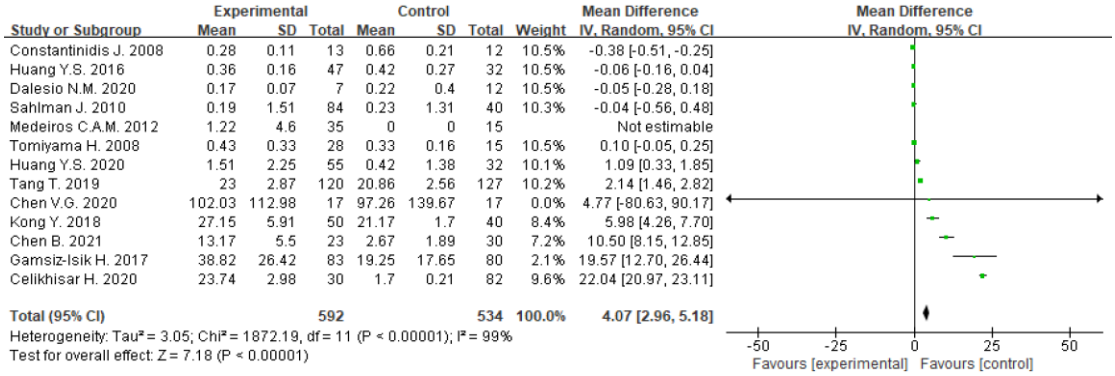
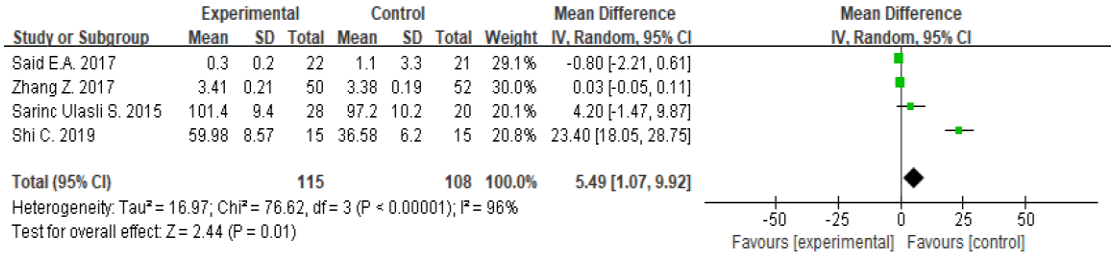
Supplemental material 2: Supplemental Figures.

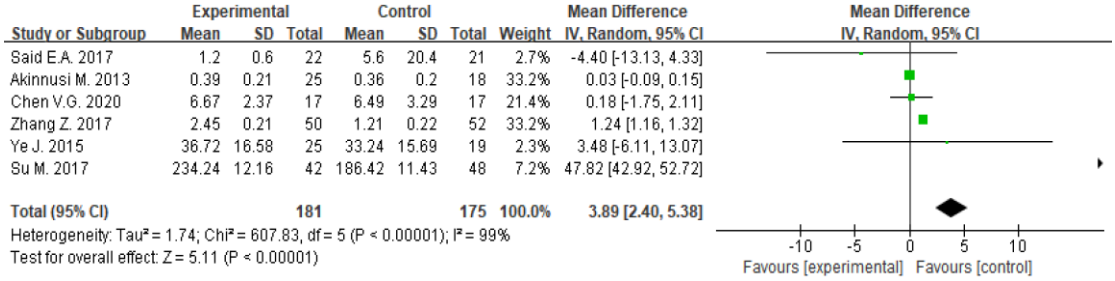
A. IL-1β



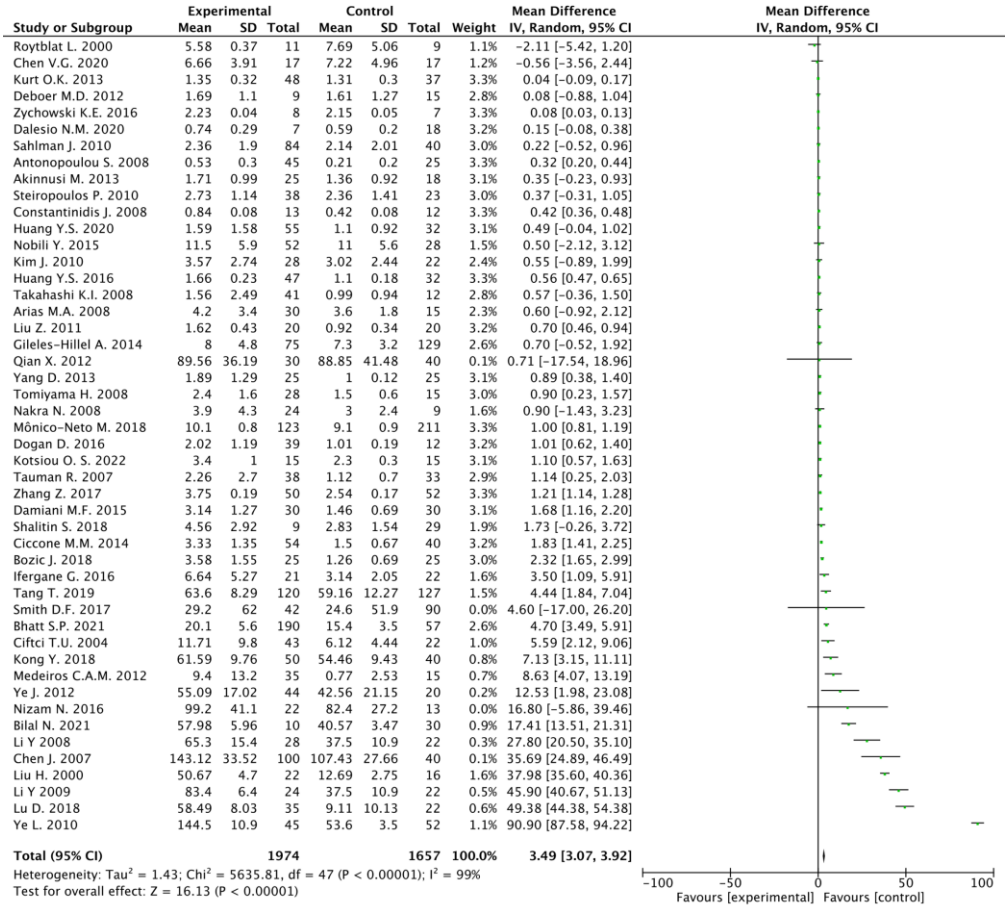
B. IL-2



C. IL-4



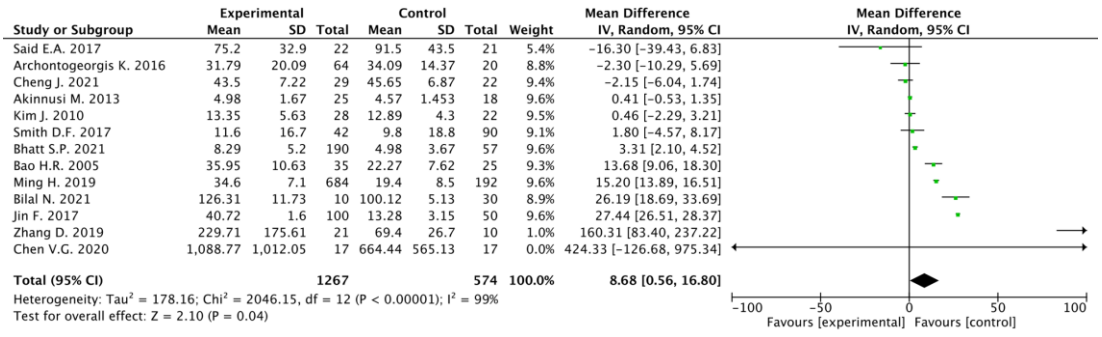
D. IL-6



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Roytblat L. 2000	5.58	0.37	11	7.69	5.06	9	1.1%	−2.11 [−5.42, 1.20]
Chen V.G. 2020	6.66	3.91	17	7.22	4.96	17	1.2%	−0.56 [−3.56, 2.44]
Kurt O.K. 2013	1.35	0.32	48	1.31	0.3	37	3.3%	0.04 [−0.09, 0.17]
Deboer M.D. 2012	1.69	1.1	9	1.61	1.27	15	2.8%	0.08 [−0.88, 1.04]
Zychowski K.E. 2016	2.23	0.04	8	2.15	0.05	7	3.3%	0.08 [0.03, 0.13]
Dalesio N.M. 2020	0.74	0.29	7	0.59	0.2	18	3.2%	0.15 [−0.08, 0.38]
Sahlman J. 2010	2.36	1.9	84	2.14	2.01	40	3.0%	0.22 [−0.52, 0.96]
Antonopoulou S. 2008	0.53	0.3	45	0.21	0.2	25	3.3%	0.32 [0.20, 0.44]
Akinnusi M. 2013	1.71	0.99	25	1.36	0.92	18	3.1%	0.35 [−0.23, 0.93]
Steiropoulos P. 2010	2.73	1.14	38	2.36	1.41	23	3.0%	0.37 [−0.31, 1.05]
Constantinidis J. 2008	0.84	0.08	13	0.42	0.08	12	3.3%	0.42 [0.36, 0.48]
Huang Y.S. 2020	1.59	1.58	55	1.1	0.92	32	3.1%	0.49 [−0.04, 1.02]
Nobili Y. 2015	11.5	5.9	52	11	5.6	28	1.5%	0.50 [−2.12, 3.12]
Kim J. 2010	3.57	2.74	28	3.02	2.44	22	2.4%	0.55 [−0.89, 1.99]
Huang Y.S. 2016	1.66	0.23	47	1.1	0.18	32	3.3%	0.56 [0.47, 0.65]
Takahashi K.I. 2008	1.56	2.49	41	0.99	0.94	12	2.8%	0.57 [−0.36, 1.50]
Arias M.A. 2008	4.2	3.4	30	3.6	1.8	15	2.3%	0.60 [−0.92, 2.12]
Liu Z. 2011	1.62	0.43	20	0.92	0.34	20	3.2%	0.70 [0.46, 0.94]
Gileles-Hillel A. 2014	8	4.8	75	7.3	3.2	129	2.6%	0.70 [−0.52, 1.92]
Qian X. 2012	89.56	36.19	30	88.85	41.48	40	0.1%	0.71 [−17.54, 18.96]
Yang D. 2013	1.89	1.29	25	1	0.12	25	3.1%	0.89 [0.38, 1.40]
Tomiyama H. 2008	2.4	1.6	28	1.5	0.6	15	3.0%	0.90 [0.23, 1.57]
Nakra N. 2008	3.9	4.3	24	3	2.4	9	1.6%	0.90 [−1.43, 3.23]
Mônico-Neto M. 2018	10.1	0.8	123	9.1	0.9	211	3.3%	1.00 [0.81, 1.19]
Dogan D. 2016	2.02	1.19	39	1.01	0.19	12	3.2%	1.01 [0.62, 1.40]
Kotsiou O. S. 2022	3.4	1	15	2.3	0.3	15	3.1%	1.10 [0.57, 1.63]
Tauman R. 2007	2.26	2.7	38	1.12	0.7	33	2.9%	1.14 [0.25, 2.03]
Zhang Z. 2017	3.75	0.19	50	2.54	0.17	52	3.3%	1.21 [1.14, 1.28]
Damiani M.F. 2015	3.14	1.27	30	1.46	0.69	30	3.1%	1.68 [1.16, 2.20]
Shalitin S. 2018	4.56	2.92	9	2.83	1.54	29	1.9%	1.73 [−0.26, 3.72]
Ciccone M.M. 2014	3.33	1.35	54	1.5	0.67	40	3.2%	1.83 [1.41, 2.25]
Bozic J. 2018	3.58	1.55	25	1.26	0.69	25	3.0%	2.32 [1.65, 2.99]
Ifergane G. 2016	6.64	5.27	21	3.14	2.05	22	1.6%	3.50 [1.09, 5.91]
Tang T. 2019	63.6	8.29	120	59.16	12.27	127	1.5%	4.44 [1.84, 7.04]
Smith D.F. 2017	29.2	62	42	24.6	51.9	90	0.0%	4.60 [−17.00, 26.20]
Bhatt S.P. 2021	20.1	5.6	190	15.4	3.5	57	2.6%	4.70 [3.49, 5.91]
Ciftci T.U. 2004	11.71	9.8	43	6.12	4.44	22	1.0%	5.59 [2.12, 9.06]
Kong Y. 2018	61.59	9.76	50	54.46	9.43	40	0.8%	7.13 [3.15, 11.11]
Medeiros C.A.M. 2012	9.4	13.2	35	0.77	2.53	15	0.7%	8.63 [4.07, 13.19]
Ye J. 2012	55.09	17.02	44	42.56	21.15	20	0.2%	12.53 [1.98, 23.08]
Nizam N. 2016	99.2	41.1	22	82.4	27.2	13	0.0%	16.80 [−5.86, 39.46]
Bilal N. 2021	57.98	5.96	10	40.57	3.47	30	0.9%	17.41 [13.51, 21.31]
Li Y 2008	65.3	15.4	28	37.5	10.9	22	0.3%	27.80 [20.50, 35.10]
Chen J. 2007	143.12	33.52	100	107.43	27.66	40	0.1%	35.69 [24.89, 46.49]
Liu H. 2000	50.67	4.7	22	12.69	2.75	16	1.6%	37.98 [35.60, 40.36]
Li Y 2009	83.4	6.4	24	37.5	10.9	22	0.5%	45.90 [40.67, 51.13]
Lu D. 2018	58.49	8.03	35	9.11	10.13	22	0.6%	49.38 [44.38, 54.38]
Ye L. 2010	144.5	10.9	45	53.6	3.5	52	1.1%	90.90 [87.58, 94.22]
Total (95% CI)			**1974**			**1657**	**100.0%**	**3.49 [3.07, 3.92]**

Heterogeneity: $Tau^2 = 1.43$; $Chi^2 = 5635.81$, df = 47 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 16.13$ ($P < 0.00001$)

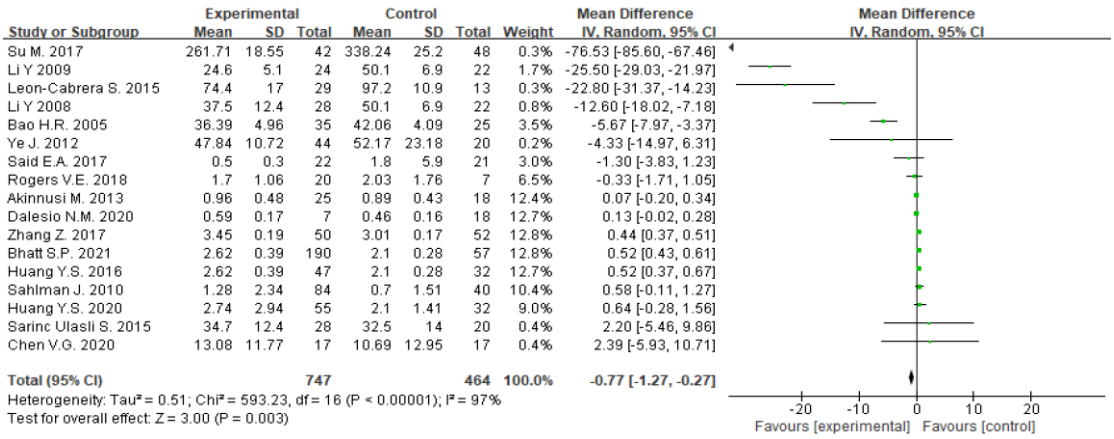
E. IL-8



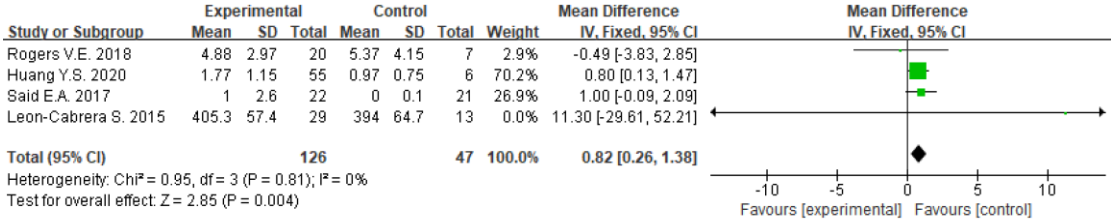
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Said E.A. 2017	75.2	32.9	22	91.5	43.5	21	5.4%	−16.30 [−39.43, 6.83]
Archontogeorgis K. 2016	31.79	20.09	64	34.09	14.37	20	8.8%	−2.30 [−10.29, 5.69]
Cheng J. 2021	43.5	7.22	29	45.65	6.87	22	9.4%	−2.15 [−6.04, 1.74]
Akinnusi M. 2013	4.98	1.67	25	4.57	1.453	18	9.6%	0.41 [−0.53, 1.35]
Kim J. 2010	13.35	5.63	28	12.89	4.3	22	9.5%	0.46 [−2.29, 3.21]
Smith D.F. 2017	11.6	16.7	42	9.8	18.8	90	9.1%	1.80 [−4.57, 8.17]
Bhatt S.P. 2021	8.29	5.2	190	4.98	3.67	57	9.6%	3.31 [2.10, 4.52]
Bao H.R. 2005	35.95	10.63	35	22.27	7.62	25	9.3%	13.68 [9.06, 18.30]
Ming H. 2019	34.6	7.1	684	19.4	8.5	192	9.6%	15.20 [13.89, 16.51]
Bilal N. 2021	126.31	11.73	10	100.12	5.13	30	8.9%	26.19 [18.69, 33.69]
Jin F. 2017	40.72	1.6	100	13.28	3.15	50	9.6%	27.44 [26.51, 28.37]
Zhang D. 2019	229.71	175.61	21	69.4	26.7	10	1.0%	160.31 [83.40, 237.22]
Chen V.G. 2020	1,088.77	1,012.05	17	664.44	565.13	17	0.0%	424.33 [−126.68, 975.34]
Total (95% CI)			**1267**			**574**	**100.0%**	**8.68 [0.56, 16.80]**

Heterogeneity: $Tau^2 = 178.16$; $Chi^2 = 2046.15$, df = 12 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 2.10$ ($P = 0.04$)

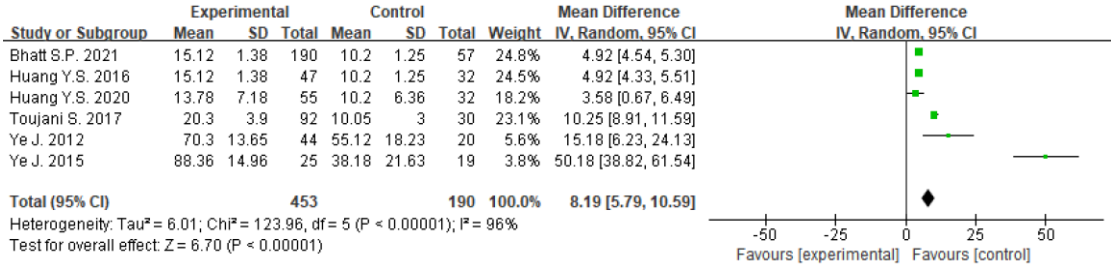
F. IL-10



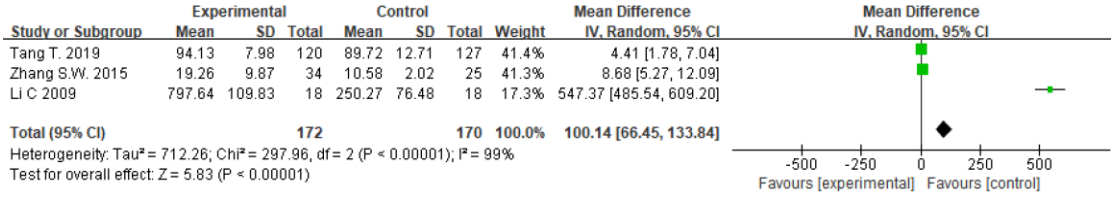
G. IL-12



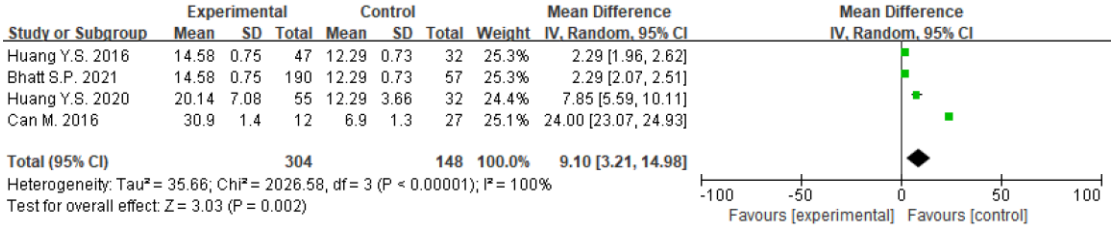
H. IL-17



I. IL-18



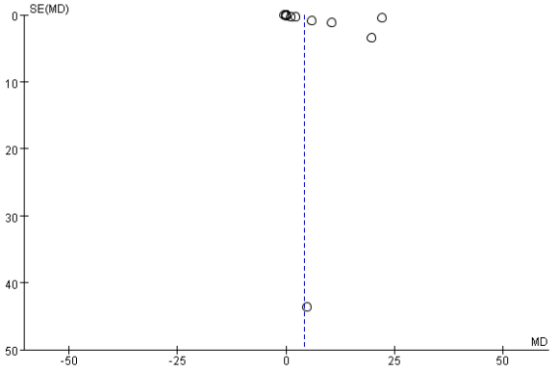
J. IL-23



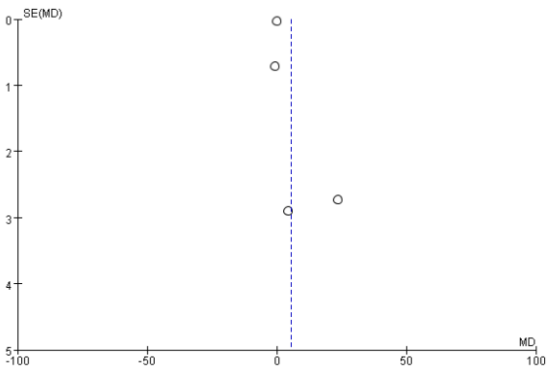
Supplemental Figure 1. Forest plots of interleukins (ILs) concentration differences between OSA patients and controls. (A) IL-1β; (B) IL-2; (C) IL-4; (D) IL-6; (E) IL-8; (F) IL-10; (G) IL-12; (H) IL-17; (I) IL-18; (J) IL-23.

The study of Medeiros C.A.M made no contribution to the pooled analysis in IL-1β.

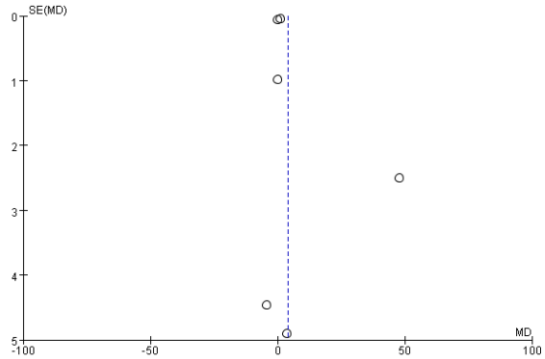
A. IL-1β



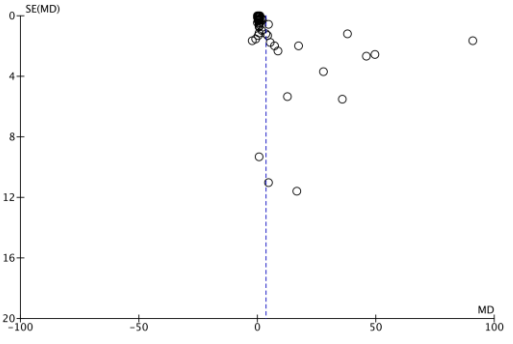
B. IL-2



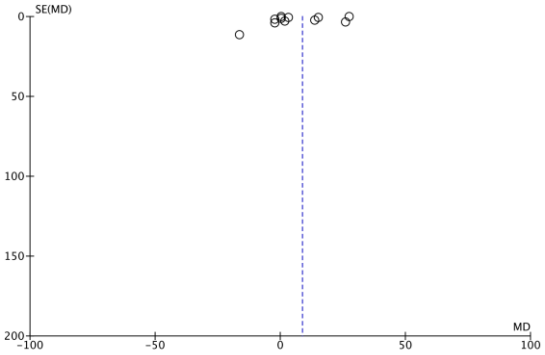
C. IL-4



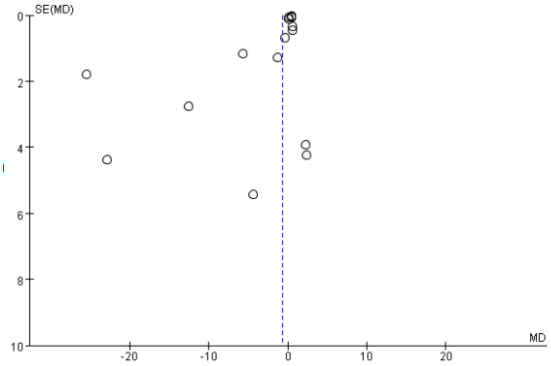
D. IL-6



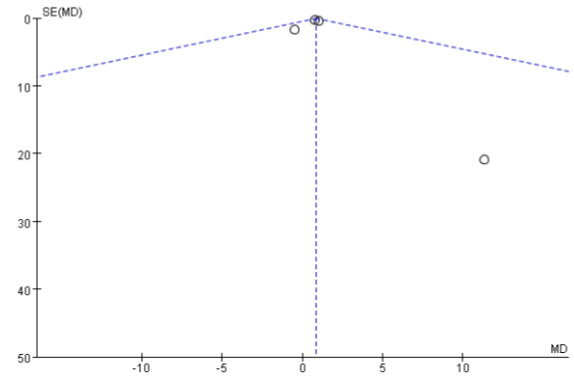
E. IL-8



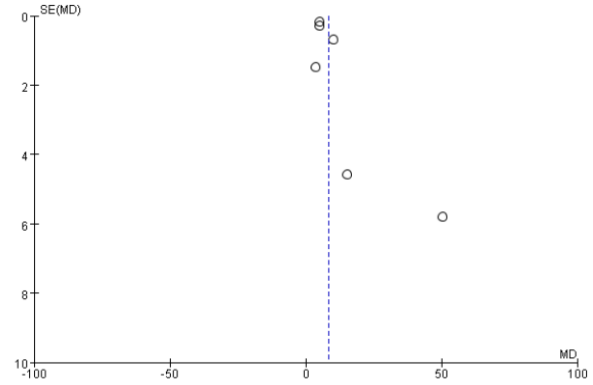
F. IL-10



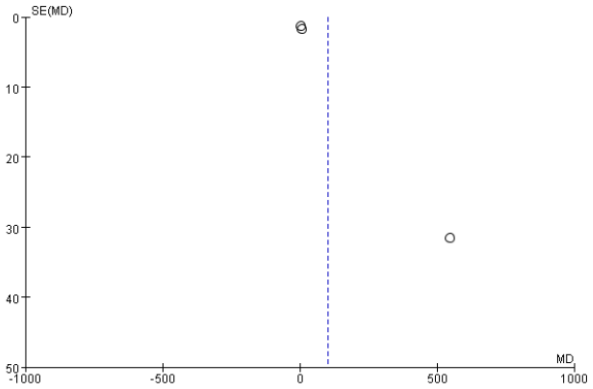
G. IL-12



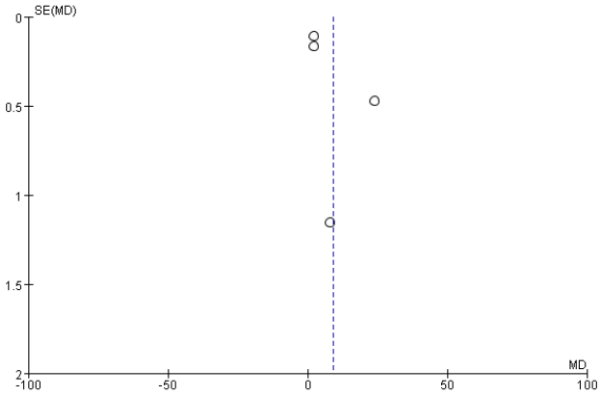
H. IL-17



I. IL-18

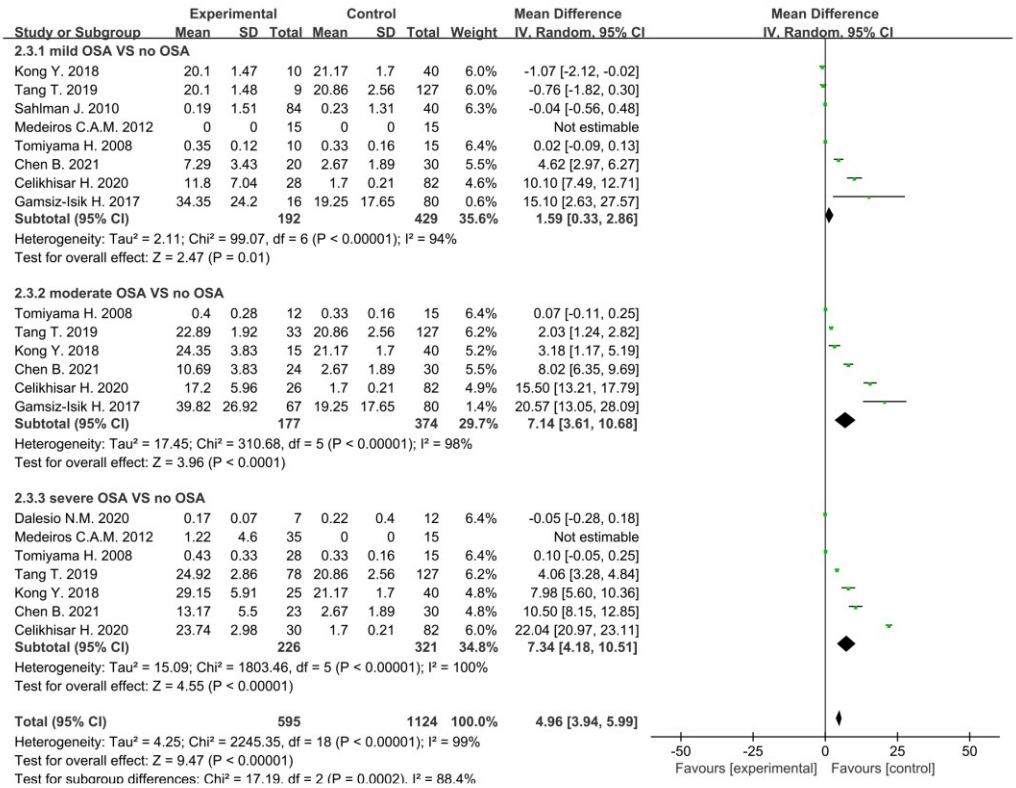


J. IL-23

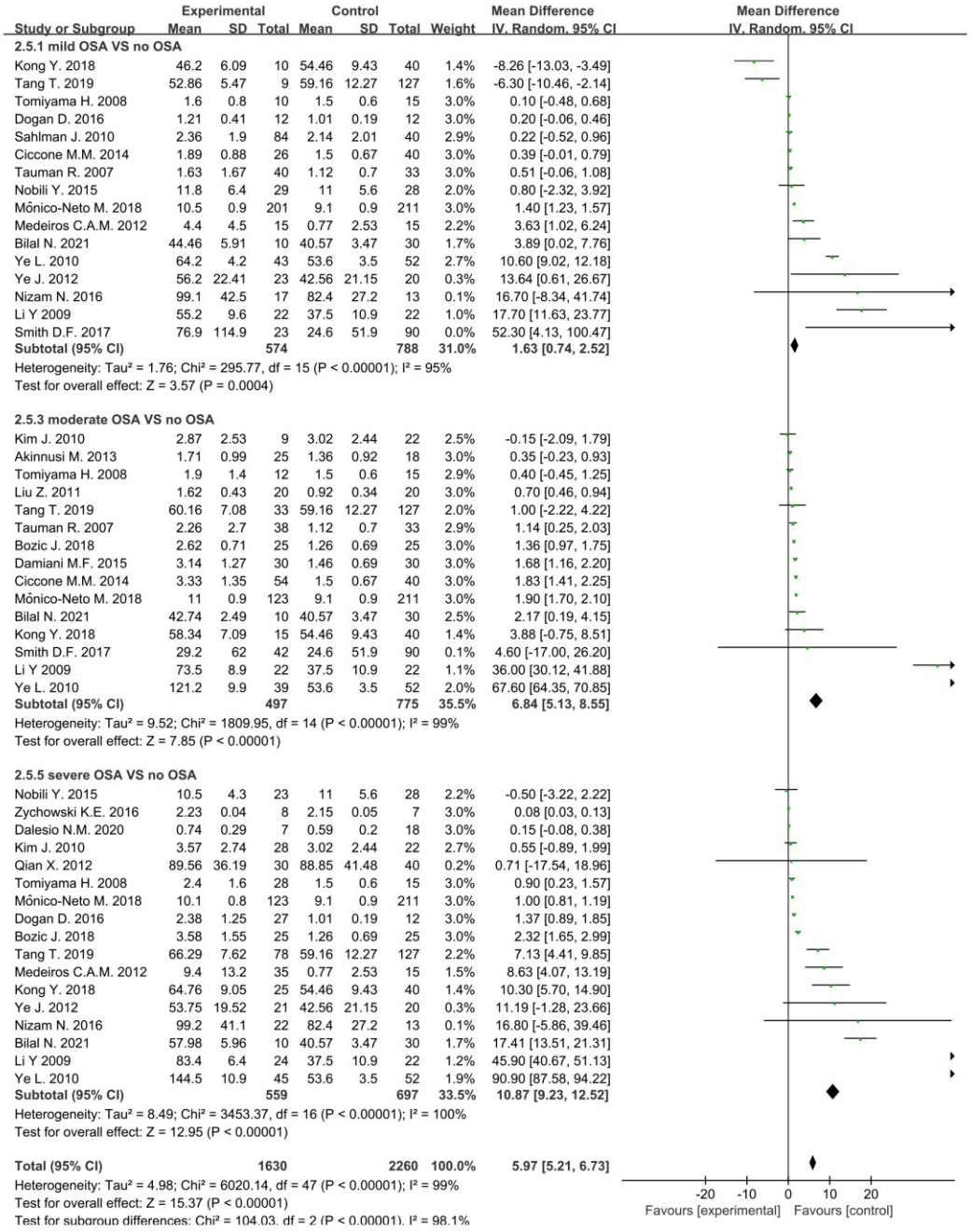


Supplemental Figure 2. Funnel plots of Interleukins (ILs) concentration differences between OSA patients and controls. (A) IL-1β; (B) IL-2; (C) IL-4; (D) IL-6; (E) IL-8; (F) IL-10; (G) IL-12; (H) IL-17; (I) IL-18; (J) IL-23.

A. IL-1β

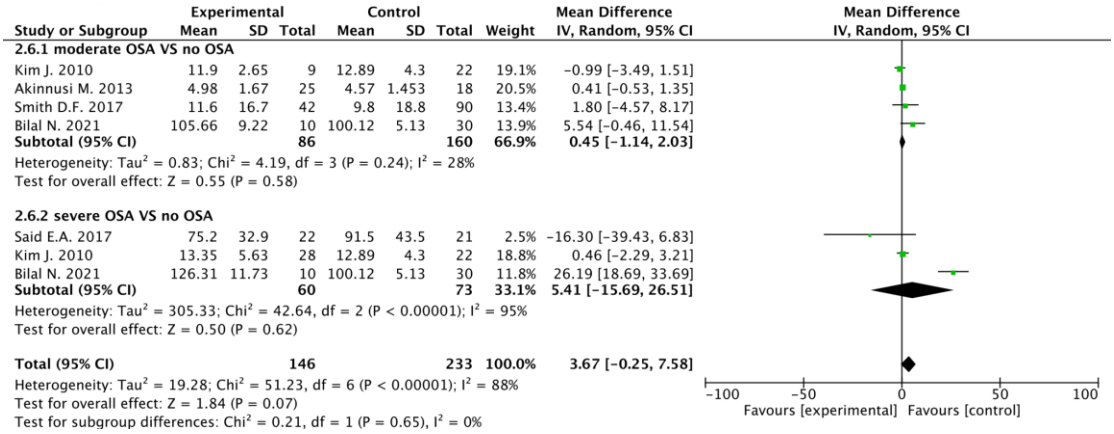

Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.3.1 mild OSA VS no OSA
Kong Y. 2018 20.1 1.47 10 21.17 1.7 40 6.0% -1.07 [-2.12, -0.02]
Tang T. 2019 20.1 1.48 9 20.86 2.56 127 6.0% -0.76 [-1.82, 0.30]
Sahlman J. 2010 0.19 1.51 84 0.23 1.31 40 6.3% -0.04 [-0.56, 0.48]
Medeiros C.A.M. 2012 0 0 15 0 0 15 Not estimable
Tomiyama H. 2008 0.35 0.12 10 0.33 0.16 15 6.4% 0.02 [-0.09, 0.13]
Chen B. 2021 7.29 3.43 20 2.67 1.89 30 5.5% 4.62 [2.97, 6.27]
Celikhisar H. 2020 11.8 7.04 28 1.7 0.21 82 4.6% 10.10 [7.49, 12.71]
Gamsiz-Isik H. 2017 34.35 24.2 16 19.25 17.65 80 0.6% 15.10 [2.63, 27.57]
Subtotal (95% CI) 192 429 35.6% 1.59 [0.33, 2.86]
Heterogeneity: Tau² = 2.11; Chi² = 99.07, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.47 (P = 0.01)
2.3.2 moderate OSA VS no OSA
Tomiyama H. 2008 0.4 0.28 12 0.33 0.16 15 6.4% 0.07 [-0.11, 0.25]
Tang T. 2019 22.89 1.92 33 20.86 2.56 127 6.2% 2.03 [1.24, 2.82]
Kong Y. 2018 24.35 3.83 15 21.17 1.7 40 5.2% 3.18 [1.17, 5.19]
Chen B. 2021 10.69 3.83 24 2.67 1.89 30 5.5% 8.02 [6.35, 9.69]
Celikhisar H. 2020 17.2 5.96 26 1.7 0.21 82 4.9% 15.50 [13.21, 17.79]
Gamsiz-Isik H. 2017 39.82 26.92 67 19.25 17.65 80 1.4% 20.57 [13.05, 28.09]
Subtotal (95% CI) 177 374 29.7% 7.14 [3.61, 10.68]
Heterogeneity: Tau² = 17.45; Chi² = 310.68, df = 5 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.96 (P < 0.0001)
2.3.3 severe OSA VS no OSA
Dalesio N.M. 2020 0.17 0.07 7 0.22 0.4 12 6.4% -0.05 [-0.28, 0.18]
Medeiros C.A.M. 2012 1.22 4.6 35 0 0 15 Not estimable
Tomiyama H. 2008 0.43 0.33 28 0.33 0.16 15 6.4% 0.10 [-0.05, 0.25]
Tang T. 2019 24.92 2.86 78 20.86 2.56 127 6.2% 4.06 [3.28, 4.84]
Kong Y. 2018 29.15 5.91 25 21.17 1.7 40 4.8% 7.98 [5.60, 10.36]
Chen B. 2021 13.17 5.5 23 2.67 1.89 30 4.8% 10.50 [8.15, 12.85]
Celikhisar H. 2020 23.74 2.98 30 1.7 0.21 82 6.0% 22.04 [20.97, 23.11]
Subtotal (95% CI) 226 321 34.8% 7.34 [4.18, 10.51]
Heterogeneity: Tau² = 15.09; Chi² = 1803.46, df = 5 (P < 0.00001); I² = 100%
Test for overall effect: Z = 4.55 (P < 0.00001)
Total (95% CI) 595 1124 100.0% 4.96 [3.94, 5.99]
Heterogeneity: Tau² = 4.25; Chi² = 2245.35, df = 18 (P < 0.00001); I² = 99%
Test for overall effect: Z = 9.47 (P < 0.00001)
Test for subgroup differences: Chi² = 17.19, df = 2 (P = 0.0002), I² = 88.4%
-50
-25
0
25
50
Favours [experimental]
Favours [control]

B. IL-6

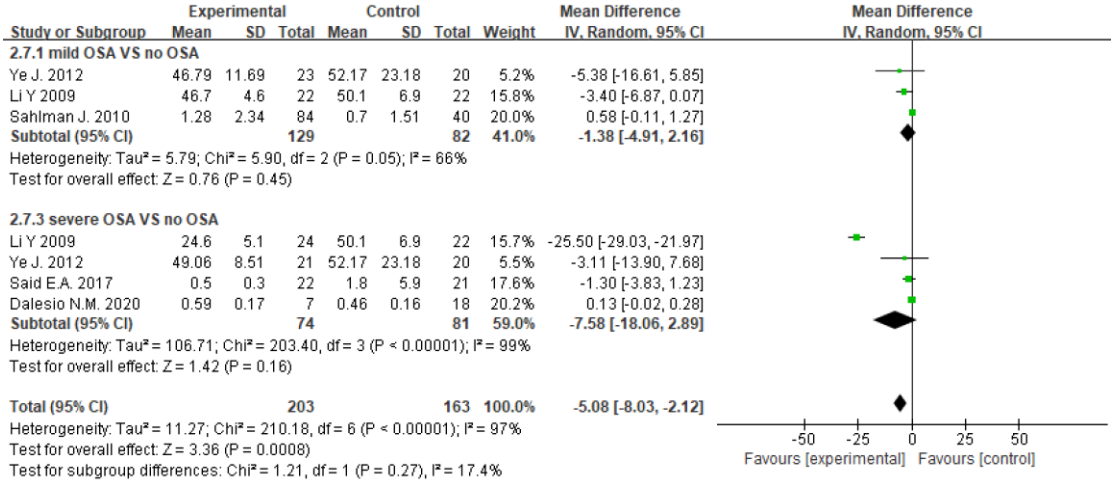


Supplemental Figure 3. Forest plots of IL-1β for IL-6 concentration differences between mild, moderate, severe OSA patients and controls. (A) IL-1β; (B) IL-6.
The study of Medeiros C.A.M made no contribution to the pooled analysis in IL-1β.

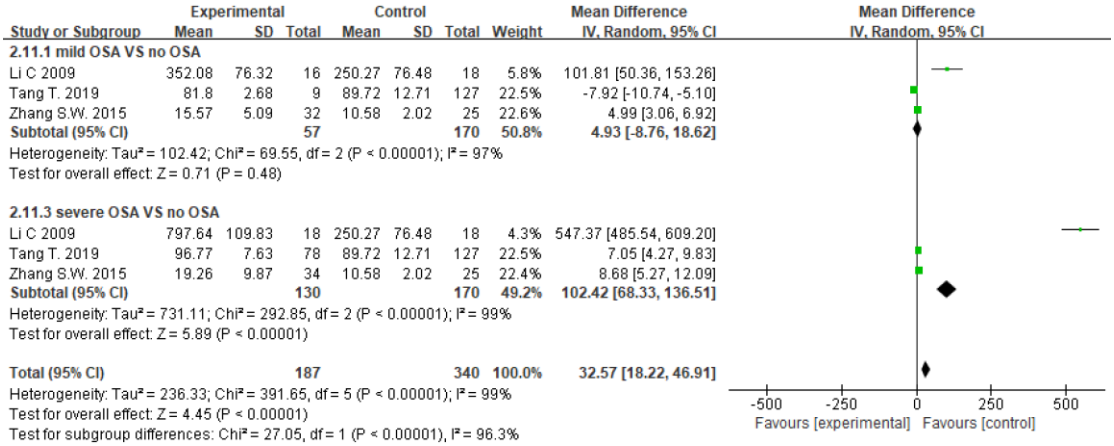
A. IL-8



B. IL-10

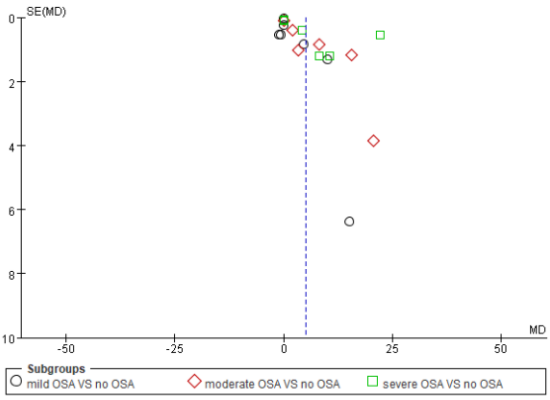


C. IL-18

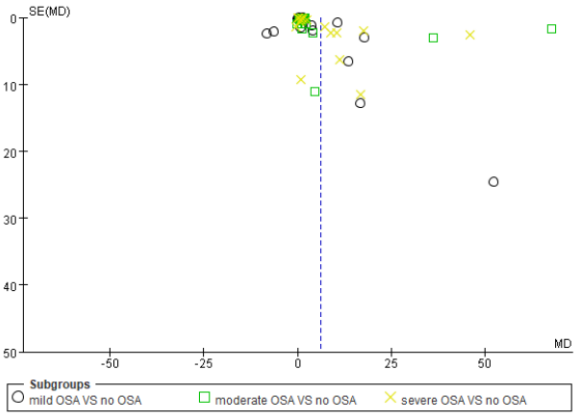


Supplemental Figure 4. Forest plots of interleukins (ILs) concentration differences between 2 subgroups of OSA patients and controls. (A) IL-8 in moderate, severe subgroups; (B) and (C) IL-10, IL-18 in mild, severe subgroups.

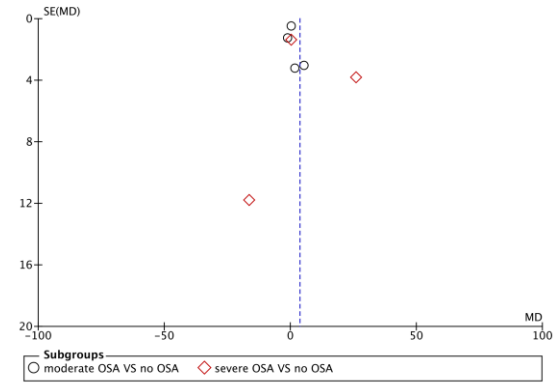
A. IL-1β



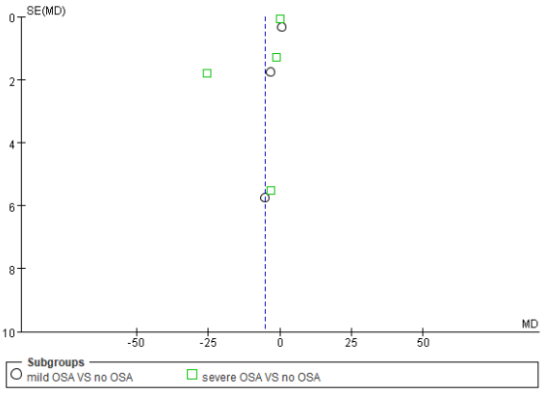
B. IL-6



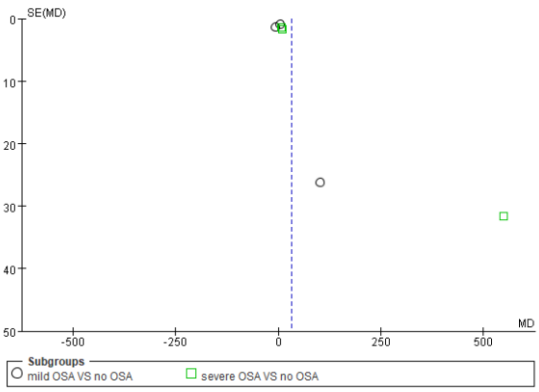
C. IL-8



D. IL-10

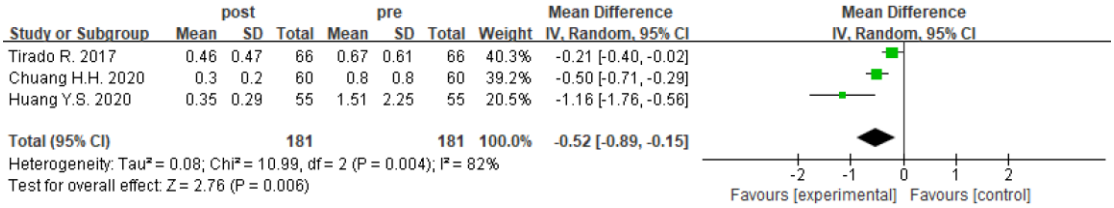


E. IL-18

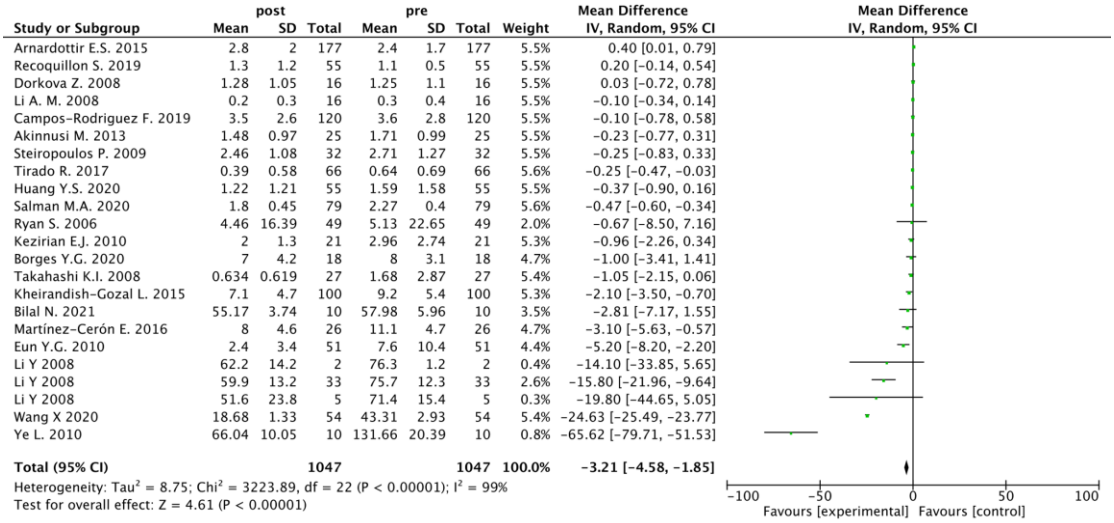


Supplemental Figure 5. Funnel plots of Interleukins (ILs) concentration differences between mild, moderate, severe OSA patients and controls. (A) IL-1β; (B) IL-6; (C) IL-8; (D) IL-10; (E) IL-18.

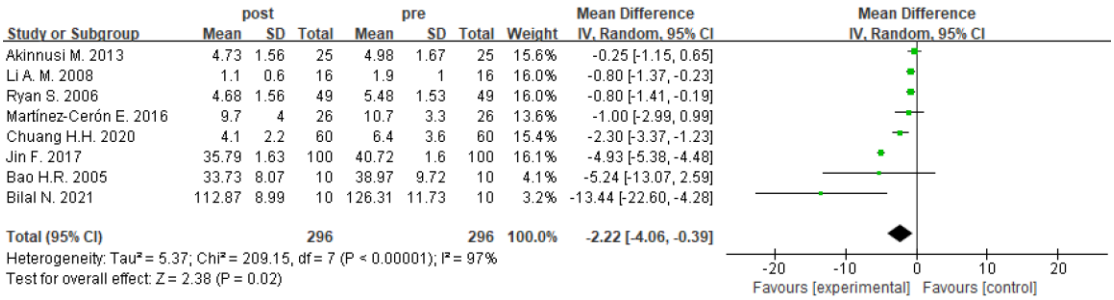
A. IL-1β



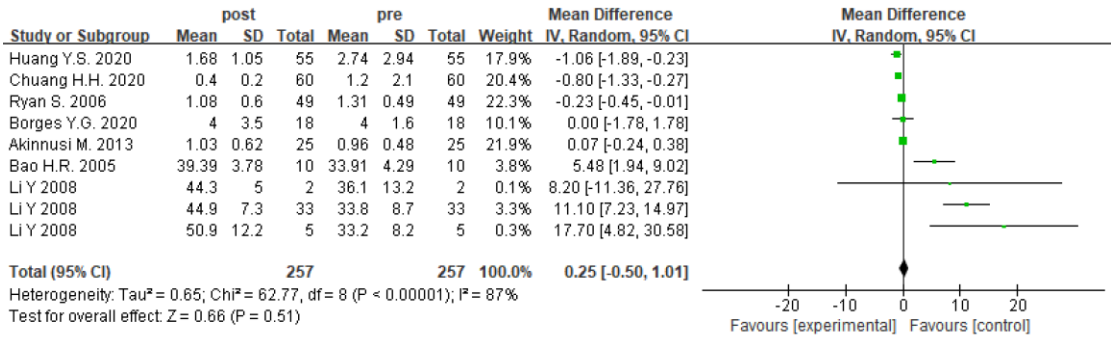
B. IL-6



C. IL-8

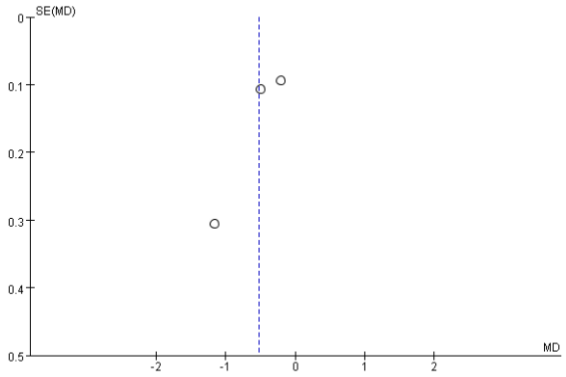


D. IL-10

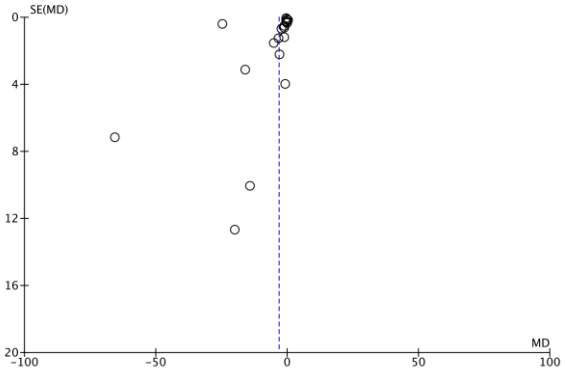


Supplemental Figure 6. Forest plots of interleukins (ILs) treatment concentration differences between post and pre OSA patients. (A) IL-1β; (B) IL-6; (C) IL-8; (D) IL-10

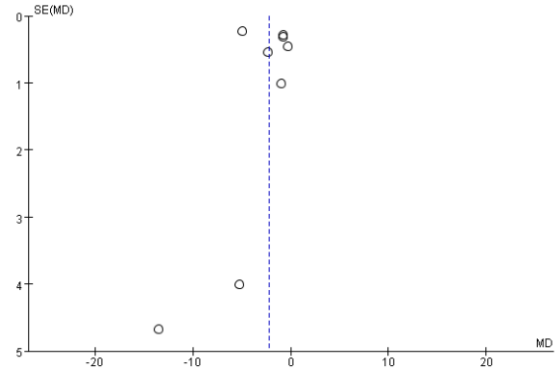
A. IL-1β



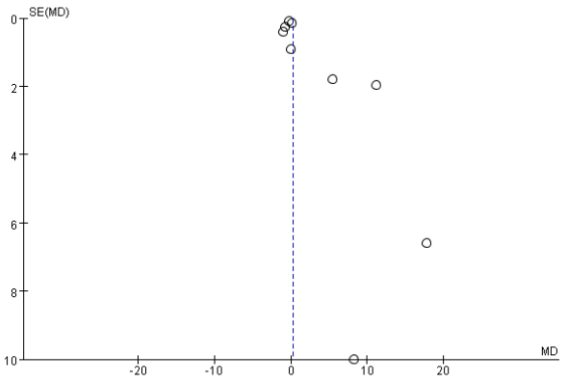
B. IL-6



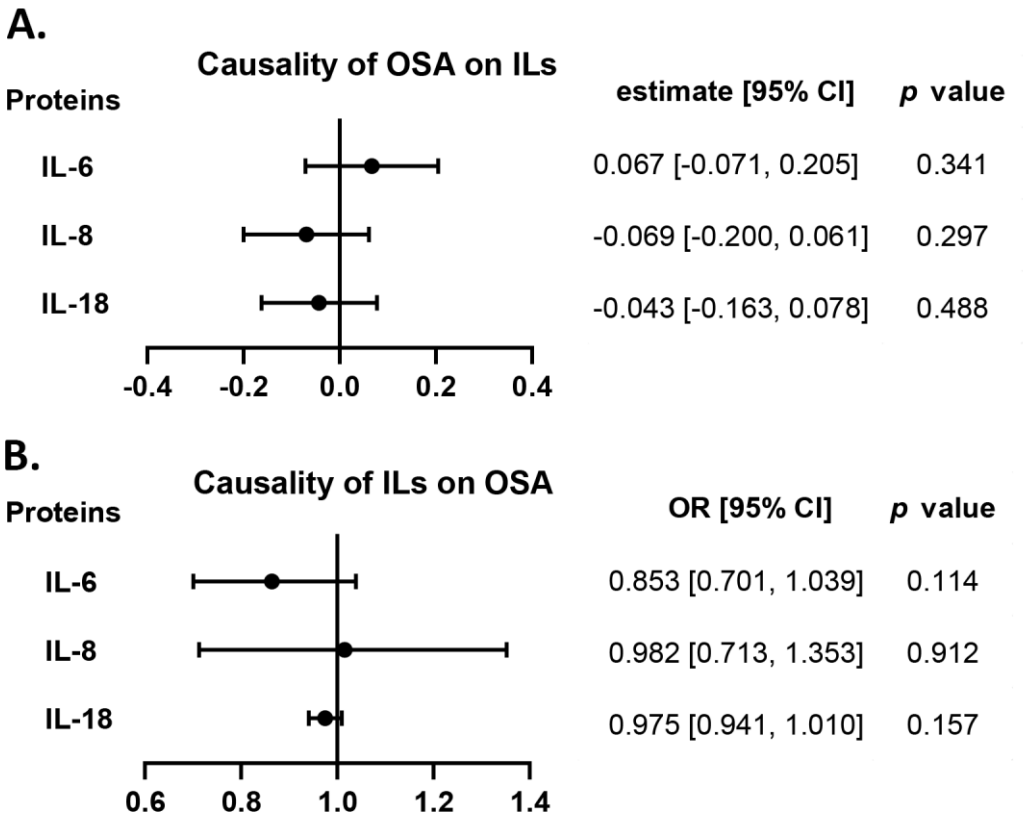
C. IL-8



D. IL-10



Supplemental Figure 7. Funnel plots of Interleukins (ILs) treatment concentration differences between post and pre OSA patients. (A) IL-1β; (B) IL-6; (C) IL-8; (D) IL-10.



Supplemental Figure 8. Verification of the negative results about the causal relationships between OSA and Interleukins (ILs) of IL-6, IL-8 and Il-18 using another large-sample GWAS

(A). Causality was analyzed with OSA as exposure, IL-6, IL-8, IL-18 individually as outcomes by MR.

(B). Causality was analyzed with IL-6, IL-8, IL-18 respectively as exposure and OSA as outcome by MR. The presented results were performed by method of inverse variance weighted (IVW). The statistically threshold was $p<0.05$.