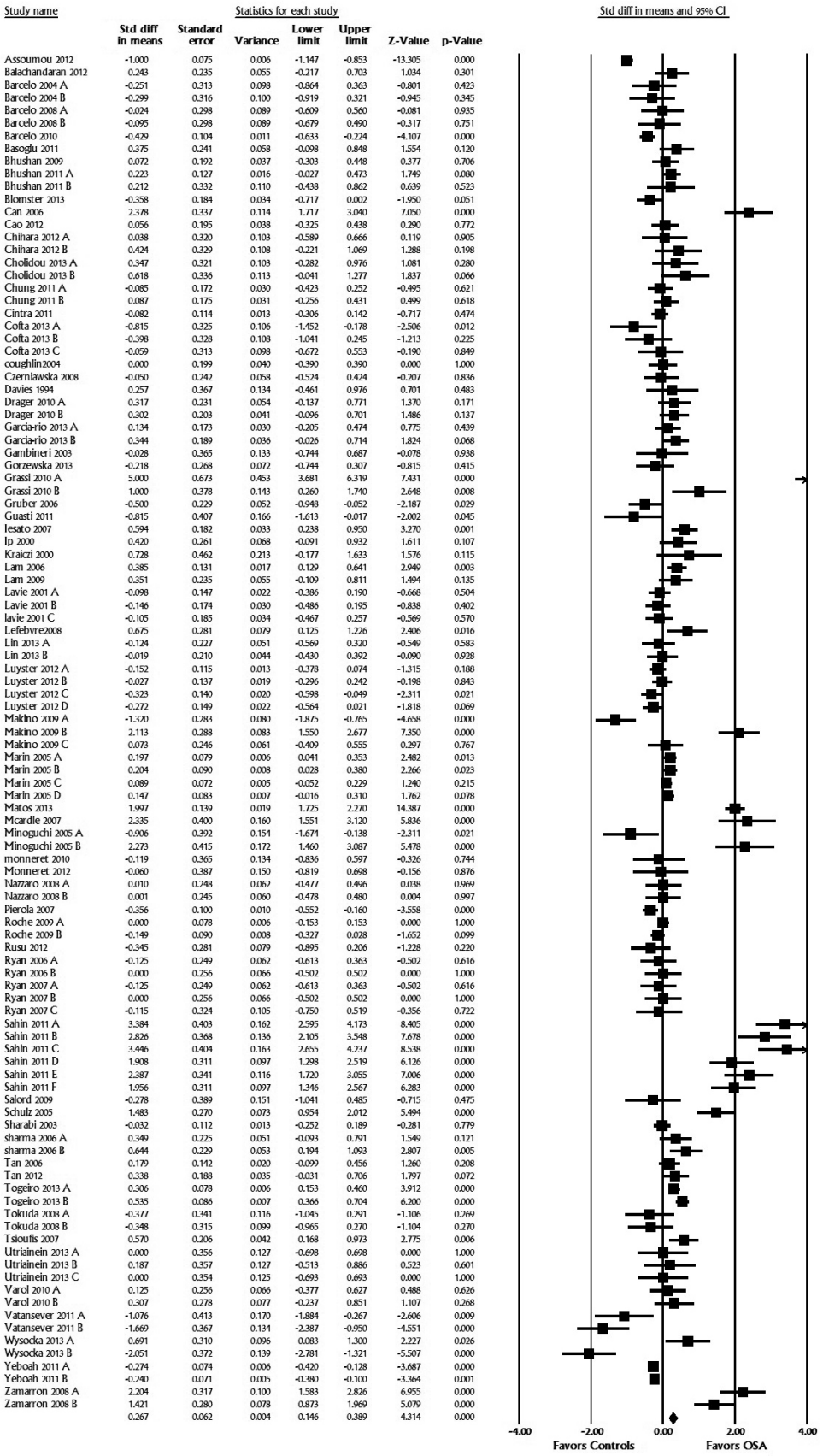
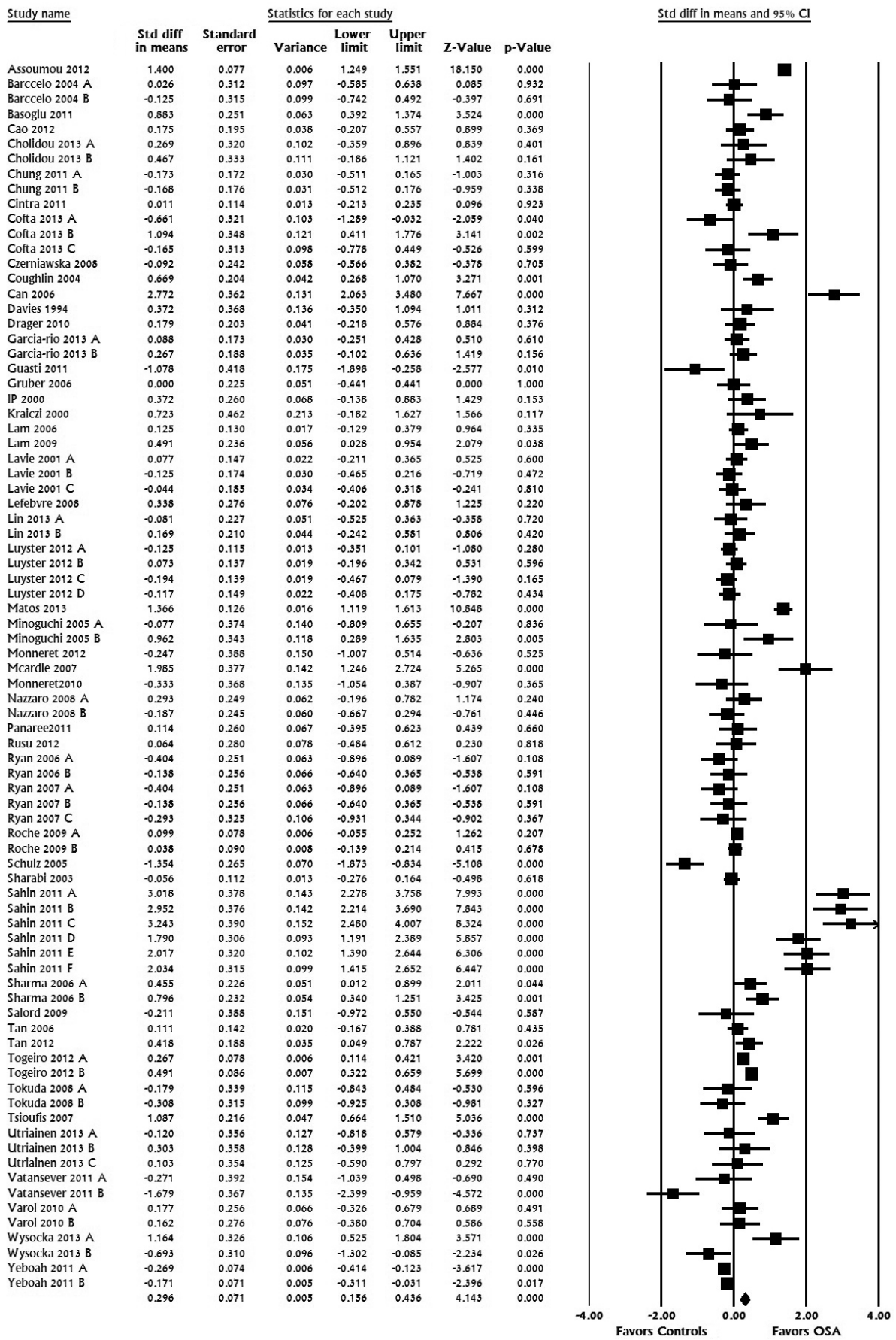
APPENDIX

Figure A1—Total cholesterol, standardized difference in means, OSA versus controls



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Assoumou 2012	-1.000	0.075	0.006	-1.147	-0.853	-13.305	0.000
Balachandaran 2012	0.243	0.235	0.055	-0.217	0.703	1.034	0.301
Barcelo 2004 A	-0.251	0.313	0.098	-0.864	0.363	-0.801	0.423
Barcelo 2004 B	-0.299	0.316	0.100	-0.919	0.321	-0.945	0.345
Barcelo 2008 A	-0.024	0.298	0.089	-0.609	0.560	-0.081	0.935
Barcelo 2008 B	-0.095	0.298	0.089	-0.679	0.490	-0.317	0.751
Barcelo 2010	-0.429	0.104	0.011	-0.633	-0.224	-4.107	0.000
Basoglu 2011	0.375	0.241	0.058	-0.098	0.848	1.554	0.120
Bhushan 2009	0.072	0.192	0.037	-0.303	0.448	0.377	0.706
Bhushan 2011 A	0.223	0.127	0.016	-0.027	0.473	1.749	0.080
Bhushan 2011 B	0.212	0.332	0.110	-0.438	0.862	0.639	0.523
Blomster 2013	-0.358	0.184	0.034	-0.717	0.002	-1.950	0.051
Can 2006	2.378	0.337	0.114	1.717	3.040	7.050	0.000
Cao 2012	0.056	0.195	0.038	-0.325	0.438	0.290	0.772
Chihara 2012 A	0.038	0.320	0.103	-0.589	0.666	0.119	0.905
Chihara 2012 B	0.424	0.329	0.108	-0.221	1.069	1.288	0.198
Cholidou 2013 A	0.347	0.321	0.103	-0.282	0.976	1.081	0.280
Cholidou 2013 B	0.618	0.336	0.113	-0.041	1.277	1.837	0.066
Chung 2011 A	-0.085	0.172	0.030	-0.423	0.252	-0.495	0.621
Chung 2011 B	0.087	0.175	0.031	-0.256	0.431	0.499	0.618
Cintra 2011	-0.082	0.114	0.013	-0.306	0.142	-0.717	0.474
Cofta 2013 A	-0.815	0.325	0.106	-1.452	-0.178	-2.506	0.012
Cofta 2013 B	-0.398	0.328	0.108	-1.041	0.245	-1.213	0.225
Cofta 2013 C	-0.059	0.313	0.098	-0.672	0.553	-0.190	0.849
coughlin2004	0.000	0.199	0.040	-0.390	0.390	0.000	1.000
Czerniawska 2008	-0.050	0.242	0.058	-0.524	0.424	-0.207	0.836
Davies 1994	0.257	0.367	0.134	-0.461	0.976	0.701	0.483
Drager 2010 A	0.317	0.231	0.054	-0.137	0.771	1.370	0.171
Drager 2010 B	0.302	0.203	0.041	-0.096	0.701	1.486	0.137
Garcia-rio 2013 A	0.134	0.173	0.030	-0.205	0.474	0.775	0.439
Garcia-rio 2013 B	0.344	0.189	0.036	-0.026	0.714	1.824	0.068
Gambineri 2003	-0.028	0.365	0.133	-0.744	0.687	-0.078	0.938
Gorzewska 2013	-0.218	0.268	0.072	-0.744	0.307	-0.815	0.415
Grassi 2010 A	5.000	0.673	0.453	3.681	6.319	7.431	0.000
Grassi 2010 B	1.000	0.378	0.143	0.260	1.740	2.648	0.008
Gruber 2006	-0.500	0.229	0.052	-0.948	-0.052	-2.187	0.029
Guasti 2011	-0.815	0.407	0.166	-1.613	-0.017	-2.002	0.045
Iesato 2007	0.594	0.182	0.033	0.238	0.950	3.270	0.001
Ip 2000	0.420	0.261	0.068	-0.091	0.932	1.611	0.107
Kraiczi 2000	0.728	0.462	0.213	-0.177	1.633	1.576	0.115
Lam 2006	0.385	0.131	0.017	0.129	0.641	2.949	0.003
Lam 2009	0.351	0.235	0.055	-0.109	0.811	1.494	0.135
Lavie 2001 A	-0.098	0.147	0.022	-0.386	0.190	-0.668	0.504
Lavie 2001 B	-0.146	0.174	0.030	-0.486	0.195	-0.838	0.402
lavie 2001 C	-0.105	0.185	0.034	-0.467	0.257	-0.569	0.570
Lefebvre2008	0.675	0.281	0.079	0.125	1.226	2.406	0.016
Lin 2013 A	-0.124	0.227	0.051	-0.569	0.320	-0.549	0.583
Lin 2013 B	-0.019	0.210	0.044	-0.430	0.392	-0.090	0.928
Luyster 2012 A	-0.152	0.115	0.013	-0.378	0.074	-1.315	0.188
Luyster 2012 B	-0.027	0.137	0.019	-0.296	0.242	-0.198	0.843
Luyster 2012 C	-0.323	0.140	0.020	-0.598	-0.049	-2.311	0.021
Luyster 2012 D	-0.272	0.149	0.022	-0.564	0.021	-1.818	0.069
Makino 2009 A	-1.320	0.283	0.080	-1.875	-0.765	-4.658	0.000
Makino 2009 B	2.113	0.288	0.083	1.550	2.677	7.350	0.000
Makino 2009 C	0.073	0.246	0.061	-0.409	0.555	0.297	0.767
Marin 2005 A	0.197	0.079	0.006	0.041	0.353	2.482	0.013
Marin 2005 B	0.204	0.090	0.008	0.028	0.380	2.266	0.023
Marin 2005 C	0.089	0.072	0.005	-0.052	0.229	1.240	0.215
Marin 2005 D	0.147	0.083	0.007	-0.016	0.310	1.762	0.078
Matos 2013	1.997	0.139	0.019	1.725	2.270	14.387	0.000
Mcardle 2007	2.335	0.400	0.160	1.551	3.120	5.836	0.000
Minoguchi 2005 A	-0.906	0.392	0.154	-1.674	-0.138	-2.311	0.021
Minoguchi 2005 B	2.273	0.415	0.172	1.460	3.087	5.478	0.000
monneret 2010	-0.119	0.365	0.134	-0.836	0.597	-0.326	0.744
Monneret 2012	-0.060	0.387	0.150	-0.819	0.698	-0.156	0.876
Nazzaro 2008 A	0.010	0.248	0.062	-0.477	0.496	0.038	0.969
Nazzaro 2008 B	0.001	0.245	0.060	-0.478	0.480	0.004	0.997
Pierola 2007	-0.356	0.100	0.010	-0.552	-0.160	-3.558	0.000
Roche 2009 A	0.000	0.078	0.006	-0.153	0.153	0.000	1.000
Roche 2009 B	-0.149	0.090	0.008	-0.327	0.028	-1.652	0.099
Rusu 2012	-0.345	0.281	0.079	-0.895	0.206	-1.228	0.220
Ryan 2006 A	-0.125	0.249	0.062	-0.613	0.363	-0.502	0.616
Ryan 2006 B	0.000	0.256	0.066	-0.502	0.502	0.000	1.000
Ryan 2007 A	-0.125	0.249	0.062	-0.613	0.363	-0.502	0.616
Ryan 2007 B	0.000	0.256	0.066	-0.502	0.502	0.000	1.000
Ryan 2007 C	-0.115	0.324	0.105	-0.750	0.519	-0.356	0.722
Sahin 2011 A	3.384	0.403	0.162	2.595	4.173	8.405	0.000
Sahin 2011 B	2.826	0.368	0.136	2.105	3.548	7.678	0.000
Sahin 2011 C	3.446	0.404	0.163	2.655	4.237	8.538	0.000
Sahin 2011 D	1.908	0.311	0.097	1.298	2.519	6.126	0.000
Sahin 2011 E	2.387	0.341	0.116	1.720	3.055	7.006	0.000
Sahin 2011 F	1.956	0.311	0.097	1.346	2.567	6.283	0.000
Salord 2009	-0.278	0.389	0.151	-1.041	0.485	-0.715	0.475
Schulz 2005	1.483	0.270	0.073	0.954	2.012	5.494	0.000
Sharabi 2003	-0.032	0.112	0.013	-0.252	0.189	-0.281	0.779
sharma 2006 A	0.349	0.225	0.051	-0.093	0.791	1.549	0.121
sharma 2006 B	0.644	0.229	0.053	0.194	1.093	2.807	0.005
Tan 2006	0.179	0.142	0.020	-0.099	0.456	1.260	0.208
Tan 2012	0.338	0.188	0.035	-0.031	0.706	1.797	0.072
Togeiro 2013 A	0.306	0.078	0.006	0.153	0.460	3.912	0.000
Togeiro 2013 B	0.535	0.086	0.007	0.366	0.704	6.200	0.000
Tokuda 2008 A	-0.377	0.341	0.116	-1.045	0.291	-1.106	0.269
Tokuda 2008 B	-0.348	0.315	0.099	-0.965	0.270	-1.104	0.270
Tsioufis 2007	0.570	0.206	0.042	0.168	0.973	2.775	0.006
Utriainein 2013 A	0.000	0.356	0.127	-0.698	0.698	0.000	1.000
Utriainein 2013 B	0.187	0.357	0.127	-0.513	0.886	0.523	0.601
Utriainein 2013 C	0.000	0.354	0.125	-0.693	0.693	0.000	1.000
Varol 2010 A	0.125	0.256	0.066	-0.377	0.627	0.488	0.626
Varol 2010 B	0.307	0.278	0.077	-0.237	0.851	1.107	0.268
Vatansever 2011 A	-1.076	0.413	0.170	-1.884	-0.267	-2.606	0.009
Vatansever 2011 B	-1.669	0.367	0.134	-2.387	-0.950	-4.551	0.000
Wysocka 2013 A	0.691	0.310	0.096	0.083	1.300	2.227	0.026
Wysocka 2013 B	-2.051	0.372	0.139	-2.781	-1.321	-5.507	0.000
Yeboah 2011 A	-0.274	0.074	0.006	-0.420	-0.128	-3.687	0.000
Yeboah 2011 B	-0.240	0.071	0.005	-0.380	-0.100	-3.364	0.001
Zamarron 2008 A	2.204	0.317	0.100	1.583	2.826	6.955	0.000
Zamarron 2008 B	1.421	0.280	0.078	0.873	1.969	5.079	0.000
	0.267	0.062	0.004	0.146	0.389	4.314	0.000

Figure A2—LDL cholesterol, standardized difference in means, OSA versus controls



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Assoumou 2012	1.400	0.077	0.006	1.249	1.551	18.150	0.000
Barccelo 2004 A	0.026	0.312	0.097	-0.585	0.638	0.085	0.932
Barccelo 2004 B	-0.125	0.315	0.099	-0.742	0.492	-0.397	0.691
Basoglu 2011	0.883	0.251	0.063	0.392	1.374	3.524	0.000
Cao 2012	0.175	0.195	0.038	-0.207	0.557	0.899	0.369
Cholidou 2013 A	0.269	0.320	0.102	-0.359	0.896	0.839	0.401
Cholidou 2013 B	0.467	0.333	0.111	-0.186	1.121	1.402	0.161
Chung 2011 A	-0.173	0.172	0.030	-0.511	0.165	-1.003	0.316
Chung 2011 B	-0.168	0.176	0.031	-0.512	0.176	-0.959	0.338
Cintra 2011	0.011	0.114	0.013	-0.213	0.235	0.096	0.923
Cofta 2013 A	-0.661	0.321	0.103	-1.289	-0.032	-2.059	0.040
Cofta 2013 B	1.094	0.348	0.121	0.411	1.776	3.141	0.002
Cofta 2013 C	-0.165	0.313	0.098	-0.778	0.449	-0.526	0.599
Czerniawska 2008	-0.092	0.242	0.058	-0.566	0.382	-0.378	0.705
Coughlin 2004	0.669	0.204	0.042	0.268	1.070	3.271	0.001
Can 2006	2.772	0.362	0.131	2.063	3.480	7.667	0.000
Davies 1994	0.372	0.368	0.136	-0.350	1.094	1.011	0.312
Drager 2010	0.179	0.203	0.041	-0.218	0.576	0.884	0.376
Garcia-rio 2013 A	0.088	0.173	0.030	-0.251	0.428	0.510	0.610
Garcia-rio 2013 B	0.267	0.188	0.035	-0.102	0.636	1.419	0.156
Guasti 2011	-1.078	0.418	0.175	-1.898	-0.258	-2.577	0.010
Gruber 2006	0.000	0.225	0.051	-0.441	0.441	0.000	1.000
IP 2000	0.372	0.260	0.068	-0.138	0.883	1.429	0.153
Kraiczi 2000	0.723	0.462	0.213	-0.182	1.627	1.566	0.117
Lam 2006	0.125	0.130	0.017	-0.129	0.379	0.964	0.335
Lam 2009	0.491	0.236	0.056	0.028	0.954	2.079	0.038
Lavie 2001 A	0.077	0.147	0.022	-0.211	0.365	0.525	0.600
Lavie 2001 B	-0.125	0.174	0.030	-0.465	0.216	-0.719	0.472
Lavie 2001 C	-0.044	0.185	0.034	-0.406	0.318	-0.241	0.810
Lefebvre 2008	0.338	0.276	0.076	-0.202	0.878	1.225	0.220
Lin 2013 A	-0.081	0.227	0.051	-0.525	0.363	-0.358	0.720
Lin 2013 B	0.169	0.210	0.044	-0.242	0.581	0.806	0.420
Luyster 2012 A	-0.125	0.115	0.013	-0.351	0.101	-1.080	0.280
Luyster 2012 B	0.073	0.137	0.019	-0.196	0.342	0.531	0.596
Luyster 2012 C	-0.194	0.139	0.019	-0.467	0.079	-1.390	0.165
Luyster 2012 D	-0.117	0.149	0.022	-0.408	0.175	-0.782	0.434
Matos 2013	1.366	0.126	0.016	1.119	1.613	10.848	0.000
Minoguchi 2005 A	-0.077	0.374	0.140	-0.809	0.655	-0.207	0.836
Minoguchi 2005 B	0.962	0.343	0.118	0.289	1.635	2.803	0.005
Monneret 2012	-0.247	0.388	0.150	-1.007	0.514	-0.636	0.525
Mcardle 2007	1.985	0.377	0.142	1.246	2.724	5.265	0.000
Monneret2010	-0.333	0.368	0.135	-1.054	0.387	-0.907	0.365
Nazzaro 2008 A	0.293	0.249	0.062	-0.196	0.782	1.174	0.240
Nazzaro 2008 B	-0.187	0.245	0.060	-0.667	0.294	-0.761	0.446
Panaree2011	0.114	0.260	0.067	-0.395	0.623	0.439	0.660
Rusu 2012	0.064	0.280	0.078	-0.484	0.612	0.230	0.818
Ryan 2006 A	-0.404	0.251	0.063	-0.896	0.089	-1.607	0.108
Ryan 2006 B	-0.138	0.256	0.066	-0.640	0.365	-0.538	0.591
Ryan 2007 A	-0.404	0.251	0.063	-0.896	0.089	-1.607	0.108
Ryan 2007 B	-0.138	0.256	0.066	-0.640	0.365	-0.538	0.591
Ryan 2007 C	-0.293	0.325	0.106	-0.931	0.344	-0.902	0.367
Roche 2009 A	0.099	0.078	0.006	-0.055	0.252	1.262	0.207
Roche 2009 B	0.038	0.090	0.008	-0.139	0.214	0.415	0.678
Schulz 2005	-1.354	0.265	0.070	-1.873	-0.834	-5.108	0.000
Sharabi 2003	-0.056	0.112	0.013	-0.276	0.164	-0.498	0.618
Sahin 2011 A	3.018	0.378	0.143	2.278	3.758	7.993	0.000
Sahin 2011 B	2.952	0.376	0.142	2.214	3.690	7.843	0.000
Sahin 2011 C	3.243	0.390	0.152	2.480	4.007	8.324	0.000
Sahin 2011 D	1.790	0.306	0.093	1.191	2.389	5.857	0.000
Sahin 2011 E	2.017	0.320	0.102	1.390	2.644	6.306	0.000
Sahin 2011 F	2.034	0.315	0.099	1.415	2.652	6.447	0.000
Sharma 2006 A	0.455	0.226	0.051	0.012	0.899	2.011	0.044
Sharma 2006 B	0.796	0.232	0.054	0.340	1.251	3.425	0.001
Salord 2009	-0.211	0.388	0.151	-0.972	0.550	-0.544	0.587
Tan 2006	0.111	0.142	0.020	-0.167	0.388	0.781	0.435
Tan 2012	0.418	0.188	0.035	0.049	0.787	2.222	0.026
Togeiro 2012 A	0.267	0.078	0.006	0.114	0.421	3.420	0.001
Togeiro 2012 B	0.491	0.086	0.007	0.322	0.659	5.699	0.000
Tokuda 2008 A	-0.179	0.339	0.115	-0.843	0.484	-0.530	0.596
Tokuda 2008 B	-0.308	0.315	0.099	-0.925	0.308	-0.981	0.327
Tsioufis 2007	1.087	0.216	0.047	0.664	1.510	5.036	0.000
Utriainen 2013 A	-0.120	0.356	0.127	-0.818	0.579	-0.336	0.737
Utriainen 2013 B	0.303	0.358	0.128	-0.399	1.004	0.846	0.398
Utriainen 2013 C	0.103	0.354	0.125	-0.590	0.797	0.292	0.770
Vatansever 2011 A	-0.271	0.392	0.154	-1.039	0.498	-0.690	0.490
Vatansever 2011 B	-1.679	0.367	0.135	-2.399	-0.959	-4.572	0.000
Varol 2010 A	0.177	0.256	0.066	-0.326	0.679	0.689	0.491
Varol 2010 B	0.162	0.276	0.076	-0.380	0.704	0.586	0.558
Wysocka 2013 A	1.164	0.326	0.106	0.525	1.804	3.571	0.000
Wysocka 2013 B	-0.693	0.310	0.096	-1.302	-0.085	-2.234	0.026
Yeboah 2011 A	-0.269	0.074	0.006	-0.414	-0.123	-3.617	0.000
Yeboah 2011 B	-0.171	0.071	0.005	-0.311	-0.031	-2.396	0.017
	0.296	0.071	0.005	0.156	0.436	4.143	0.000

Figure A3—HDL cholesterol, standardized difference in means, OSA versus controls

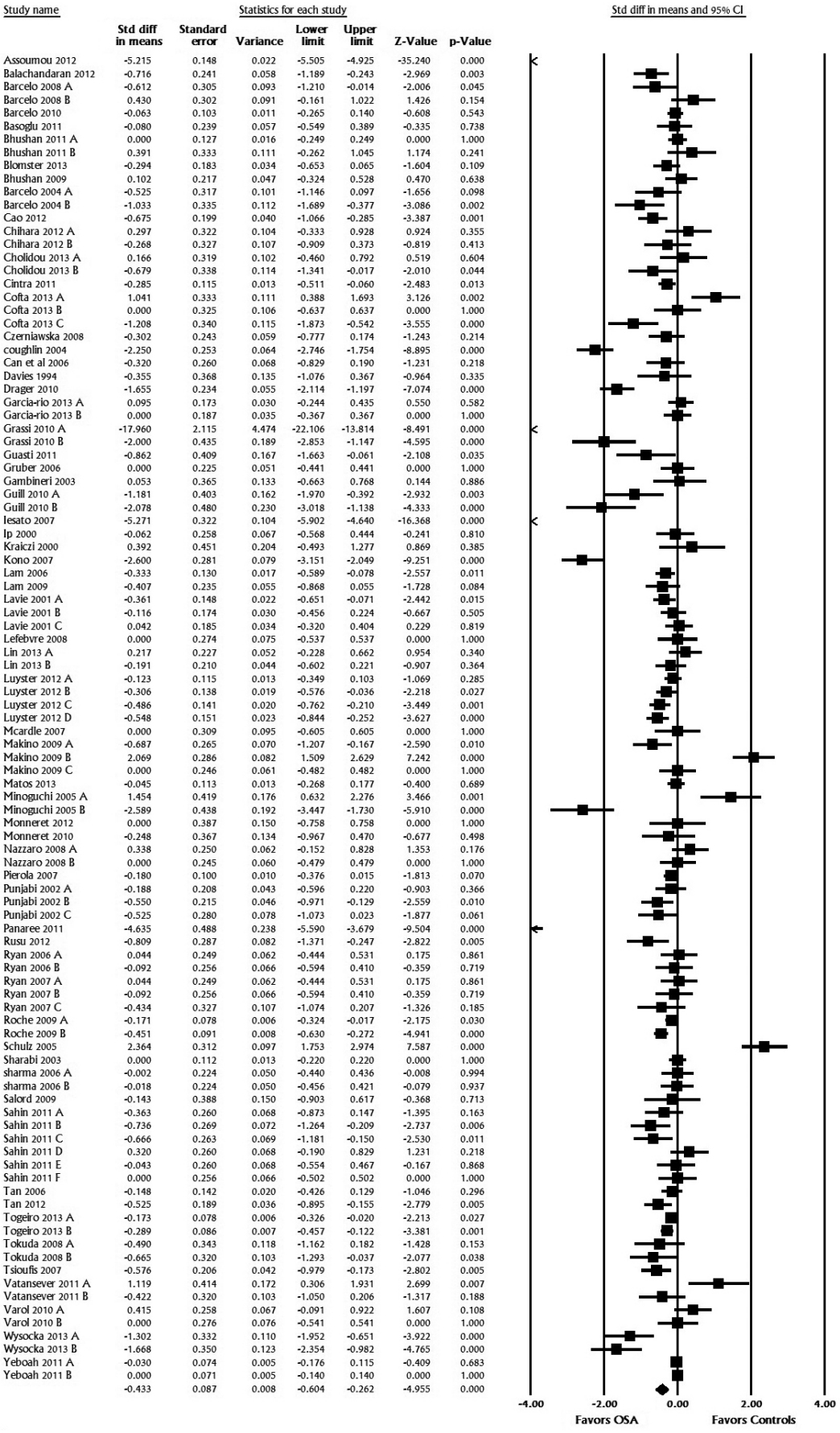
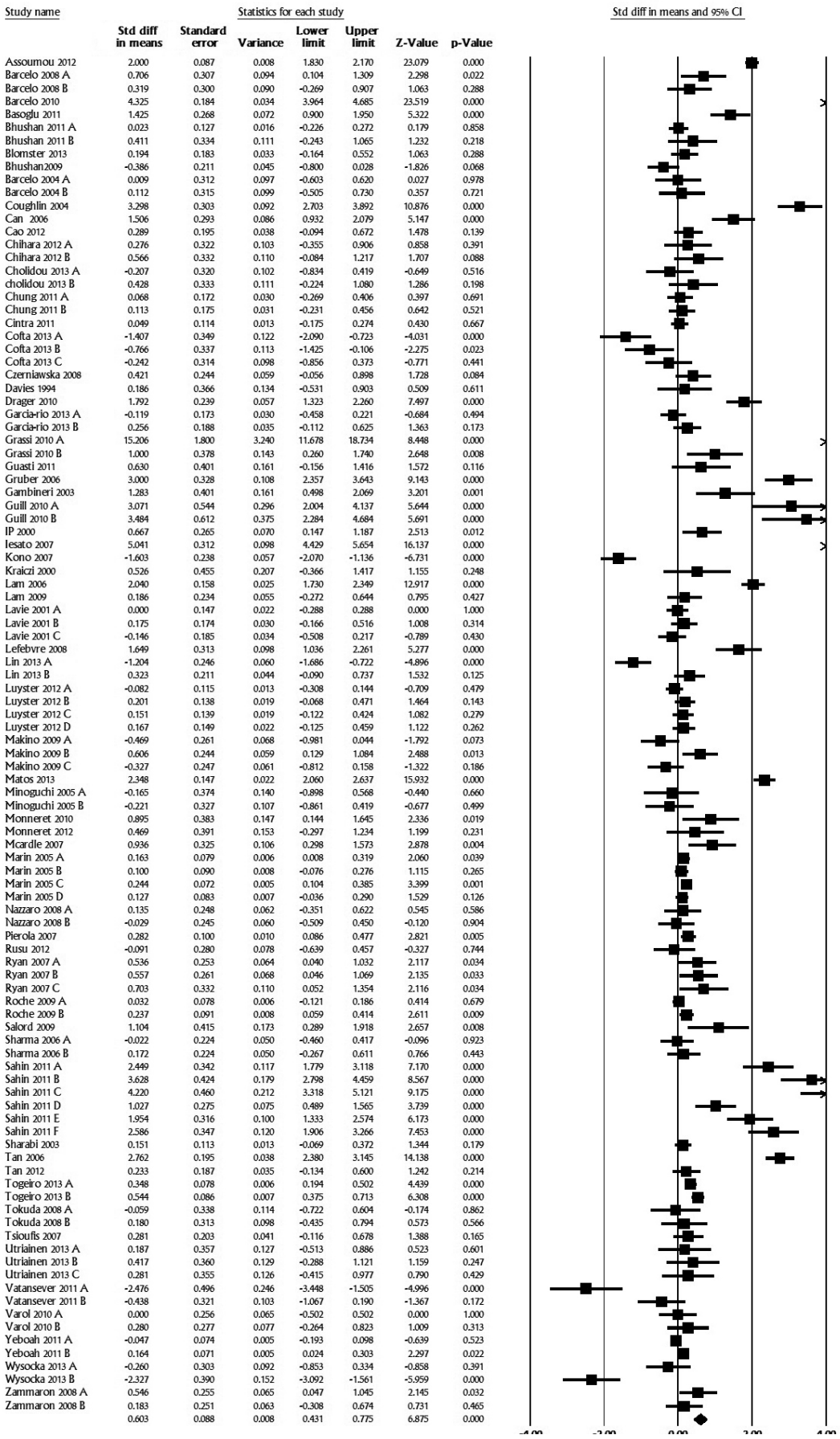


Figure A4—Triglycerides, standardized difference in means, OSA versus controls



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Assoumou 2012	2.000	0.087	0.008	1.830	2.170	23.079	0.000
Barcelo 2008 A	0.706	0.307	0.094	0.104	1.309	2.298	0.022
Barcelo 2008 B	0.319	0.300	0.090	-0.269	0.907	1.063	0.288
Barcelo 2010	4.325	0.184	0.034	3.964	4.685	23.519	0.000
Basoglu 2011	1.425	0.268	0.072	0.900	1.950	5.322	0.000
Bhushan 2011 A	0.023	0.127	0.016	-0.226	0.272	0.179	0.858
Bhushan 2011 B	0.411	0.334	0.111	-0.243	1.065	1.232	0.218
Blomster 2013	0.194	0.183	0.033	-0.164	0.552	1.063	0.288
Bhushan2009	-0.386	0.211	0.045	-0.800	0.028	-1.826	0.068
Barcelo 2004 A	0.009	0.312	0.097	-0.603	0.620	0.027	0.978
Barcelo 2004 B	0.112	0.315	0.099	-0.505	0.730	0.357	0.721
Coughlin 2004	3.298	0.303	0.092	2.703	3.892	10.876	0.000
Can 2006	1.506	0.293	0.086	0.932	2.079	5.147	0.000
Cao 2012	0.289	0.195	0.038	-0.094	0.672	1.478	0.139
Chihara 2012 A	0.276	0.322	0.103	-0.355	0.906	0.858	0.391
Chihara 2012 B	0.566	0.332	0.110	-0.084	1.217	1.707	0.088
Cholidou 2013 A	-0.207	0.320	0.102	-0.834	0.419	-0.649	0.516
cholidou 2013 B	0.428	0.333	0.111	-0.224	1.080	1.286	0.198
Chung 2011 A	0.068	0.172	0.030	-0.269	0.406	0.397	0.691
Chung 2011 B	0.113	0.175	0.031	-0.231	0.456	0.642	0.521
Cintra 2011	0.049	0.114	0.013	-0.175	0.274	0.430	0.667
Cofta 2013 A	-1.407	0.349	0.122	-2.090	-0.723	-4.031	0.000
Cofta 2013 B	-0.766	0.337	0.113	-1.425	-0.106	-2.275	0.023
Cofta 2013 C	-0.242	0.314	0.098	-0.856	0.373	-0.771	0.441
Czerniawska 2008	0.421	0.244	0.059	-0.056	0.898	1.728	0.084
Davies 1994	0.186	0.366	0.134	-0.531	0.903	0.509	0.611
Drager 2010	1.792	0.239	0.057	1.323	2.260	7.497	0.000
Garcia-rio 2013 A	-0.119	0.173	0.030	-0.458	0.221	-0.684	0.494
Garcia-rio 2013 B	0.256	0.188	0.035	-0.112	0.625	1.363	0.173
Grassi 2010 A	15.206	1.800	3.240	11.678	18.734	8.448	0.000
Grassi 2010 B	1.000	0.378	0.143	0.260	1.740	2.648	0.008
Guasti 2011	0.630	0.401	0.161	-0.156	1.416	1.572	0.116
Gruber 2006	3.000	0.328	0.108	2.357	3.643	9.143	0.000
Gambineri 2003	1.283	0.401	0.161	0.498	2.069	3.201	0.001
Guill 2010 A	3.071	0.544	0.296	2.004	4.137	5.644	0.000
Guill 2010 B	3.484	0.612	0.375	2.284	4.684	5.691	0.000
IP 2000	0.667	0.265	0.070	0.147	1.187	2.513	0.012
Iesato 2007	5.041	0.312	0.098	4.429	5.654	16.137	0.000
Kono 2007	-1.603	0.238	0.057	-2.070	-1.136	-6.731	0.000
Kraiczi 2000	0.526	0.455	0.207	-0.366	1.417	1.155	0.248
Lam 2006	2.040	0.158	0.025	1.730	2.349	12.917	0.000
Lam 2009	0.186	0.234	0.055	-0.272	0.644	0.795	0.427
Lavie 2001 A	0.000	0.147	0.022	-0.288	0.288	0.000	1.000
Lavie 2001 B	0.175	0.174	0.030	-0.166	0.516	1.008	0.314
Lavie 2001 C	-0.146	0.185	0.034	-0.508	0.217	-0.789	0.430
Lefebvre 2008	1.649	0.313	0.098	1.036	2.261	5.277	0.000
Lin 2013 A	-1.204	0.246	0.060	-1.686	-0.722	-4.896	0.000
Lin 2013 B	0.323	0.211	0.044	-0.090	0.737	1.532	0.125
Luyster 2012 A	-0.082	0.115	0.013	-0.308	0.144	-0.709	0.479
Luyster 2012 B	0.201	0.138	0.019	-0.068	0.471	1.464	0.143
Luyster 2012 C	0.151	0.139	0.019	-0.122	0.424	1.082	0.279
Luyster 2012 D	0.167	0.149	0.022	-0.125	0.459	1.122	0.262
Makino 2009 A	-0.469	0.261	0.068	-0.981	0.044	-1.792	0.073
Makino 2009 B	0.606	0.244	0.059	0.129	1.084	2.488	0.013
Makino 2009 C	-0.327	0.247	0.061	-0.812	0.158	-1.322	0.186
Matos 2013	2.348	0.147	0.022	2.060	2.637	15.932	0.000
Minoguchi 2005 A	-0.165	0.374	0.140	-0.898	0.568	-0.440	0.660
Minoguchi 2005 B	-0.221	0.327	0.107	-0.861	0.419	-0.677	0.499
Monneret 2010	0.895	0.383	0.147	0.144	1.645	2.336	0.019
Monneret 2012	0.469	0.391	0.153	-0.297	1.234	1.199	0.231
Mcardle 2007	0.936	0.325	0.106	0.298	1.573	2.878	0.004
Marin 2005 A	0.163	0.079	0.006	0.008	0.319	2.060	0.039
Marin 2005 B	0.100	0.090	0.008	-0.076	0.276	1.115	0.265
Marin 2005 C	0.244	0.072	0.005	0.104	0.385	3.399	0.001
Marin 2005 D	0.127	0.083	0.007	-0.036	0.290	1.529	0.126
Nazzaro 2008 A	0.135	0.248	0.062	-0.351	0.622	0.545	0.586
Nazzaro 2008 B	-0.029	0.245	0.060	-0.509	0.450	-0.120	0.904
Pierola 2007	0.282	0.100	0.010	0.086	0.477	2.821	0.005
Rusu 2012	-0.091	0.280	0.078	-0.639	0.457	-0.327	0.744
Ryan 2007 A	0.536	0.253	0.064	0.040	1.032	2.117	0.034
Ryan 2007 B	0.557	0.261	0.068	0.046	1.069	2.135	0.033
Ryan 2007 C	0.703	0.332	0.110	0.052	1.354	2.116	0.034
Roche 2009 A	0.032	0.078	0.006	-0.121	0.186	0.414	0.679
Roche 2009 B	0.237	0.091	0.008	0.059	0.414	2.611	0.009
Salord 2009	1.104	0.415	0.173	0.289	1.918	2.657	0.008
Sharma 2006 A	-0.022	0.224	0.050	-0.460	0.417	-0.096	0.923
Sharma 2006 B	0.172	0.224	0.050	-0.267	0.611	0.766	0.443
Sahin 2011 A	2.449	0.342	0.117	1.779	3.118	7.170	0.000
Sahin 2011 B	3.628	0.424	0.179	2.798	4.459	8.567	0.000
Sahin 2011 C	4.220	0.460	0.212	3.318	5.121	9.175	0.000
Sahin 2011 D	1.027	0.275	0.075	0.489	1.565	3.739	0.000
Sahin 2011 E	1.954	0.316	0.100	1.333	2.574	6.173	0.000
Sahin 2011 F	2.586	0.347	0.120	1.906	3.266	7.453	0.000
Sharabi 2003	0.151	0.113	0.013	-0.069	0.372	1.344	0.179
Tan 2006	2.762	0.195	0.038	2.380	3.145	14.138	0.000
Tan 2012	0.233	0.187	0.035	-0.134	0.600	1.242	0.214
Togeiro 2013 A	0.348	0.078	0.006	0.194	0.502	4.439	0.000
Togeiro 2013 B	0.544	0.086	0.007	0.375	0.713	6.308	0.000
Tokuda 2008 A	-0.059	0.338	0.114	-0.722	0.604	-0.174	0.862
Tokuda 2008 B	0.180	0.313	0.098	-0.435	0.794	0.573	0.566
Tsioufis 2007	0.281	0.203	0.041	-0.116	0.678	1.388	0.165
Utriainen 2013 A	0.187	0.357	0.127	-0.513	0.886	0.523	0.601
Utriainen 2013 B	0.417	0.360	0.129	-0.288	1.121	1.159	0.247
Utriainen 2013 C	0.281	0.355	0.126	-0.415	0.977	0.790	0.429
Vatansever 2011 A	-2.476	0.496	0.246	-3.448	-1.505	-4.996	0.000
Vatansever 2011 B	-0.438	0.321	0.103	-1.067	0.190	-1.367	0.172
Varol 2010 A	0.000	0.256	0.065	-0.502	0.502	0.000	1.000
Varol 2010 B	0.280	0.277	0.077	-0.264	0.823	1.009	0.313
Yeboah 2011 A	-0.047	0.074	0.005	-0.193	0.098	-0.639	0.523
Yeboah 2011 B	0.164	0.071	0.005	0.024	0.303	2.297	0.022
Wysocka 2013 A	-0.260	0.303	0.092	-0.853	0.334	-0.858	0.391
Wysocka 2013 B	-2.327	0.390	0.152	-3.092	-1.561	-5.959	0.000
Zammaron 2008 A	0.546	0.255	0.065	0.047	1.045	2.145	0.032
Zammaron 2008 B	0.183	0.251	0.063	-0.308	0.674	0.731	0.465
	0.603	0.088	0.008	0.431	0.775	6.875	0.000

Figure A5—TC sensitivity analysis

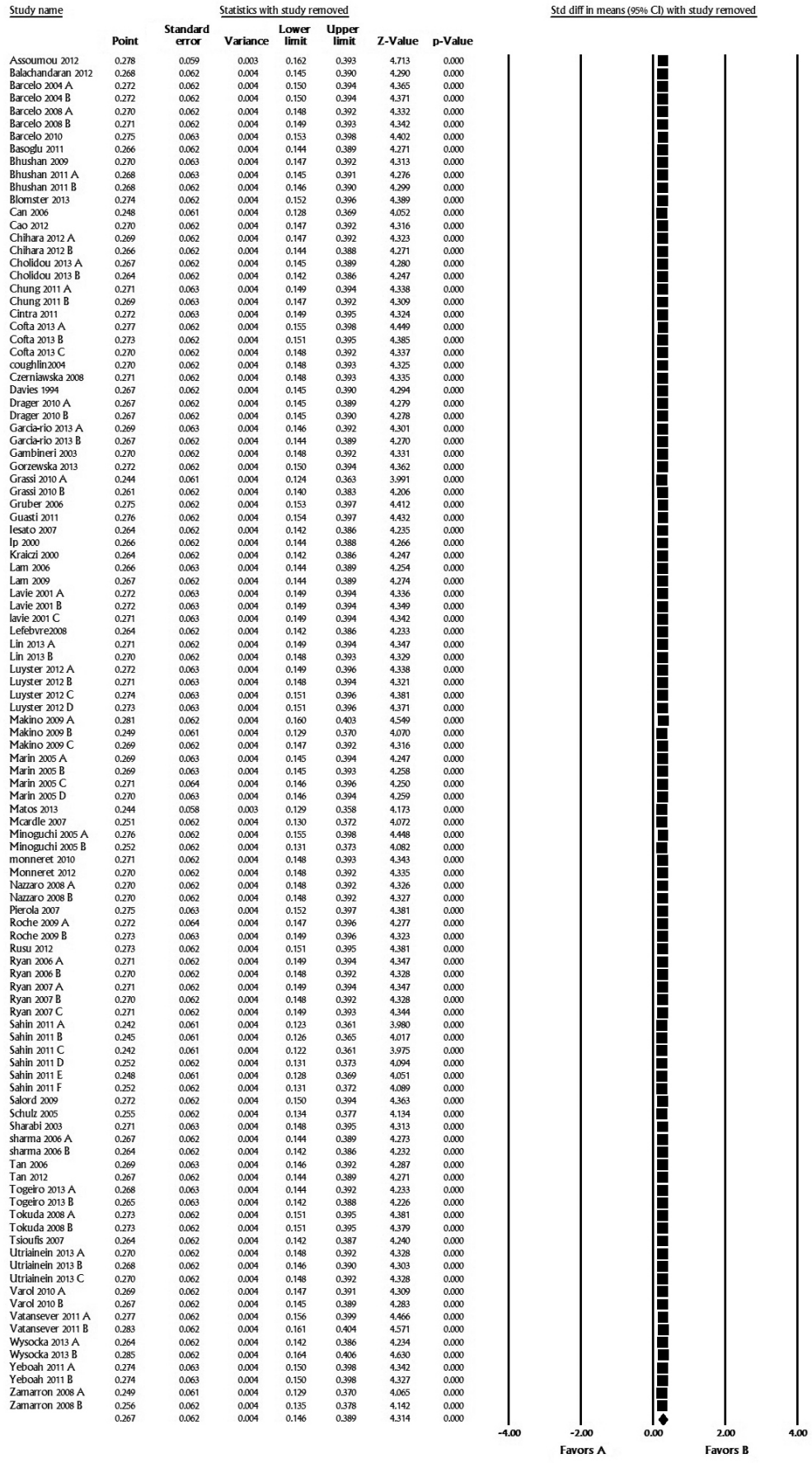
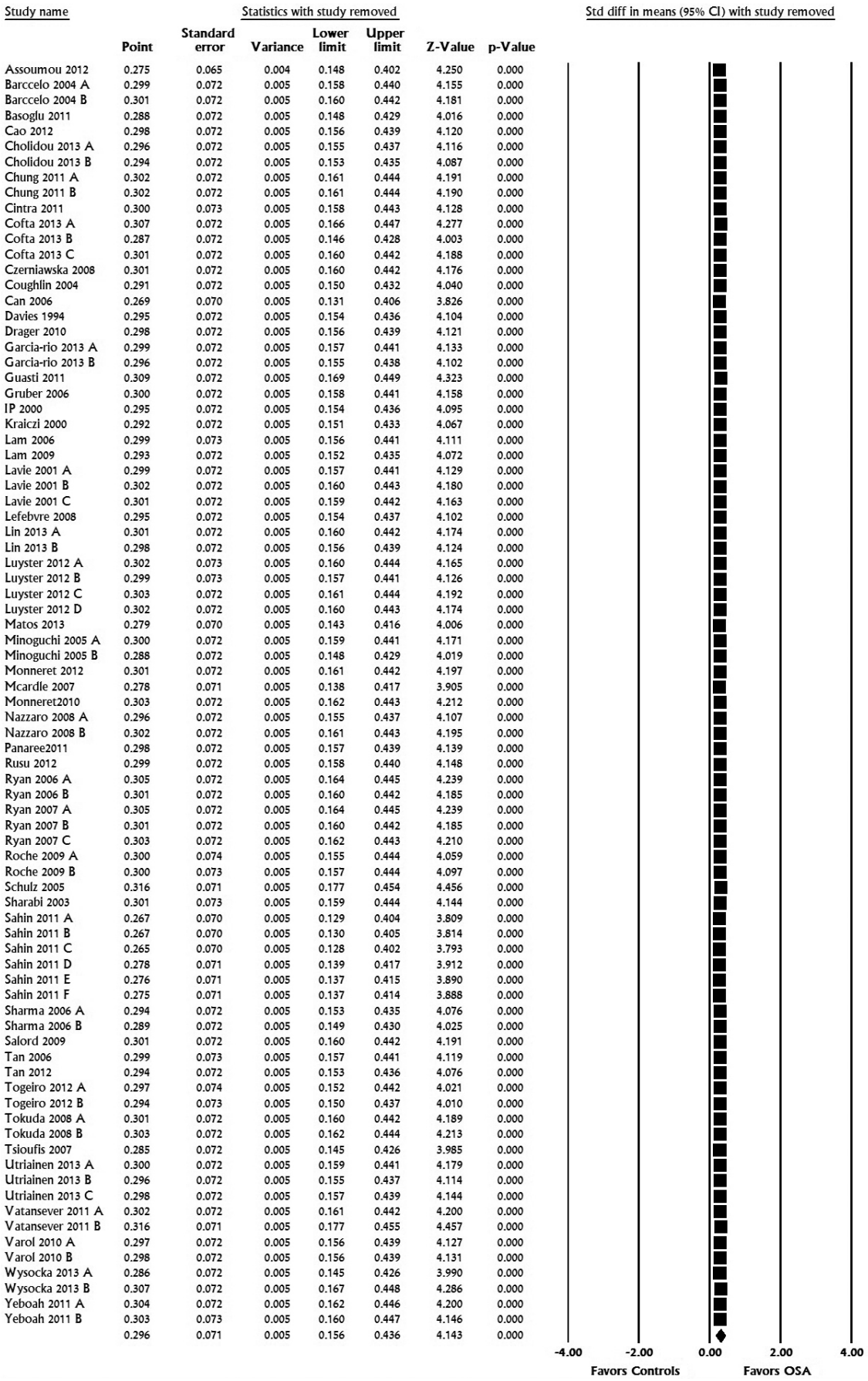


Figure A6—LDL sensitivity analysis



Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Assoumou 2012	0.275	0.065	0.004	0.148	0.402	4.250	0.000
Barccelo 2004 A	0.299	0.072	0.005	0.158	0.440	4.155	0.000
Barccelo 2004 B	0.301	0.072	0.005	0.160	0.442	4.181	0.000
Basoglu 2011	0.288	0.072	0.005	0.148	0.429	4.016	0.000
Cao 2012	0.298	0.072	0.005	0.156	0.439	4.120	0.000
Cholidou 2013 A	0.296	0.072	0.005	0.155	0.437	4.116	0.000
Cholidou 2013 B	0.294	0.072	0.005	0.153	0.435	4.087	0.000
Chung 2011 A	0.302	0.072	0.005	0.161	0.444	4.191	0.000
Chung 2011 B	0.302	0.072	0.005	0.161	0.444	4.190	0.000
Cintra 2011	0.300	0.073	0.005	0.158	0.443	4.128	0.000
Cofta 2013 A	0.307	0.072	0.005	0.166	0.447	4.277	0.000
Cofta 2013 B	0.287	0.072	0.005	0.146	0.428	4.003	0.000
Cofta 2013 C	0.301	0.072	0.005	0.160	0.442	4.188	0.000
Czerniawska 2008	0.301	0.072	0.005	0.160	0.442	4.176	0.000
Coughlin 2004	0.291	0.072	0.005	0.150	0.432	4.040	0.000
Can 2006	0.269	0.070	0.005	0.131	0.406	3.826	0.000
Davies 1994	0.295	0.072	0.005	0.154	0.436	4.104	0.000
Drager 2010	0.298	0.072	0.005	0.156	0.439	4.121	0.000
Garcia-rio 2013 A	0.299	0.072	0.005	0.157	0.441	4.133	0.000
Garcia-rio 2013 B	0.296	0.072	0.005	0.155	0.438	4.102	0.000
Guasti 2011	0.309	0.072	0.005	0.169	0.449	4.323	0.000
Gruber 2006	0.300	0.072	0.005	0.158	0.441	4.158	0.000
IP 2000	0.295	0.072	0.005	0.154	0.436	4.095	0.000
Kraiczi 2000	0.292	0.072	0.005	0.151	0.433	4.067	0.000
Lam 2006	0.299	0.073	0.005	0.156	0.441	4.111	0.000
Lam 2009	0.293	0.072	0.005	0.152	0.435	4.072	0.000
Lavie 2001 A	0.299	0.072	0.005	0.157	0.441	4.129	0.000
Lavie 2001 B	0.302	0.072	0.005	0.160	0.443	4.180	0.000
Lavie 2001 C	0.301	0.072	0.005	0.159	0.442	4.163	0.000
Lefebvre 2008	0.295	0.072	0.005	0.154	0.437	4.102	0.000
Lin 2013 A	0.301	0.072	0.005	0.160	0.442	4.174	0.000
Lin 2013 B	0.298	0.072	0.005	0.156	0.439	4.124	0.000
Luyster 2012 A	0.302	0.073	0.005	0.160	0.444	4.165	0.000
Luyster 2012 B	0.299	0.073	0.005	0.157	0.441	4.126	0.000
Luyster 2012 C	0.303	0.072	0.005	0.161	0.444	4.192	0.000
Luyster 2012 D	0.302	0.072	0.005	0.160	0.443	4.174	0.000
Matos 2013	0.279	0.070	0.005	0.143	0.416	4.006	0.000
Minoguchi 2005 A	0.300	0.072	0.005	0.159	0.441	4.171	0.000
Minoguchi 2005 B	0.288	0.072	0.005	0.148	0.429	4.019	0.000
Monneret 2012	0.301	0.072	0.005	0.161	0.442	4.197	0.000
Mcardle 2007	0.278	0.071	0.005	0.138	0.417	3.905	0.000
Monneret2010	0.303	0.072	0.005	0.162	0.443	4.212	0.000
Nazzaro 2008 A	0.296	0.072	0.005	0.155	0.437	4.107	0.000
Nazzaro 2008 B	0.302	0.072	0.005	0.161	0.443	4.195	0.000
Panaree2011	0.298	0.072	0.005	0.157	0.439	4.139	0.000
Rusu 2012	0.299	0.072	0.005	0.158	0.440	4.148	0.000
Ryan 2006 A	0.305	0.072	0.005	0.164	0.445	4.239	0.000
Ryan 2006 B	0.301	0.072	0.005	0.160	0.442	4.185	0.000
Ryan 2007 A	0.305	0.072	0.005	0.164	0.445	4.239	0.000
Ryan 2007 B	0.301	0.072	0.005	0.160	0.442	4.185	0.000
Ryan 2007 C	0.303	0.072	0.005	0.162	0.443	4.210	0.000
Roche 2009 A	0.300	0.074	0.005	0.155	0.444	4.059	0.000
Roche 2009 B	0.300	0.073	0.005	0.157	0.444	4.097	0.000
Schulz 2005	0.316	0.071	0.005	0.177	0.454	4.456	0.000
Sharabi 2003	0.301	0.073	0.005	0.159	0.444	4.144	0.000
Sahin 2011 A	0.267	0.070	0.005	0.129	0.404	3.809	0.000
Sahin 2011 B	0.267	0.070	0.005	0.130	0.405	3.814	0.000
Sahin 2011 C	0.265	0.070	0.005	0.128	0.402	3.793	0.000
Sahin 2011 D	0.278	0.071	0.005	0.139	0.417	3.912	0.000
Sahin 2011 E	0.276	0.071	0.005	0.137	0.415	3.890	0.000
Sahin 2011 F	0.275	0.071	0.005	0.137	0.414	3.888	0.000
Sharma 2006 A	0.294	0.072	0.005	0.153	0.435	4.076	0.000
Sharma 2006 B	0.289	0.072	0.005	0.149	0.430	4.025	0.000
Salord 2009	0.301	0.072	0.005	0.160	0.442	4.191	0.000
Tan 2006	0.299	0.073	0.005	0.157	0.441	4.119	0.000
Tan 2012	0.294	0.072	0.005	0.153	0.436	4.076	0.000
Togeiro 2012 A	0.297	0.074	0.005	0.152	0.442	4.021	0.000
Togeiro 2012 B	0.294	0.073	0.005	0.150	0.437	4.010	0.000
Tokuda 2008 A	0.301	0.072	0.005	0.160	0.442	4.189	0.000
Tokuda 2008 B	0.303	0.072	0.005	0.162	0.444	4.213	0.000
Tsioufis 2007	0.285	0.072	0.005	0.145	0.426	3.985	0.000
Utriainen 2013 A	0.300	0.072	0.005	0.159	0.441	4.179	0.000
Utriainen 2013 B	0.296	0.072	0.005	0.155	0.437	4.114	0.000
Utriainen 2013 C	0.298	0.072	0.005	0.157	0.439	4.144	0.000
Vatansever 2011 A	0.302	0.072	0.005	0.161	0.442	4.200	0.000
Vatansever 2011 B	0.316	0.071	0.005	0.177	0.455	4.457	0.000
Varol 2010 A	0.297	0.072	0.005	0.156	0.439	4.127	0.000
Varol 2010 B	0.298	0.072	0.005	0.156	0.439	4.131	0.000
Wysocka 2013 A	0.286	0.072	0.005	0.145	0.426	3.990	0.000
Wysocka 2013 B	0.307	0.072	0.005	0.167	0.448	4.286	0.000
Yeboah 2011 A	0.304	0.072	0.005	0.162	0.446	4.200	0.000
Yeboah 2011 B	0.303	0.073	0.005	0.160	0.447	4.146	0.000
	0.296	0.071	0.005	0.156	0.436	4.143	0.000

Figure A7—HDL sensitivity analysis

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Assoumou 2012	-0.191	0.060	0.004	-0.308	-0.073	-3.181	0.001
Balachandaran 2012	-0.291	0.108	0.012	-0.503	-0.078	-2.683	0.007
Barcelo 2008 A	-0.293	0.108	0.012	-0.505	-0.080	-2.702	0.007
Barcelo 2008 B	-0.308	0.108	0.012	-0.520	-0.096	-2.848	0.004
Barcelo 2010	-0.302	0.110	0.012	-0.518	-0.086	-2.742	0.006
Basoglu 2011	-0.301	0.108	0.012	-0.513	-0.088	-2.772	0.006
Bhushan 2011 A	-0.303	0.109	0.012	-0.517	-0.088	-2.766	0.006
Bhushan 2011 B	-0.307	0.108	0.012	-0.519	-0.095	-2.841	0.004
Blomster 2013	-0.298	0.109	0.012	-0.511	-0.084	-2.735	0.006
Cao 2012	-0.291	0.109	0.012	-0.504	-0.079	-2.684	0.007
Chihara 2012 A	-0.306	0.108	0.012	-0.518	-0.094	-2.828	0.005
Chihara 2012 B	-0.298	0.108	0.012	-0.510	-0.085	-2.750	0.006
Cholidou 2013 A	-0.304	0.108	0.012	-0.516	-0.092	-2.809	0.005
Cholidou 2013 B	-0.292	0.108	0.012	-0.504	-0.080	-2.696	0.007
Cintra 2011	-0.298	0.110	0.012	-0.514	-0.083	-2.714	0.007
Cofta 2013 A	-0.316	0.108	0.012	-0.528	-0.105	-2.936	0.003
Cofta 2013 B	-0.302	0.108	0.012	-0.514	-0.089	-2.786	0.005
Cofta 2013 C	-0.284	0.108	0.012	-0.496	-0.072	-2.630	0.009
Czerniawska 2008	-0.297	0.108	0.012	-0.510	-0.085	-2.740	0.006
Davies 1994	-0.296	0.108	0.012	-0.508	-0.084	-2.740	0.006
Drager 2010	-0.276	0.107	0.012	-0.486	-0.065	-2.567	0.010
Garcia-rio 2013 A	-0.304	0.109	0.012	-0.517	-0.091	-2.793	0.005
Garcia-rio 2013 B	-0.302	0.109	0.012	-0.515	-0.089	-2.780	0.005
Grassi 2010 A	-0.258	0.105	0.011	-0.464	-0.052	-2.454	0.014
Grassi 2010 B	-0.275	0.108	0.012	-0.485	-0.064	-2.552	0.011
Guasti 2011	-0.290	0.108	0.012	-0.501	-0.078	-2.679	0.007
Kraiczi 2000	-0.306	0.108	0.012	-0.518	-0.094	-2.834	0.005
Lam 2006	-0.297	0.110	0.012	-0.512	-0.083	-2.715	0.007
Lam 2009	-0.296	0.109	0.012	-0.508	-0.083	-2.725	0.006
Lavie 2001 A	-0.297	0.109	0.012	-0.511	-0.083	-2.717	0.007
Lavie 2001 B	-0.300	0.109	0.012	-0.514	-0.087	-2.760	0.006
Lavie 2001 C	-0.303	0.109	0.012	-0.516	-0.090	-2.786	0.005
Lefebvre 2008	-0.302	0.108	0.012	-0.514	-0.089	-2.785	0.005
Lin 2013 A	-0.305	0.108	0.012	-0.518	-0.093	-2.817	0.005
Lin 2013 B	-0.299	0.109	0.012	-0.512	-0.086	-2.753	0.006
Luyster 2012 A	-0.301	0.110	0.012	-0.516	-0.086	-2.739	0.006
Luyster 2012 B	-0.298	0.109	0.012	-0.512	-0.083	-2.722	0.006
Luyster 2012 C	-0.295	0.109	0.012	-0.509	-0.081	-2.697	0.007
Luyster 2012 D	-0.294	0.109	0.012	-0.507	-0.080	-2.692	0.007
Makino 2009 A	-0.291	0.108	0.012	-0.504	-0.079	-2.689	0.007
Makino 2009 B	-0.332	0.106	0.011	-0.540	-0.124	-3.125	0.002
Makino 2009 C	-0.302	0.108	0.012	-0.514	-0.089	-2.784	0.005
Matos 2013	-0.302	0.110	0.012	-0.518	-0.087	-2.752	0.006
Minoguchi 2005 A	-0.320	0.108	0.012	-0.531	-0.110	-2.978	0.003
Minoguchi 2005 B	-0.267	0.107	0.011	-0.477	-0.057	-2.488	0.013
Monneret 2012	-0.301	0.108	0.012	-0.513	-0.089	-2.786	0.005
Pierola 2007	-0.300	0.110	0.012	-0.517	-0.084	-2.719	0.007
Punjabi 2002 A	-0.299	0.109	0.012	-0.512	-0.086	-2.753	0.006
Punjabi 2002 B	-0.293	0.109	0.012	-0.506	-0.081	-2.703	0.007
Punjabi 2002 C	-0.294	0.108	0.012	-0.506	-0.081	-2.712	0.007
Rusu 2012	-0.290	0.108	0.012	-0.502	-0.077	-2.675	0.007
Ryan 2006 A	-0.303	0.108	0.012	-0.515	-0.090	-2.791	0.005
Ryan 2006 B	-0.300	0.108	0.012	-0.513	-0.088	-2.771	0.006
Ryan 2007 A	-0.303	0.108	0.012	-0.515	-0.090	-2.791	0.005
Ryan 2007 B	-0.300	0.108	0.012	-0.513	-0.088	-2.771	0.006
Ryan 2007 C	-0.295	0.108	0.012	-0.507	-0.083	-2.727	0.006
Schulz 2005	-0.335	0.106	0.011	-0.543	-0.128	-3.164	0.002
Sharabi 2003	-0.303	0.110	0.012	-0.518	-0.088	-2.759	0.006
Tan 2012	-0.294	0.109	0.012	-0.507	-0.081	-2.703	0.007
Togeiro 2013 A	-0.301	0.112	0.013	-0.521	-0.082	-2.692	0.007
Togeiro 2013 B	-0.299	0.111	0.012	-0.517	-0.081	-2.686	0.007
Tokuda 2008 A	-0.294	0.108	0.012	-0.507	-0.082	-2.721	0.007
Tokuda 2008 B	-0.292	0.108	0.012	-0.504	-0.080	-2.697	0.007
Vatansever 2011 A	-0.316	0.108	0.012	-0.527	-0.105	-2.933	0.003
Vatansever 2011 B	-0.295	0.108	0.012	-0.508	-0.083	-2.729	0.006
Yeboah 2011 A	-0.304	0.112	0.013	-0.523	-0.084	-2.712	0.007
Yeboah 2011 B	-0.304	0.112	0.013	-0.524	-0.085	-2.713	0.007
	-0.297	0.107	0.011	-0.507	-0.087	-2.771	0.006

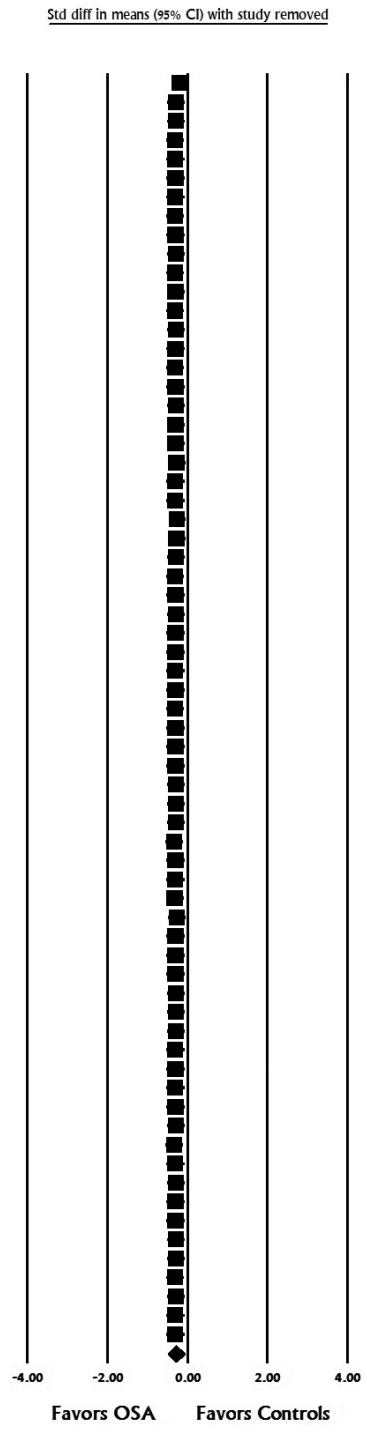
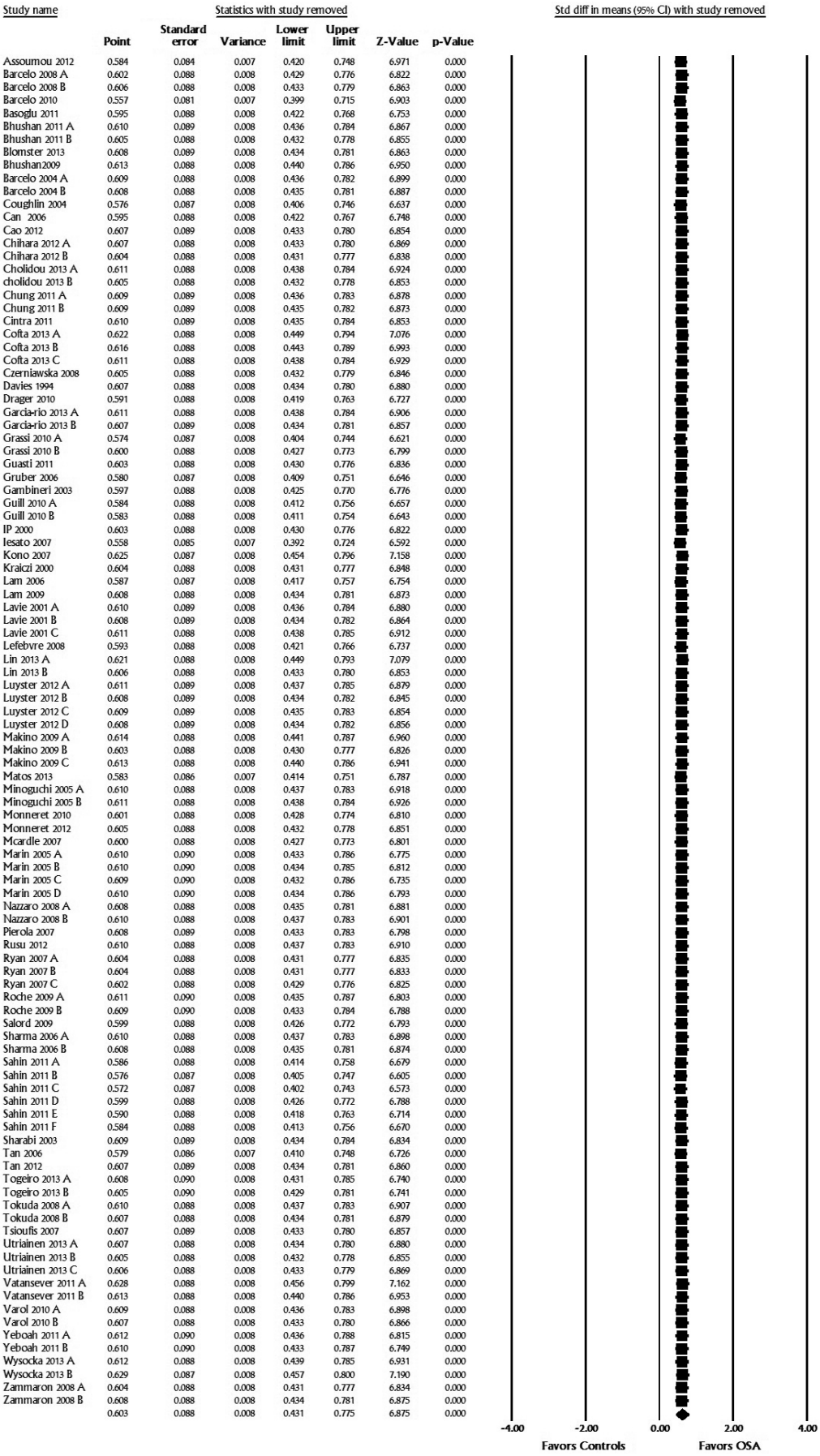


Figure A8—TG sensitivity analysis



Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Assoumou 2012	0.584	0.084	0.007	0.420	0.748	6.971	0.000
Barcelo 2008 A	0.602	0.088	0.008	0.429	0.776	6.822	0.000
Barcelo 2008 B	0.606	0.088	0.008	0.433	0.779	6.863	0.000
Barcelo 2010	0.557	0.081	0.007	0.399	0.715	6.903	0.000
Basoglu 2011	0.595	0.088	0.008	0.422	0.768	6.753	0.000
Bhushan 2011 A	0.610	0.089	0.008	0.436	0.784	6.867	0.000
Bhushan 2011 B	0.605	0.088	0.008	0.432	0.778	6.855	0.000
Blomster 2013	0.608	0.089	0.008	0.434	0.781	6.863	0.000
Bhushan2009	0.613	0.088	0.008	0.440	0.786	6.950	0.000
Barcelo 2004 A	0.609	0.088	0.008	0.436	0.782	6.899	0.000
Barcelo 2004 B	0.608	0.088	0.008	0.435	0.781	6.887	0.000
Coughlin 2004	0.576	0.087	0.008	0.406	0.746	6.637	0.000
Can 2006	0.595	0.088	0.008	0.422	0.767	6.748	0.000
Cao 2012	0.607	0.089	0.008	0.433	0.780	6.854	0.000
Chihara 2012 A	0.607	0.088	0.008	0.433	0.780	6.869	0.000
Chihara 2012 B	0.604	0.088	0.008	0.431	0.777	6.838	0.000
Cholidou 2013 A	0.611	0.088	0.008	0.438	0.784	6.924	0.000
cholidou 2013 B	0.605	0.088	0.008	0.432	0.778	6.853	0.000
Chung 2011 A	0.609	0.089	0.008	0.436	0.783	6.878	0.000
Chung 2011 B	0.609	0.089	0.008	0.435	0.782	6.873	0.000
Cintra 2011	0.610	0.089	0.008	0.435	0.784	6.853	0.000
Cofta 2013 A	0.622	0.088	0.008	0.449	0.794	7.076	0.000
Cofta 2013 B	0.616	0.088	0.008	0.443	0.789	6.993	0.000
Cofta 2013 C	0.611	0.088	0.008	0.438	0.784	6.929	0.000
Czerniawska 2008	0.605	0.088	0.008	0.432	0.779	6.846	0.000
Davies 1994	0.607	0.088	0.008	0.434	0.780	6.880	0.000
Drager 2010	0.591	0.088	0.008	0.419	0.763	6.727	0.000
Garcia-rio 2013 A	0.611	0.088	0.008	0.438	0.784	6.906	0.000
Garcia-rio 2013 B	0.607	0.089	0.008	0.434	0.781	6.857	0.000
Grassi 2010 A	0.574	0.087	0.008	0.404	0.744	6.621	0.000
Grassi 2010 B	0.600	0.088	0.008	0.427	0.773	6.799	0.000
Guasti 2011	0.603	0.088	0.008	0.430	0.776	6.836	0.000
Gruber 2006	0.580	0.087	0.008	0.409	0.751	6.646	0.000
Gambineri 2003	0.597	0.088	0.008	0.425	0.770	6.776	0.000
Guill 2010 A	0.584	0.088	0.008	0.412	0.756	6.657	0.000
Guill 2010 B	0.583	0.088	0.008	0.411	0.754	6.643	0.000
IP 2000	0.603	0.088	0.008	0.430	0.776	6.822	0.000
Iesato 2007	0.558	0.085	0.007	0.392	0.724	6.592	0.000
Kono 2007	0.625	0.087	0.008	0.454	0.796	7.158	0.000
Kraiczi 2000	0.604	0.088	0.008	0.431	0.777	6.848	0.000
Lam 2006	0.587	0.087	0.008	0.417	0.757	6.754	0.000
Lam 2009	0.608	0.088	0.008	0.434	0.781	6.873	0.000
Lavie 2001 A	0.610	0.089	0.008	0.436	0.784	6.880	0.000
Lavie 2001 B	0.608	0.089	0.008	0.434	0.782	6.864	0.000
Lavie 2001 C	0.611	0.088	0.008	0.438	0.785	6.912	0.000
Lefebvre 2008	0.593	0.088	0.008	0.421	0.766	6.737	0.000
Lin 2013 A	0.621	0.088	0.008	0.449	0.793	7.079	0.000
Lin 2013 B	0.606	0.088	0.008	0.433	0.780	6.853	0.000
Luyster 2012 A	0.611	0.089	0.008	0.437	0.785	6.879	0.000
Luyster 2012 B	0.608	0.089	0.008	0.434	0.782	6.845	0.000
Luyster 2012 C	0.609	0.089	0.008	0.435	0.783	6.854	0.000
Luyster 2012 D	0.608	0.089	0.008	0.434	0.782	6.856	0.000
Makino 2009 A	0.614	0.088	0.008	0.441	0.787	6.960	0.000
Makino 2009 B	0.603	0.088	0.008	0.430	0.777	6.826	0.000
Makino 2009 C	0.613	0.088	0.008	0.440	0.786	6.941	0.000
Matos 2013	0.583	0.086	0.007	0.414	0.751	6.787	0.000
Minoguchi 2005 A	0.610	0.088	0.008	0.437	0.783	6.918	0.000
Minoguchi 2005 B	0.611	0.088	0.008	0.438	0.784	6.926	0.000
Monneret 2010	0.601	0.088	0.008	0.428	0.774	6.810	0.000
Monneret 2012	0.605	0.088	0.008	0.432	0.778	6.851	0.000
Mcardle 2007	0.600	0.088	0.008	0.427	0.773	6.801	0.000
Marin 2005 A	0.610	0.090	0.008	0.433	0.786	6.775	0.000
Marin 2005 B	0.610	0.090	0.008	0.434	0.785	6.812	0.000
Marin 2005 C	0.609	0.090	0.008	0.432	0.786	6.735	0.000
Marin 2005 D	0.610	0.090	0.008	0.434	0.786	6.793	0.000
Nazzaro 2008 A	0.608	0.088	0.008	0.435	0.781	6.881	0.000
Nazzaro 2008 B	0.610	0.088	0.008	0.437	0.783	6.901	0.000
Pierola 2007	0.608	0.089	0.008	0.433	0.783	6.798	0.000
Rusu 2012	0.610	0.088	0.008	0.437	0.783	6.910	0.000
Ryan 2007 A	0.604	0.088	0.008	0.431	0.777	6.835	0.000
Ryan 2007 B	0.604	0.088	0.008	0.431	0.777	6.833	0.000
Ryan 2007 C	0.602	0.088	0.008	0.429	0.776	6.825	0.000
Roche 2009 A	0.611	0.090	0.008	0.435	0.787	6.803	0.000
Roche 2009 B	0.609	0.090	0.008	0.433	0.784	6.788	0.000
Salord 2009	0.599	0.088	0.008	0.426	0.772	6.793	0.000
Sharma 2006 A	0.610	0.088	0.008	0.437	0.783	6.898	0.000
Sharma 2006 B	0.608	0.088	0.008	0.435	0.781	6.874	0.000
Sahin 2011 A	0.586	0.088	0.008	0.414	0.758	6.679	0.000
Sahin 2011 B	0.576	0.087	0.008	0.405	0.747	6.605	0.000
Sahin 2011 C	0.572	0.087	0.008	0.402	0.743	6.573	0.000
Sahin 2011 D	0.599	0.088	0.008	0.426	0.772	6.788	0.000
Sahin 2011 E	0.590	0.088	0.008	0.418	0.763	6.714	0.000
Sahin 2011 F	0.584	0.088	0.008	0.413	0.756	6.670	0.000
Sharabi 2003	0.609	0.089	0.008	0.434	0.784	6.834	0.000
Tan 2006	0.579	0.086	0.007	0.410	0.748	6.726	0.000
Tan 2012	0.607	0.089	0.008	0.434	0.781	6.860	0.000
Togeiro 2013 A	0.608	0.090	0.008	0.431	0.785	6.740	0.000
Togeiro 2013 B	0.605	0.090	0.008	0.429	0.781	6.741	0.000
Tokuda 2008 A	0.610	0.088	0.008	0.437	0.783	6.907	0.000
Tokuda 2008 B	0.607	0.088	0.008	0.434	0.781	6.879	0.000
Tsioufis 2007	0.607	0.089	0.008	0.433	0.780	6.857	0.000
Utriainen 2013 A	0.607	0.088	0.008	0.434	0.780	6.880	0.000
Utriainen 2013 B	0.605	0.088	0.008	0.432	0.778	6.855	0.000
Utriainen 2013 C	0.606	0.088	0.008	0.433	0.779	6.869	0.000
Vatansever 2011 A	0.628	0.088	0.008	0.456	0.799	7.162	0.000
Vatansever 2011 B	0.613	0.088	0.008	0.440	0.786	6.953	0.000
Varol 2010 A	0.609	0.088	0.008	0.436	0.783	6.898	0.000
Varol 2010 B	0.607	0.088	0.008	0.433	0.780	6.866	0.000
Yeboah 2011 A	0.612	0.090	0.008	0.436	0.788	6.815	0.000
Yeboah 2011 B	0.610	0.090	0.008	0.433	0.787	6.749	0.000
Wysocka 2013 A	0.612	0.088	0.008	0.439	0.785	6.931	0.000
Wysocka 2013 B	0.629	0.087	0.008	0.457	0.800	7.190	0.000
Zammaron 2008 A	0.604	0.088	0.008	0.431	0.777	6.834	0.000
Zammaron 2008 B	0.608	0.088	0.008	0.434	0.781	6.875	0.000
	0.603	0.088	0.008	0.431	0.775	6.875	0.000