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Baseline and postoperative levels of C-reactive protein and interleukins as inflammatory predictors of atrial fibrillation following cardiac surgery: a systematic review and meta-analysis

Running Title: Inflammatory markers as predictors of POAF

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Abstract

Background and aim: Postoperative atrial fibrillation (POAF) is a leading arrhythmia with high incidence and serious clinical implications after cardiac surgery. Cardiac surgery is associated with systemic inflammatory response including increase in cytokines and activation of endothelial and leukocyte responses. This systematic review and meta-analysis aimed to determine the strength of evidence for evaluating the association of inflammatory markers, such as C-reactive protein (CRP) and interleukins (IL) with POAF following isolated coronary artery bypass grafting (CABG), isolated valvular surgery or combination of these procedures.

Methods: We conducted a meta-analysis of studies evaluating measured baseline (from one week before surgical procedures) and postoperative levels (until one week after surgical procedures) of inflammatory markers in patients with POAF. A comprehensive search was performed in electronic medical databases (Medline/PubMed, Web of Science, Embase, Science Direct, and Google Scholar) from their inception through May 2017 to identify relevant studies. A comprehensive subgroup analysis was performed to explore potential sources of heterogeneity.

Results: The literature search of all major databases retrieved 1014 studies. After screening, 42 studies were analyzed including a total of 8398 patients. Pooled analysis showed baseline levels of CRP (standard mean difference (SMD) 0.457 mg/L, $p<0.001$), baseline levels of IL-6 (SMD 0.398 pg/mL, $p<0.001$), postoperative levels of CRP (SMD 0.576 mg/L, $p<0.001$), postoperative levels of IL-6 (SMD 1.66 pg/mL, $p<0.001$), postoperative levels of IL-8 (SMD 0.839 pg/mL, $p<0.001$), and postoperative levels of IL-10 (SMD 0.590 pg/mL, $p<0.001$) to be relevant inflammatory parameters significantly associated with POAF.

Conclusions: According to our findings, perioperative inflammation is proposed to be involved in the pathogenesis of POAF. Therefore, perioperative assessment of CRP, IL-6, IL-8, and IL-10 can help clinicians in terms of predicting and monitoring for POAF.

Key words: atrial fibrillation, inflammation, C-reactive protein, cytokines, interleukins, review, meta-analysis

INTRODUCTION

Postoperative atrial fibrillation (POAF) is a leading arrhythmia with serious clinical implications after cardiac surgery precipitating wide spectrum of complications and morbidities, such as hemodynamic instability, thromboembolism, transient ischemic attack, stroke, end organ failure, prolonged hospitalization, and associated increase in health care costs and mortality [1-2]. Atrial fibrillation (AF) is diagnosed in up to 50% of patients after coronary artery bypass grafting (CABG) and in over 60% of patients after combined CABG and valve surgery with incidence peaks occurring the first three days after surgery [2-3]. AF is based on highly complex and multifactorial pathophysiological mechanisms, such as oxidative stress, inflammation, prothrombotic state and sympathetic/parasympathetic activation [3-4]. An appropriate modality for diagnosis and monitoring of AF should, on the one hand, facilitate preventive and therapeutic measures by timely diagnosis, and, on the other hand, not burden patients with excessive healthcare costs, while being applicable in a majority of health centers worldwide[4]. Administration of antiarrhythmic and antioxidants therapeutics for prevention or treatment of AF can reduce its incidence and recurrence rate. Simple surgical method such as posterior pericardiotomy may reduce the risk of POAF [3-4].

As widely known, cardiac surgery and the use cardiopulmonary bypass (CPB) are associated with systemic inflammatory response including activation of clotting factors, platelets and fibrinolysis, increase in inflammatory cytokines and activation of endothelial and leukocyte responses [5-6]. AF is also associated with infiltration of immune cells and proteins mediating inflammatory response in cardiac tissue and circulatory processes [5-6].

Various studies have been recently published focusing on the relationship between inflammation and the occurrence of POAF. However, so far the data from the studies have been largely inconclusive. This comprehensive meta-analysis sought to determine the strength of evidence for evaluating the association of baseline and postoperative levels of high sensitivity C-reactive protein (CRP) and interleukins (IL), such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15 and IL-17 with the occurrence of POAF.

METHODS

Literature search

A comprehensive search was performed by four co-authors independently in electronic medical databases (Medline/PubMed, Web of Science, Embase, Science Direct, and Google Scholar) from their inception through 10th May 2017 to identify relevant studies on the association of measured baseline (from one week before surgery) and postoperative levels (until one week after surgery) of inflammatory markers, such as CRP and interleukins 1-17, with the occurrence of AF after isolated CABG, valvular surgery or combined procedures. Predefined keywords for searching were "C-reactive protein", "CRP", "acute phase reactant", "interleukin", "interleukin-1", "IL-1", "interleukin-2", "IL-2", "interleukin-3", "IL-3", "interleukin-4", "IL-4", "interleukin-5", "IL-5", "interleukin-6", "IL-6", "interleukin-7", "IL-7", "interleukin-8", "IL-8", "interleukin-9", "IL-9", "interleukin-10", "IL-10", "interleukin-11", "IL-11", "interleukin-12", "IL-12", "interleukin-13", "IL-13", "interleukin-15", "IL-15", "interleukin-17", "IL-17", and "atrial fibrillation", "supraventricular arrhythmia", "cardiac surgery", "open heart surgery", "cardiovascular surgery", "coronary artery bypass surgery", "CABG", "valvular surgery", "surgery". There were no limitations for the sample size of the studies, time, and language of publications. Abstracts without peer-review or those only published as congress presentations were not enrolled in the meta-analysis. Two investigators checked to find additional studies not indexed in medical databases by searching in retrieved references of the enrolled studies, recent published review articles, and meta-analyses.

Study selection

Studies which met the following inclusion criteria were enrolled in the analysis: 1) human subjects; 2) case-control or cohort studies; 3) patients undergoing either CABG or heart valve surgery, or a combination of both; 4) comparing patients with POAF and postoperative sinus rhythm (POSR) in terms of inflammatory markers.

Data extraction and outcome measures

Six investigators (S.A-H-S, A.S, M-R.L., S.Y., M-P.S, and S.J.M) independently extracted the data, whereas two of them integrated and compared all of filled checklists. A consensus standardized abstraction checklist was applied for recording data in each enrolled study in order to resolve the discrepancies. The following items were examined through subgroup analyses of disparities in the patients' characteristics for exploration of heterogeneity among the studies: (1) year of publication (before 2000 vs. after 2000); (2) geographical area (Africa, Asia, Europe, North-America, Oceania, South-America); (3) type of study (case-control vs. cohort); (4) number of patients (≤200 vs. >200); (5) average age (≤60 vs. >60 years); (6) percentage of male patients (≤70% vs. >70%); (7) history of diabetes mellitus (≤30% vs. >30%); (8) history of arterial hypertension (≤70% vs. >70%); (9) history of cigarette smoking (≤30% vs. >30%); (10) history of myocardial infarction (≤20% vs. >20%); (11) baseline left ventricular ejection fraction (≤50% vs. >50%); (12) preoperative use of medications, such as diuretics, beta-blockers, statins, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (for each: ≤70% vs. >70%); (13) type of surgical procedure (isolated CABG, isolated valvular surgery, combined procedures); (14) utilization of CPB (on-pump vs. off-pump); (15) status of surgery (elective, non-elective); (16) duration of cross clamping (≤60 minutes vs. >60 minutes); and (17) duration of CPB (≤100 minutes vs. >100 minutes).

Homogenization of extracted data

Continuous data were expressed as mean ± standard deviation (SD). In cases when interquartile ranges were reported, the mean was calculated as [minimum+maximum+2(median)]/4 and SD as (maximum-minimum)/4 for groups with sample sizes of n≤70, and (maximum-minimum)/6 for n>70 [7].

Quality assessment and statistical analysis

Two investigators (L.M. and M.G.) evaluated the Newcastle-Ottawa scale and design of the studies to assess the quality of the studies [8]. Total scores ranged between 0 (worst) and 9 (best quality) for case-control or cohort studies. For non-categorical data, pooled effect size was presented as standard mean difference (SMD) with 95% confidence interval (CI). Significant heterogeneity was found among the studies considering p value < 0.1 for Q test or $I^2 > 50\%$. Heterogeneity among the trials was tested by applying a random effect model when indicated. Begg's test, which examines the presence of association between the effect estimates and their variances, was used to evaluate publication bias. *P* values < 0.05 were considered statistically significant. Data analysis was carried out by STATA (version 11.0, Stata Corporation, College Station, Texas) using METAN and METABIAS commands.

RESULTS

Literature search strategy and included studies

A total of 1014 studies were extracted from the literature search and screened databases, of which 972 were excluded after detailed evaluation through the first review for unnecessary information (n=870), insufficient report of endpoints of interest (n= 95), or reports on non-matched data (n=7). Finally, 42 studies with a total of 8398 patients were included in the present meta-analysis [9-50] (Details about excluded and included studies are shown in Supplemental Table 1).

Association of baseline levels of inflammatory markers with the occurrence of POAF CRP

A total of 7671 patients were enrolled from 36 studies, of which 2240 were assigned to the POAF and 5431 to the postoperative sinus rhythm (POSR) group (Table 1). The sample size of included studies ranged from 20 to 1138 cases (Table 1). Mean baseline level of CRP was 13.16 mg/L in POAF group and 10.46 mg/L in POSR (Table 2). Pooled analysis showed that the mean baseline level of CRP was significantly higher in patients with POAF (positive predictor) than POSR cases with SMD 0.457 mg/L (95% CI: 0.405 to 0.509; p<0.001) using the random effect model (Figure 1) with considerable heterogeneity among the studies (I^2=95.5%; heterogeneity p<0.001).

Interleukins

A total of 649 cases were selected from 6 studies on IL-6, of whom 237 were allocated to the POAF group and 412 to the POSR group (Table 1). Mean baseline level of IL-6 was 15.1

pg/mL in the POAF and 10.6 pg/mL in the POSR group (Table 2). Pooled analysis indicated that IL-6 was significantly higher in patients with POAF (positive predictor) compared to POSR with SMD of 0.398 pg/mL (95% CI: 0.227 to 0.569; $p<0.001$, $I^2=92.1\%$; heterogeneity p=0.001) (Figure 2). Regarding pooled assessment analysis, both groups were similar regarding the baseline level of IL-8 (number of studies=2, SMD -0.09pg/mL, 95% CI: -0.37 to 0.19; p=0.54 and $I^2=72.6\%$; heterogeneity p=0.05, Supplemental Figure 1) and IL-10 (number of studies=3, SMD -0.241 pg/mL, 95% CI: -0.50 to 0.018; p=0.06 and $I^2=0.0\%$; heterogeneity p=0.39, Supplemental Figure 2). There were no reports on comparing baseline levels of other interleukins between POAF and POSR.

Association of postoperative levels of inflammatory markers with the occurrence of POAF

CRP

A total of 5382 cases were included from 23 studies, of which 1605 were assigned to the POAF and 3777 to the postoperative sinus rhythm (POSR) group (Table 1). Mean postoperative level of CRP was 240.7 mg/L in POAF group and 219.9 mg/L in POSR (Table 2). Pooled analysis showed that the mean postoperative level of CRP was significantly higher in patients with POAF (positive predictor) than POSR patients with SMD 0.576 mg/L (95% CI: 0.512 to 0.636; $p<0.001$) utilizing the random effect model (Figure 3). There was remarkable heterogeneity among the studies ($I^2=96.4\%$; heterogeneity $p<0.001$).

Interleukins

Regarding pooled assessment analysis, there were more patients with POAF regarding the postoperative level of IL-6 as compared to POSR (number of studies=5, SMD 1.66 pg/mL, 95% CI: 1.42 to 1.89; $p<0.001$, and $I^2=93\%$; heterogeneity p=0.001, Figure 4), IL-8 (number of studies=3, SMD 0.839 pg/mL, 95% CI: 0.620 to 1.057; $p<0.001$, and $I^2=98.1\%$; heterogeneity p=0.001, Supplemental Figure 3), and IL-10 (number of studies=4, SMD 0.590 pg/mL, 95% CI: 0.395 to 0.785; $p<0.001$, and $I^2=90\%$; heterogeneity p=0.001, Supplemental Figure 4). There were no reports about comparing postoperative levels of other interleukins between POAF and POSR.

Publication bias and subgroup analysis

Begg's tests showed that all analyses were without publication bias except for the relationship between baseline level of CRP and the occurrence of POAF (Supplemental

Figures 5-12). Classification in relation to potential heterogeneity agents and subgroup analyses are reported in detail in Supplemental Tables 2 and 3, respectively.

DISCUSSION

POAF is considered a serious and common postoperative complication with a peak incidence in the first three days after cardiac surgery [51]. POAF is of high clinical importance for its negative effects on short-, average-, and long-term clinical outcomes. Despite good response to therapy and a number of various tretament modalities for this common arrhythmia, preliminary diagnosis of POAF as well as prophylactic therapy could prevent potential complications and morbidities, lower health care costs, mortality rates and reduce length of stay on ICU and in hospital.

On the other hand, it is well-known that coronary artery disease (CAD) is considered one of the most important and common chronic diseases, while CABG is being extensively performed worldwide as an appropriate revascularization procedure for this disease [51-53]. The incidence of POAF after CABG is significant accounting for ca. 50% of patients after surgery. In this respect, diagnosis, prophylaxis, treatment, and follow-up of POAF require high amount of laboratory and clinical investigations [51-53].

Today, inflammation is believed to be a critical pathological mechanism responsible for AF. Firstly, patients with CAD often present with preoperative chronic inflammatory state with physiological and cardiac hemodynamic changes or coexisting co-morbidities [54-56]. Secondly, the major inflammatory response develops during surgery and is related to a wide range of factors, such as surgical trauma, CPB and organ reperfusion injury [55-56]. Thirdly, myocardial ischemia, reperfusion and re-oxygenation activate further pro-inflammatory processes [57-58]. Evidence increasingly supports the influence of an acute inflammation on the pathogenesis of AF which is largely based on association between the levels and activity of WBCs and the incidence of AF [57-59]. Patients with higher leukocyte count are more likely to develop AF and patients developing AF show higher monocyte activation with increased neutrophil to lymphocyte ratio [52].

In the present meta-analysis, the association of CRP and interleukins with the occurrence of new-onset POAF was investigated. The results of our study indicated significantly higher baseline levels of CRP in patients with POAF compared to those with POSR, thus being considered as a positive predictor. Subgroup analysis showed that the association of baseline CRP with the occurrence of POAF was not related to the type of surgery, as this association existed in isolated CABG, isolated valvular surgery as well as combined CABG and valvular surgery. Previsous research also showed an association of AF and CRP in various clinical settings. Yo et al. reported that the level of CRP was directly associated with the recurrence of AF who underwent cardioversion, thus being a positive predictor [60]. Rezaei et al. showed that treatment with anti-inflammatory drugs not only decreased levels of CRP, but also decreased the occurrence of AF [61]. Therefore, they affirmed a direct relationship between CRP levels as an inflammatory marker and the occurrence of AF [61].

Our findings also revealed that higher postoperative levels of CRP were associated with the occurrence of AF. In total, it can be concluded that measuring CRP levels before surgery, during postoperative ICU stay and on ward can obviously warn of the risk of AF occurrence and help clinicians as an additional source for diagnosis and monitoring purposes. According to the literature, interleukins are believed to be capable of modulating cardiovascular function by a variety of mechanisms including promotion of the left ventricle remodeling, induction of contractile dysfunction, and changing the response of myocardial Β-adrenergic receptors [57-59]. Thus, our findings regrading involvement of various interleukins in pathophysiological mechanisms of development of POAF might be supported by this previous evidence.

On the other hand, it is noteworthy that according to previous findings, a number of inflammatory mediators generated in response to CPB and ischemia-reperfusion could contribute to cardiac functional depression and apoptosis [57-59]. Among other things these changes may alter electrical activity and trigger arrhythmias [57-59]. The present study demonstrated that the baseline level of IL-6 was significantly higher in patients with POAF compared to POSR and could be used as a pre-operative positive predictor. Interestingly, the baseline levels of IL-8 and IL-10 were not significantly different in the two groups. On the other hand, measuring interleukin levels after surgery indicated that IL-6, IL-8, and IL-10 were strongly higher in POAF group than POSR.

Consequently, IL-6 can be introduced as an inflammatory marker sensitive to the physiological changes of cardiac tissue before surgery and prior to activation and release of other inflammatory markers during surgery [57-59]. It should be noted that after surgery an increase in other interleukins was probably observed due to perioperative trauma, CPB, and myocardial ischemia-reperfusion. Zakkar et al. pointed out that cytokines, particularly IL-6, IL-8, and IL-10 significantly increased during and following cardiac surgery and might influence the occurrence of AF as acute-inflammatory markers [57].

CONCLUSIONS

Finally, we conclude that inflammation is proposed to be a possible mechanism in pathogenesis of POAF. Measuring the levels of inflammatory markers such as CRP, IL-6, IL-8, and IL-10 perioperatively can work as positive predictors for POAF. Therefore, these inflammatory markers should be taken into account during hospital stay of patients referred for cardiac surgery, as they might help clinicians in terms of prediction, diagnosis and monitoring of POAF. Another consideration, that should be the aim of further research is potential use of prophylactic treatment for POAF as a response to increased levels of imflammatory markers with the view to preventing the occurrence of this arrhythmia and its consequent complications.

Limitations of the study

This review is study-level meta-analysis with a natural lack of available data on end-points assessed in studies included in the meta-analysis. Also, there are different definitions of arrhythmia and sinus rhythm between studies and there is a lack of data on different types of surgical procedures.

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Table 1. Characteristics of included studies for meta-analysis of association of pre and postoperative inflammatory markers with POAF.

First Author	Year	Country	Design	N-AF	N-SR	Age-AF	Age-SR	Male-AF	Male-SR	TOS	CPB pump: on or off	ES or NES	NOS
Xu [9]	2017	China	case-control	108	400	63.51	61.9	74.07	75	alone CABG	off	ND	7
Saskin [10]	2017	Turkey	cohort	153	509	62	61	77.8	82.9	alone CABG	on	elective	7
Saskin [11]	2016	Turkey	cohort	294	844	60.5	60	25.1	74.9	alone CABG	on	elective	7
Cerit [12]	2016	Turkey	cohort	36	70	67.3	63.2	83.3	92.9	alone CABG	on	elective	7
Anatolevna [13]	2016	Russia	case-control	22	59	67.7	65.8	90.9	74.6	alone CABG	combined	ND	7
Gecmen [14]	2016	Turkey	cohort	31	63	66	59	87	71	alone CABG	on	elective	8
Korantzopoulos [15]	2015	Greece	cohort	44	65	65.4	67.7	70	74	CABG and/or Valve	combined	elective	8
Erdem [16]	2014	Turkey	cohort	43	92	67.2	61.3	69.7	72.8	alone CABG	on	elective	8
Narducci [17]	2014	Italy	case-control	14	24	71	69	64	75	alone CABG	on	elective	8
Limite [18]	2014	Italy	cohort	173	271	66.2	56.4	74	73.4	CABG and/or Valve	on	ND	9
Erdem [19]	2014	Turkey	cohort	38	127	67	64.9	81.57	77.16	alone CABG	on	elective	8
Pilatis [20]	2013	Greece	cohort	44	81	68	63	98	93	alone	combined	elective	9

										CABG			
Cao [21]	2013	Norway	case-control	61	93	50.7	45.2	54.09	46.23	Valve alone	on	ND	8
Bjorgvinsdottir [22]	2013	Denmark	case-control	62	63	69	66	79	84.1	alone CABG	combined	elective	6
Sabol [23]	2012	Slovakia	case-control	30	15	62.5	61.9	76.7	66.7	alone CABG	ND	ND	7
Garcia [24]	2012	Chile	cohort	38	142	73.5	62.4	76.3	81	alone CABG	on	elective	8
Skuladottir [25]	2011	Iceland	case-control	62	63	69	66	79	84.1	alone CABG	combined	elective and semi-emergency	6
Gabrielli [26]	2011	Chile	cohort	18	52	70	62	66	73	alone CABG	on	elective	9
Kaireviciute [27]	2010	Lithuania	cohort	30	70	67	63.2	93.3	82.9	alone CABG	on	elective	8
Gasparovic [28]	2010	Croatia	cohort	55	160	66	60	67	73	alone CABG	on	elective	8
Gibson [29]	2010	UK	cohort	107	168	68	63	87.9	81	alone CABG	combined	elective	9
Ji [30]	2009	China	case-control	33	107	68.8	64.5	ND	ND	alone CABG	off	elective	7
Girerd [31]	2009	Canada	case-control	147	147	55.7	58.4	100	100	alone CABG	combined	elective	8
Choi [32]	2009	South Korea	cohort	66	249	67.1	64.6	74.24	70.68	alone CABG	off	elective	7
Antoniades [33]	2009	UK	cohort	43	101	66.7	65.2	79.06	86.13	alone CABG	off	elective	9

Sezai [34]	2009	Japan	case-control	73	161	72.1	66.05	69.8	80.12	alone CABG	on	ND	8
Fontes [35]	2009	USA	cohort	17	43	71.8	70.3	94.1	74.4	alone CABG	on	elective	8
Ziabakhsh-Tabari [36]	2008	Iran	cohort	11	43	51.4	57.28	ND	ND	alone CABG	on	elective	7
Mehmet OC [[37]	2008	Turkey	case-control	10	10	62.1	61.9	60	80	alone CABG	on	elective	7
Canbaz [38]	2008	Turkey	case-control	13	58	56	57	84.6	79.3	alone CABG	on	elective	7
Qian [39]	2008	China	case-control	24	23	ND	ND	ND	ND	Valve alone	on	elective	8
Pretorius [40]	2007	USA	cohort	67	186	66.1	56.9	71.6	63.4	CABG and/or Valve	on	elective	7
Ucar [41]	2007	Turkey	cohort	14	35	64.3	58.8	14.28	14.28	alone CABG	on	elective	7
Ahlsson [42]	2007	Sweden	cohort	182	342	70.6	65.4	75	72	CABG and/or Valve	on	ND	8
Houge JR [43]	2006	USA	case-control	46	84	72	70	0	0	CABG and/or Valve	on	elective	6
Ishida [44]	2006	Japan	cohort	11	28	70	60	64	75	alone CABG	off	elective	8
Lo [45]	2005	Netherland	case-control	34	122	67	60	68	71	alone CABG	combined	elective	7
Cosgrave [46]	2005	Ireland	cohort	55	94	65.2	60.9	ND	ND	alone CABG	on	elective	8

Mandal [47]	2005	UK	case-control	15	15	65	65	80	80	alone CABG	combined	elective	7
Fontes [48]	2005	USA	cohort	26	46	71	63	81	80	CABG and/or Valve	on	elective	8
Wang [49]	2005	China	case-control	93	301	ND	ND	ND	ND	alone CABG	on	elective	7
Mandal [50]	2004	UK	cohort	62	267	65	64	79	83	alone CABG	combined	elective	9

Abbreviation: N: number, AF: atrial fibrillation, SR: sinus rhythm, TOS: type of surgery, CPB: cardiopulmonary bypass, ES: elective surgery, NES: non-elective surgery, NOS: Newcastle Ottawa scale, CABG: coronary artery bypass graft, ND: no data

Table 2. Information about hematologic indices and these levels in each study

First author	Markers	Levels
➢ **Measurement of inflammatory markers**		
Xu [9]	CRP	Preoperative: CRP [AF: 4.52±2.88 vs SR: 3.99±3.48] Postoperative: CRP [AF: 29.35±19.1 vs SR: 24.98±12.68]
Saskin [10]	CRP	Preoperative: CRP [AF: 1.64±0.76 vs SR: 0.85±0.35]
Saskin [11]	CRP	Preoperative: CRP [AF: 10.3±8.3 vs SR: 5.4±2.9] Postoperative: CRP [AF: 309±34 vs SR: 249±48]
Cerit [12]	CRP	Preoperative: CRP [AF: 21±47 vs SR: 9±14]
Anatolevna [13]	CRP, IL-6, IL-8, IL-10	Preoperative: CRP [AF: 1.4±1.3 vs SR: 1.2±0.93] IL-6 [AF: 30.1±26.5 vs SR: 25.7±13.2] IL-8 [AF: 2.7±2.4 vs SR: 2.2±1.3] IL-10 [AF: 6.3±3.3 vs SR: 7.4±4.7] Postoperative: CRP [AF: 4.7±0.7 vs SR: 4.5±0.8] IL-6 [AF: 72.7±60.8 vs SR: 38±34.6] IL-8 [AF: 11.9±6 vs SR: 7.7±5.4] IL-10 [AF: 11.9±6.4 vs SR: 11.6±5.7]
Gecmen [14]	CRP	Preoperative: CRP [AF: 33.9±27.5 vs SR: 27.5±22.7]
Korantzopoulos [15]	CRP	Preoperative: CRP [AF: 83.25±49.75 vs SR: 43.75±1.6]
Erdem [16]	CRP	Preoperative: CRP [AF: 10.6±8.5 vs SR: 5.6±6.5]
Narducci [17]	CRP	Preoperative: CRP [AF: 10.4±4.2 vs SR: 5.67±2.72] Postoperative: CRP [AF: 41.35±3.25 vs SR: 45.95±5.25]
Limite [18]	CRP	Preoperative: CRP [AF: 2.92±0.28 vs SR: 2.95±0.3] Postoperative:

		CRP [AF: 196.92±25.65 vs SR: 172.2±20.46]
Erdem [19]	CRP	Preoperative: CRP [AF: 8.9±19.6 vs SR: 5.3±8.7]
Pilatis [20]	CRP	Preoperative: CRP [AF: 4.82±1.47 vs SR: 3.95±0.51] Postoperative: CRP [AF: 114.78±11 vs SR: 128.25±7.83]
Cao [21]	CRP	Preoperative: CRP [AF: 5.76±1.61 vs SR: 2.73±0.94]
Bjorgvinsdottir [22]	CRP, IL-8, IL-10	Preoperative: IL-8 [AF: 12±8 vs SR: 14.75±10.75] IL-10 [AF: 30.75±22.75 vs SR: 40.75±31.75] Postoperative: CRP [AF: 221.25±95 vs SR: 199.5±84] IL-8 [AF: 54.5±50.5 vs SR: 92±88] IL-10 [AF: 71±54.25 vs SR: 68±51.5]
Sabol [23]	CRP	Postoperative: CRP [AF: 138.1±41.1 vs SR: 69.9±25.8]
Garcia [24]	CRP	Preoperative: CRP [AF: 24±23 vs SR: 25±27]
Skuladottir [25]	CRP	Postoperative: CRP [AF: 221.25±95 vs SR: 199.5±84]
Gabrielli [26]	CRP	Preoperative: CRP [AF: 68±14 vs SR: 57±12]
Kaireviciute [27]	CRP, IL-6	Postoperative: CRP [AF: 4.47±1.57 vs SR: 2.15±0.56] IL-6 [AF: 39.8±20.6 vs SR: 20.9±9.3]
Gasparovic [28]	CRP	Preoperative: CRP [AF: 6±16 vs SR: 6±13] Postoperative: CRP [AF: 149±82 vs SR: 137±72]
Gibson [29]	CRP	Preoperative: CRP [AF: 2.44±0.69 vs SR: 1.91±0.5] Postoperative: CRP [AF: 175.5±13.66 vs SR: 163.25±8.83]
Ji [30]	CRP	Postoperative: CRP [AF: 165.7±29.4 vs SR: 105.3±18.7]

Girerd [31]	CRP, IL-6	Preoperative: CRP [AF: 1.95±2.67 vs SR: 1.49±2.74] IL-6 [AF: 2.3±1.6 vs SR: 2.2±2.1]
Choi [32]	CRP	Preoperative: CRP [AF: 6.6±12.7 vs SR: 4.7±11.4] Postoperative: CRP [AF: 177.1±99.2 vs SR: 150.3±55.7]
Antoniades [33]	CRP	Preoperative: CRP [AF: 1.4±0.55 vs SR: 1.52±0.42]
Sezai [34]	CRP	Preoperative: CRP [AF: 6.9±17.4 vs SR: 11.9±27.9] Postoperative: CRP [AF: 45.6±29.2 vs SR: 47.1±29]
Fontes [35]	CRP	Preoperative: CRP [AF: 12±22 vs SR: 13±18] Postoperative: CRP [AF: 189±74 vs SR: 179±54]
Ziabakhsh-Tabari [36]	CRP, IL-6	Preoperative: CRP [AF: 10.42±9.58 vs SR: 8.4±4.9] IL-6 [AF: 3.95±1.02 vs SR: 1.24±0.8] Postoperative: CRP [AF: 175.3±60.1 vs SR: 175.4±64.4]
Mehmet OC [[37]	CRP	Preoperative: CRP [AF: 5.4±3.1 vs SR: 6.5±4.4] Postoperative: CRP [AF: 4.6±1.7 vs SR: 5±1.4]
Canbaz [38]	CRP, IL-6, IL-10	Preoperative: CRP [AF: 23±17 vs SR: 17±14] IL-6 [AF: 11±19 vs SR: 9±11] IL-10 [AF: 60±80 vs SR: 50±80] Postoperative: CRP [AF: 53±17 vs SR: 45±17] IL-6 [AF: 38±36 vs SR: 27±37] IL-10 [AF: 190±130 vs SR: 120±150]
Qian [39]	CRP	Preoperative: CRP [AF: 2.73±1.73 vs SR: 2.34±1.54]
Pretorius [40]	CRP, IL-6, IL-8, IL-10	Postoperative: CRP [AF: 13.1±3.6 vs SR: 14.1±2.6]

		IL-6 [AF: 380.6±151.1 vs SR: 174.8±16.9] IL-8 [AF: 85.2±63.1 vs SR: 18.6±2.3] IL-10 [AF: 2712.5±298.6 vs SR: 2463.6±162]
Ucar [41]	CRP, IL-6	Preoperative: CRP [AF: 0.6±0.2 vs SR: 0.3±0.2] IL-6 [AF: 7.4±3.6 vs SR: 6.2±2.9] Postoperative: CRP [AF: 22.4±4.1 vs SR: 16.9±1.9] IL-6 [AF: 100.7±65.8 vs SR: 36.9±15.9]
Ahlsson [42]	CRP	Preoperative: CRP [AF: 5.6±9.1 vs SR: 5±6.4] Postoperative: CRP [AF: 175.3±60.1 vs SR: 175.4±64.4]
Houge JR [43]	CRP	Preoperative: CRP [AF: 13.3±2.5 vs SR: 11.7±1.4]
Ishida [44]	IL-6	Postoperative: IL-6 [AF: 435±175 vs SR: 247±102]
Lo [45]	CRP	Preoperative: CRP [AF: 4.07±1.57 vs SR: 1.7±0.45]
Cosgrave [46]	CRP	Preoperative: CRP [AF: 26.05±7.25 vs SR: 36.07±8.05] Postoperative: CRP [AF: 2372.5±297.5 vs SR: 2532.5±201.6]
Mandal [47]	CRP	Preoperative: CRP [AF: 2.4±1.2 vs SR: 1.95±1]
Fontes [48]	CRP	Preoperative: CRP [AF: 2.2±3.2 vs SR: 1.8±2.1]
Wang [49]	CRP	Preoperative: CRP [AF: 43±38 vs SR: 39±36] Postoperative: CRP [AF: 542±279 vs SR: 219±164]
Mandal [50]	CRP	Preoperative: CRP [AF: 1.92±0.97 vs SR: 2.56±0.8]
Abbreviation: CRP: C-reactive protein, IL: interleukin, AF: atrial fibrillation, SR: sinus rhythm		

Supplemental Table 1. Included, and excluded studies according to inflammatory markers

Clinical outcomes and biomarkers	**Studies were identified and screened [n]**	**Studies were excluded according to title, abstract or full text (Secondary exclude) [n]**	**Studies were included [n]**
CRP	752	712	40
IL-6	201	193	8
IL-8	28	15	3
IL-10	33	29	4
There are not reports about other interleukins with postoperative atrial fibrillation			

Supplemental Table 2. Extra details of characteristics of each study for exploration of heterogeneity factors.

First Author	Geographic Area	Total N	Total age	Total male	Total DM	Total HTN	Total CS	Total Hx of MI	Total Diuretic	Total ACEI	Total. Statin	Total BB	Total mean LVEF	Mean time of CCT	Mean time of CPB
Xu [9]	Asia	508	62.705	74.535	43.7	66.7	67	54.1	ND	43.35	63.3	90.9	54.5	ND	ND
Saskin [10]	European	662	61.5	80.35	34.35	43.35	39.65	ND	ND	30.55	41.95	66.4	53.25	52.625	85
Saskin [11]	European	1138	60.25	50	34.85	59.6	40.05	ND	ND	ND	ND	ND	55.5	52.15	83.25
Cerit [12]	European	106	65.25	88.1	61.6	93.55	42.9	ND	53.4	91.55	100	100	52.85	ND	ND
Anatolevna [13]	European	81	66.75	82.75	22.35	100	31.7	55.8	11.05	79.35	70.05	83.25	57.15	ND	ND
Gecmen [14]	European	94	62.5	79	42	64	54	33	ND	ND	ND	ND	50	ND	ND
Korantzopoulos [15]	European	109	66.55	72	28.5	94.5	39.5	ND	ND	64	99	91.5	54.25	62	ND
Erdem [16]	European	135	64.25	71.25	33.7	70.75	56.75	36.5	ND	49.4	47.15	47.05	53.7	64.5	95
Narducci [17]	European	38	70	69.5	56.5	94	28	ND	47.5	56.5	64	86	ND	52	60
Limite [18]	European	444	61.3	73.7	17.1	50.25	11.05	ND	ND	ND	ND	ND	54.85	ND	ND
Erdem [19]	European	165	65.95	79.365	41	48.5	28.5	ND	ND	ND	ND	ND	52	ND	ND
Pilatis [20]	European	125	65.5	95.5	31	68.5	32	ND	21.75	62.5	ND	77.15	ND	ND	ND
Cao [21]	European	154	47.95	50.16	ND	ND	ND	ND	ND	16.46	ND	18.835	ND	61	100
Bjorgvinsdottir [22]	European	125	67.5	81.55	15.95	64.8	20.75	ND	ND	ND	87.2	80.75	52.5	ND	86.475
Sabol [23]	European	45	62.2	71.7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Garcia [24]	South America	180	67.95	78.65	30.3	73	ND	ND	ND	59.4	64.15	52.4	42.05	66.25	103.9
Skuladottir [25]	European	125	67.5	81.55	15.95	64.8	20.75	ND	ND	ND	87.2	80.75	ND	ND	ND
Gabrielli [26]	South America	70	66	69.5	24	48	ND	ND	ND	ND	100	100	63	ND	ND
Kaireviciute [27]	European	100	65.1	88.1	17.65	83.8	32.65	45.7	ND	ND	ND	100	51.1	ND	ND
Gasparovic [28]	European	215	63	70	27.5	87	45.5	51	ND	69.5	86	78	58	ND	89
Gibson [29]	European	275	65.5	84.45	18	68.25	11.75	50	ND	60.5	95	75	51.55	40.875	72.25
Ji [30]	Asia	140	66.65	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Girerd [31]	America	294	57.05	100	ND	59.5	ND	ND	ND	ND	ND	ND	ND	ND	ND
Choi [32]	Asia	315	65.85	72.46	44	71.5	ND	36.5	ND	25	70	73	54.5	ND	ND
Antoniades [33]	European	144	65.95	82.595	28	73.5	30	ND	ND	49.5	97.5	81	ND	ND	ND
Sezai [34]	Asia	234	69.075	74.96	51.8	78.98	30.955	34.39	ND	27.53	ND	13.18	60.05	28	101.05
Fontes [35]	America	60	71.05	84.25	ND	71.9	ND	32.8	ND	ND	50.85	67.85	48	ND	67.9
Ziabakhsh-Tabari [36]	Asia	54	54.34	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Mehmet OC [[37]	European	20	62	70	25	25	65	ND	ND	ND	ND	ND	44.65	34.8	66

Canbaz [38]	European	71	56.5	81.95	ND	43.5	ND	ND	ND	ND	ND	100	51.5	59	98
Qian [39]	Asia	47	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	34.56	ND	ND
Pretorius [40]	America	253	61.5	67.5	27.3	80.45	18.05	ND	51.2	45.75	46.4	57	45.5	ND	ND
Ucar [41]	European	49	61.55	14.28	32.14	26.42	58.57	ND	ND	74.96	82.85	100	ND	ND	ND
Ahlsson [42]	European	524	68	73.5	21	ND	54.5	42.5	ND	ND	ND	70.5	ND	72	106.5
Houge JR [43]	America	130	71	0	17.5	87	28.5	ND	ND	54.5	64.5	62	ND	84	107.5
Ishida [44]	Asia	39	65	69.5	62.5	68	ND	49	ND	52.5	ND	68.5	ND	ND	ND
Lo [45]	European	156	63.5	69.5	9.5	48.5	ND	ND	ND	ND	ND	84	ND	ND	ND
Cosgrave [46]	European	149	63.05	ND	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Mandal [47]	European	30	65	80	33	90	53	ND	ND	ND	ND	93	ND	50	80
Fontes [48]	America	72	67	80.5	ND	72	ND	ND	ND	ND	ND	ND	ND	ND	100.5
Wang [49]	Asia	394	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Mandal [50]	European	329	64.5	81	28	76.5	65.5	36	ND	ND	ND	63.5	ND	61	101.5

Abbreviation: N: number, DM: diabetes mellitus, HTN: hypertension, CS: cigarette smoking, Hx: history, MI: myocardial infarction, ACEI: Angiotensin converting enzyme inhibitors, BB: beta-blocker, LVEF: left ventricle ejection fraction, CCT: cross clamping time, CPBT: cardiopulmonary bypass, ND: no data

Supplemental Table 3. Subgroup-analysis

Subgroup	Studies (N)	SMD (95% CI)	I-squared and Heterogeneity-P-value and Effect-P-value respectively	Is this general item as heterogeneity factor? 1.Yes, probably 2. No
➢ **Preoperative inflammatory markers**				
C-Reactive Protein				
Year of Publication				
>2000	All of studies: after 2000			
≤2000				
Geographic area				- Yes, probably
Asian	6	0.091 (-0.026 to 0.209)	11.2% and 0.344 and 0.129	
European	24	0.592 (0.530 to 0.655)	96.7% and 0.001 and 0.001	
Africa	0	-	-	
North American	4	0.293 (0.121 to 0.466)	74.2% and 0.009 and 0.001	
South American	2	0.230 (-0.071 to 0.531)	86.4% and 0.007 and 0.134	
Australia	0	-	-	
Design of study				- No
Cohort	23	0.474 (0.413 to 0.535)	95.9% and 0.001 and 0.001	
Case-control	13	0.413 (0.315 to 0.511)	94.8% and 0.001 and 0.001	
Type of surgery				- No
CABG alone	29	0.493 (0.434 to 0.552)	95.5% and 0.001 and 0.001	
Valve alone	2	1.657 (1.317 to 1.998)	97.2% and 0.001 and 0.001	
CABG and Valve	5	0.181 (0.066 to 0.296)	91.6% and 0.001 and 0.002	
Using of CPB				- No

On-pump Off-pump Combined data	25 3 8	0.510 (0.448 to 0.572) 0.084 (-0.067 to 0.236) 0.491 (0.371 to 0.611)	95.6% and 0.001 and 0.001 53.7% and 0.115 and 0.276 96.5% and 0.001 and 0.001	
Status of surgery Elective Non-elective	All of studies: Elective surgery			
Number of population >200 ≤200	 12 24	 0.405 (0.343 to 0.467) 0.577 (0.483 to 0.672)	 97.1% and 0.001 and 0.001 94% and 0.001 and 0.001	- No
Mean Age >60 years ≤60 years	 30 4	 0.463 (0.407 to 0.519) 0.631 (0.447 to 0.814)	 95.7% and 0.001 and 0.001 95.5% and 0.001 and 0.001	- No
Male >70% ≤70%	 25 7	 0.319 (0.257 to 0.380) 1.211 (1.096 to 1.326)	 94% and 0.001 and 0.001 93.2% and 0.001 and 0.001	- No
Diabetes mellitus >30% ≤30%	 15 13	 0.601 (0.530 to 0.671) 0.237 (0.142 to 0.332)	 94.6% and 0.001 and 0.001 96.8% and 0.001 and 0.001	- No
Hypertension >70% ≤70%	 16 14	 0.193 (0.098 to 0.288) 0.717 (0.645 to 0.788)	 91.7% and 0.001 and 0.001 95.9% and 0.001 and 0.001	- No
Cigarette smoking				- No

>30%	17	0.548 (0.480 to 0.617)	96.1% and 0.001 and 0.001	
≤30%	6	0.376 (0.248 to 0.504)	91% and 0.001 and 0.001	
Myocardial infarction				- No
>20%	12	0.178 (0.094 to 0.262)	93% and 0.001 and 0.001	
≤20%	0	-	-	
Medication: Diuretic				- No
>70%	-	-	-	
≤70%	4	0.637 (0.407 to 0.868)	71.7% and 0.014 and 0.001	
Medication: ACEI				- No
>70%	3	0.520 (0.235 to 0.805)	79.5% and 0.008 and 0.001	
≤70%	14	0.645 (0.563 to 0.727)	95.8% and 0.001 and 0.001	
Medication: Statin				- No
>70%	9	0.447 (0.326 to 0.567)	88% and 0.001 and 0.001	
≤70%	7	0.779 (0.663 to 0.895)	95.6% and 0.001 and 0.001	
Medication: Beta-Blocker				- No
>70%	17	0.471 (0.387 to 0.554)	93.4% and 0.001 and 0.001	
≤70%	8	0.652 (0.541 to 0.763)	97.8% and 0.001 and 0.001	
Mean LVEF				- Yes, probably
>50%	17	0.616 (0.550 to 0.683)	95.1% and 0.001 and 0.001	
≤50%	4	-0.007 (-0.263 to 0.248)	0.0% and 0.766 and 0.955	
Cross clamp time				- No
>60 minutes	7	0.318 (0.204 to 0.432)	96.9% and 0.001 and 0.001	

≤60 minutes	8	0.961 (0.866 to 1.055)	94.5% and 0.001 and 0.001	
CPB time				- No
>100 minutes	7	0.128 (0.017 to 0.238)	96.5% and 0.001 and 0.024	
≤ 100 minutes	10	0.958 (0.867 to 1.049)	92% and 0.001 and 0.001	
IL-6				
Year of Publication				
>2000	All of studies: after 2000			
≤2000				
Geographic area				- Yes, probably
Asian	1	3.200 (2.297 to 4.104)	-	
European	4	0.623 (0.356 to 0.890)	80.2% and 0.002 and 0.001	
Africa	-	-	-	
North American	1	0.054 (-0.175 to 0.282)	-	
South American	-	-	-	
Australia	-	-	-	
Design of study				- Yes, probably
Cohort	3	1.344 (0.997 to 1.691)	92.1% and 0.001 and 0.001	
Case-control	3	0.095 (-0.101 to 0.291)	0.0% and 0.763 and 0.340	
Type of surgery				
CABG alone	All of surgeries: alone CABG			
Valve alone				
CABG and Valve				
Using of CPB				- Yes, probably

On-pump Off-pump Combined data	4 - 2	1.048 (0.748 to 1.349) - 0.088 (-0.119 to 0.296)	91.8% and 0.001 and 0.001 - 0.0% and 0.482 and 0.404	
Status of surgery Elective Non-elective	 5 -	 0.418 (0.237 to 0.600) -	 93.7% and 0.001 and 0.001 -	- No
Number of population >200 ≤200	 1 5	 0.054 (-0.175 to 0.282) 0.830 (0.574 to 1.087)	 - 90.9% and 0.001 and 0.001	- No
Mean Age >60 years ≤60 years	 3 3	 0.738 (0.440 to 1.036) 0.233 (0.025 to 0.441)	 83.8% and 0.002 and 0.001 95.4% and 0.001 and 0.028	- No
Male >70% ≤70%	 4 1	 0.287 (0.106 to 0.468) 0.386 (-0.239 to 1.011)	 88.1% and 0.001 and 0.002 -	- No
Diabetes mellitus >30% ≤30%	 1 2	 0.386 (-0.239 to 1.011) 0.842 (0.502 to 1.181)	 - 90.7% and 0.001 and 0.001	- No
Hypertension >70% ≤70%	 2 3	 0.842 (0.502 to 1.181) 0.100 (-0.102 to 0.302)	 90.7% and 0.001 and 0.001 0.0% and 0.607 and 0.332	- Yes, probably
Cigarette smoking				- No

>30%	3	0.738 (0.440 to 1.036)	83.6% and 0.002 and 0.001	
≤30%	-	-	-	
Myocardial infarction				- No
>20%	2	0.842 (0.502 to 1.181)	90.7% and 0.001 and 0.001	
≤20%	-	-	-	
Medication: Diuretic				- No
>70%	-	-	-	
≤70%	1	0.248 (-0.243 to 0.739)	-	
Medication: ACEI				- No
>70%	2	0.301 (-0.217 to 0.617)	0.0% and 0.734 and 0.127	
≤70%	-	-	-	
Medication: Statin				- No
>70%	2	0.301 (-0.217 to 0.617)	0.0% and 0.734 and 0.127	
≤70%	-	-	-	
Medication: Beta-Blocker				- No
>70%	4	0.623 (0.356 to 0.890)	80.2% and 0.002 and 0.001	
≤70%	-	-	-	
Mean LVEF				- No
>50%	3	0.676 (0.381 to 0.972)	86.2% and 0.001 and 0.001	
≤50%	-	-	-	
Cross clamp time				- No
>60 minutes	-	-	-	

≤60 minutes	1	0.157 (-0.445 to 0.759)	-	
CPB time				- No
>100 minutes	-	-	-	
≤ 100 minutes	1	0.157 (-0.445 to 0.759)	-	
➢ **Postoperative inflammatory markers**				
C-Reactive Protein				
Year of Publication				
>2000	All of studies: after 2000			
≤2000				
Geographic area				- No
Asian	6	0.669 (0.549 to 0.789)	97% and 0.001 and 0.001	
European	15	0.611 (0.535 to 0.687)	96.5% and 0.001 and 0.001	
Africa	-	-	-	
North American	2	-0.243 (0.494 to 0.008)	60.7% and 0.111 and 0.058	
South American	-	-	-	
Australia	-	-	-	
Design of study				- No
Cohort	12	0.566 (0.491 to 0.642)	97.3% and 0.001 and 0.001	
Case-control	11	0.591 (0.481 to 0.702)	95.1% and 0.001 and 0.001	
Type of surgery				- No
CABG alone	20	0.663 (0.591 to 0.736)	96.2% and 0.001 and 0.001	
Valve alone	-	-	-	
CABG and Valve	3	0.323 (0.202 to 0.445)	97.8% and 0.001 and 0.001	

Using of CPB				- No
On-pump	14	0.620 (0.545 to 0.696)	96.7% and 0.001 and 0.001	
Off-pump	3	0.581 (0.421 to 0.741)	97.5% and 0.001 and 0.001	
Combined data	5	0.311 (0.155 to 0.467)	96.4% and 0.001 and 0.001	
Status of surgery				- No
Elective	16	0.710 (0.630 to 0.791)	97% and 0.001 and 0.001	
Non-elective	1	0.243 (-0.109 to 0.595)	-	
Number of population				- No
>200	10	0.687 (0.617 to 0.757)	97.2% and 0.001 and 0.001	
≤200	13	0.145 (0.008 to 0.281)	95.1% and 0.001 and 0.038	
Mean Age				- No
>60 years	20	0.515 (0.450 to 0.579)	96.5% and 0.001 and 0.001	
≤60 years	2	0.255 (-0.192 to 0.702)	5.8% and 0.303 and 0.263	
Male				- No
>70%	15	0.347 (0.269 to 0.426)	93.2% and 0.001 and 0.001	
≤70%	4	0.956 (0.832 to 1.081)	98% and 0.001 and 0.001	
Diabetes mellitus				- No
>30%	8	0.502 (0.417 to 0.587)	97.7% and 0.001 and 0.001	
≤30%	9	0.424 (0.320 to 0.528)	94.4% and 0.001 and 0.001	
Hypertension				- No
>70%	7	0.026 (-0.104 to 0.157)	75.2% and 0.001 and 0.690	
≤70%	5	0.833 (0.747 to 0.918)	96.3% and 0.001 and 0.001	

Cigarette smoking				- No
>30%	9	0.494 (0.408 to 0.579)	97.3% and 0.001 and 0.001	
≤30%	6	0.578 (0.459 to 0.698)	95.4% and 0.001 and 0.001	
Myocardial infarction				- No
>20%	8	0.278 (0.184 to 0.373)	87.6% and 0.001 and 0.001	
≤20%	-	-	-	
Medication: Diuretic				- No
>70%	-	-	-	
≤70%	4	-0.570 (-0.771 to -0.369)	91.1% and 0.001 and 0.001	
Medication: ACEI				- No
>70%	2	0.799 (0.389 to 1.209)	93.5% and 0.001 and 0.001	
≤70%	8	0.153 (0.050 to 0.256)	95.1% and 0.001 and 0.004	
Medication: Statin				- Yes, probably
>70%	7	0.530 (0.402 to 0.658)	87.6% and 0.001 and 0.001	
≤70%	4	0.021 (-0.138 to 0.179)	86.2% and 0.001 and 0.796	
Medication: Beta-Blocker				- No
>70%	12	0.236 (0.147 to 0.326)	92.9% and 0.001 and 0.001	
≤70%	3	-0.157 (-0.343 to 0.029)	43.7% and 0.169 and 0.099	
Mean LVEF				- No
>50%	10	0.776 (0.697 to 0.854)	94.5% and 0.001 and 0.001	
≤50%	3	-0.244 (-0.486 to -0.003)	21.4% and 0.280 and 0.048	
Cross clamp time				- No

>60 minutes ≤60 minutes	1 6	-0.002 (-0.181 to 0.178) 0.967 (0.857 to 1.077)	- 95.8% and 0.001 and 0.001	
CPB time >100 minutes ≤ 100 minutes	 2 8	 -0.016 (-0.167 to 0.134) 0.927 (0.822 to 1.032)	 0.0% and 0.766 and 0.831 94% and 0.001 and 0.001	- Yes, probably
IL-6				
Year of Publication >2000 ≤2000	All of studies: after 2000			
Geographic area Asian European Africa North American South American Australia	 1 3 - 1 - -	 1.492 (0.716 to 2.268) 0.835 (0.513 to 1.193) - 2.611 (2.250 to 2.971) - -	 - 77.7% and 0.011 and 0.001 - - - -	- No
Design of study Cohort Case-control	 3 2	 2.290 (1.993 to 2.588) 0.596 (0.208 to 0.983)	 79.2% and 0.008 and 0.001 36.9% and 0.208 and 0.003	- No
Type of surgery CABG alone Valve alone CABG and Valve	 4 - 1	 0.956 (0.644 to 1.268) - 2.611 (2.250 to 2.971)	 73.1% and 0.011 and 0.001 - -	- No

Using of CPB				- No
On-pump	3	1.957 (1.673 to 2.240)	95.2% and 0.001 and 0.001	
Off-pump	1	1.492 (0.716 to 2.268)	-	
Combined data	1	0.804 (0.229 to 1.310)	-	
Status of surgery				- No
Elective	4	1.902 (1.635 to 2.168)	93.1% and 0.001 and 0.001	
Non-elective	-	-	-	
Number of population				- No
>200	1	2.611 (2.250 to 2.971)	-	
≤200	4	0.956 (0.644 to 1.268)	73.1% and 0.011 and 0.001	
Mean Age				- No
>60 years	4	1.909 (1.653 to 2.165)	91.2% and 0.001 and 0.001	
≤60 years	1	0.299 (-0.305 to 0.902)	-	
Male				- No
>70%	2	0.596 (0.208 to 0.983)	36.9% and 0.208 and 0.003	
≤70%	3	2.290 (1.993 to 2.588)	79.2% and 0.008 and 0.001	
Diabetes mellitus				- No
>30%	2	1.615 (1.091 to 2.139)	0.0% and 0.675 and 0.001	
≤30%	2	2.001 (1.707 to 2.295)	96.9% and 0.001 and 0.001	
Hypertension				- No
>70%	2	2.001 (1.707 to 2.295)	96.9% and 0.001 and 0.001	
≤70%	3	1.049 (0.653 to 1.445)	81.1% and 0.005 and 0.001	

Cigarette smoking				- No
>30%	2	1.111 (0.699 to 1.523)	76.3% and 0.040 and 0.001	
≤30%	1	2.611 (2.250 to 2.971)	-	
Myocardial infarction				- No
>20%	2	1.009 (0.586 to 1.433)	52.9% and 0.145 and 0.001	
≤20%	-	-	-	
Medication: Diuretic				- No
>70%	-	-	-	
≤70%	2	2.001 (1.707 to 2.295)	96.9% and 0.001 and 0.001	
Medication: ACEI				- No
>70%	2	1.111 (0.699 to 1.523)	76.3% and 0.040 and 0.001	
≤70%	2	2.412 (2.085 to 2.739)	84.8% and 0.010 and 0.001	
Medication: Statin				- No
>70%	2	1.111 (0.699 to 1.523)	76.3% and 0.040 and 0.001	
≤70%	1	2.611 (2.250 to 2.971)	-	
Medication: Beta-Blocker				- No
>70%	3	0.853 (0.513 to 1.193)	77.7% and 0.011 and 0.001	
≤70%	2	2.412 (2.085 to 2.739)	84.8% and 0.010 and 0.001	
Mean LVEF				- No
>50%	2	0.596 (0.208 to 0.983)	36.9% and 0.208 and 0.003	
≤50%	1	2.611 (2.250 to 2.971)	-	
Cross clamp time				- No

>60 minutes ≤60 minutes	- 1	- 0.299 (-0.305 to 0.902)	 -	
CPB time >100 minutes ≤ 100 minutes	 - 1	 - 0.299 (-0.305 to 0.902)	 -	- No
Abbreviation: N: number, SMD: standard mean difference, CI: confidence interval, CABG: coronary artery bypass graft, CPB: cardiopulmonary bypass, ACEI: Angiotensin converting enzyme inhibitors, LVEF: left ventricle ejection fraction, IL: interleukin				

Figure legends:

Figure 1. Forest plot of SMD for association between baseline level of CRP and occurrence of POAF.

Figure 2. Forest plot of SMD for association between baseline level of IL-6 and occurrence of POAF.

Figure 3. Forest plot of SMD for association between postoperative level of CRP and occurrence of POAF.

Figure 4. Forest plot of SMD for association between postoperative level of IL-6 and occurrence of POAF.

Supplemental Figure 1. Forest plot of SMD for association between baseline level of IL-8 and occurrence of POAF.

Supplemental Figure 2. Forest plot of SMD for association between baseline level of IL-10 and occurrence of POAF.

Supplemental Figure 3. Forest plot of SMD for association between postoperative level of IL-8 and occurrence of POAF.

Supplemental Figure 4. Forest plot of SMD for association between postoperative level of IL-10 and occurrence of POAF.

Supplemental Figure 5. Funnel plot for publication bias of studies investigating of baseline level of CRP

Supplemental Figure 6. Funnel plot for publication bias of studies investigating of baseline level of IL-6

Supplemental Figure 7. Funnel plot for publication bias of studies investigating of baseline level of IL-8

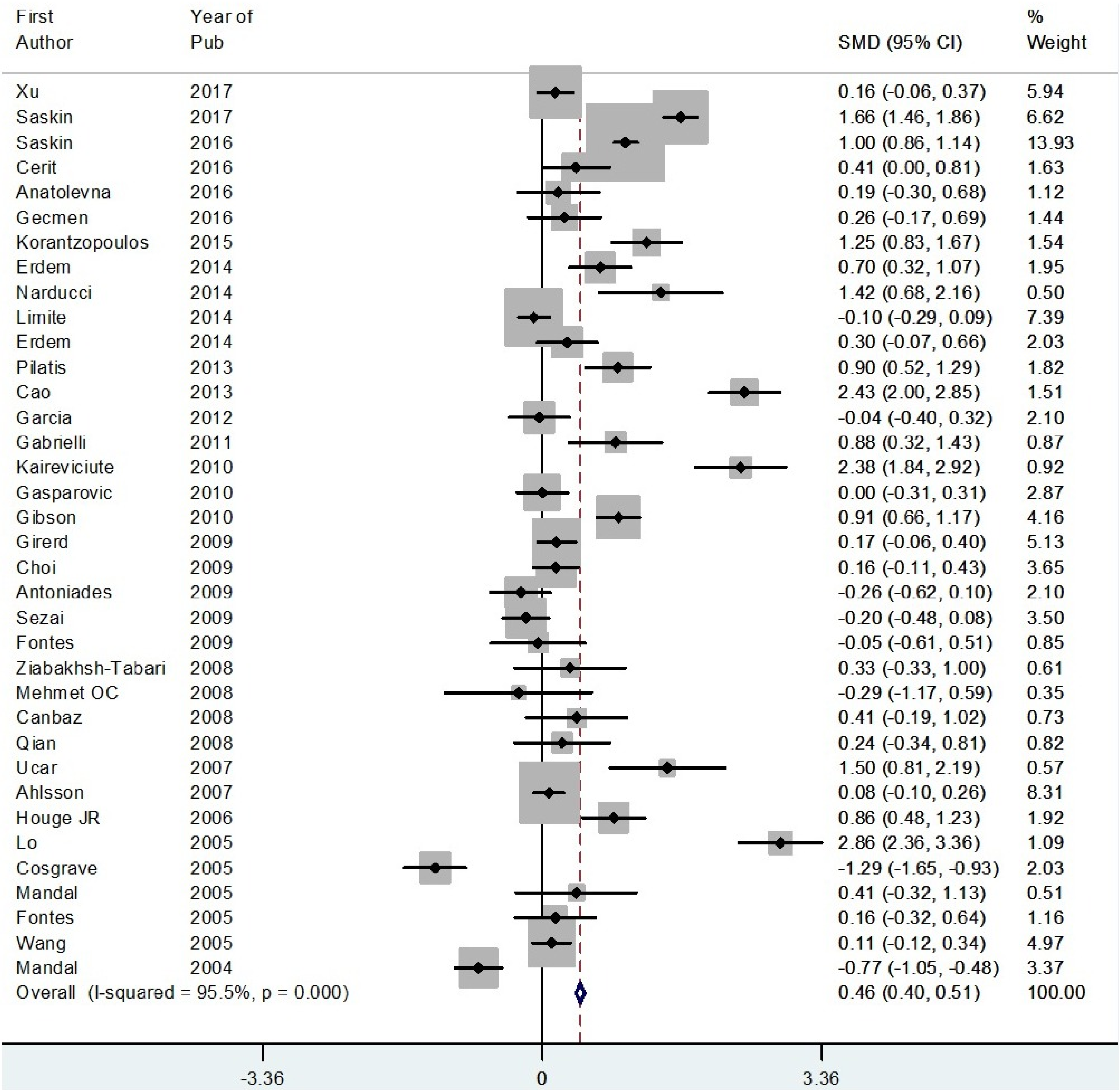
Supplemental Figure 8. Funnel plot for publication bias of studies investigating of baseline level of IL-10

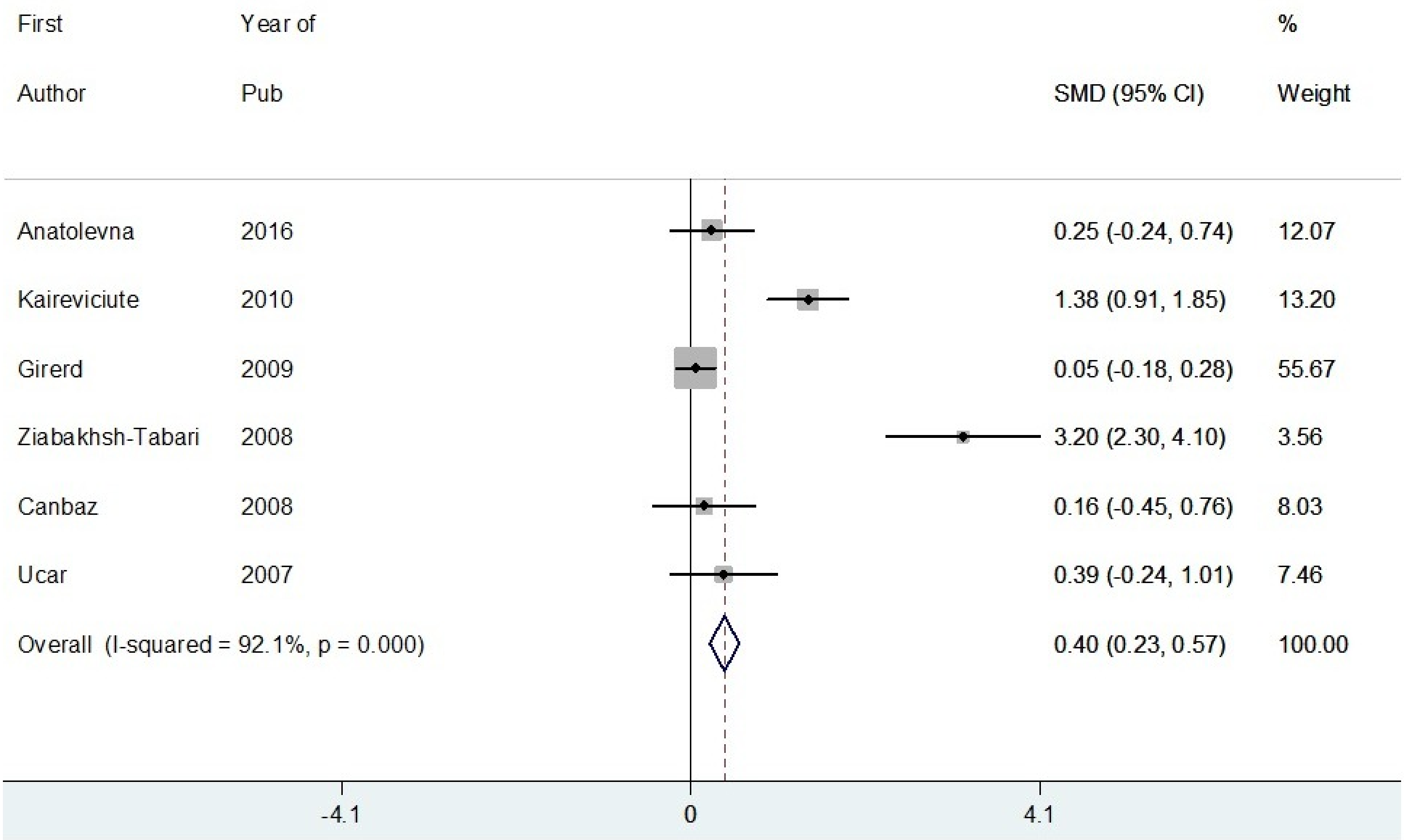
Supplemental Figure 9. Funnel plot for publication bias of studies investigating of postoperative level of CRP

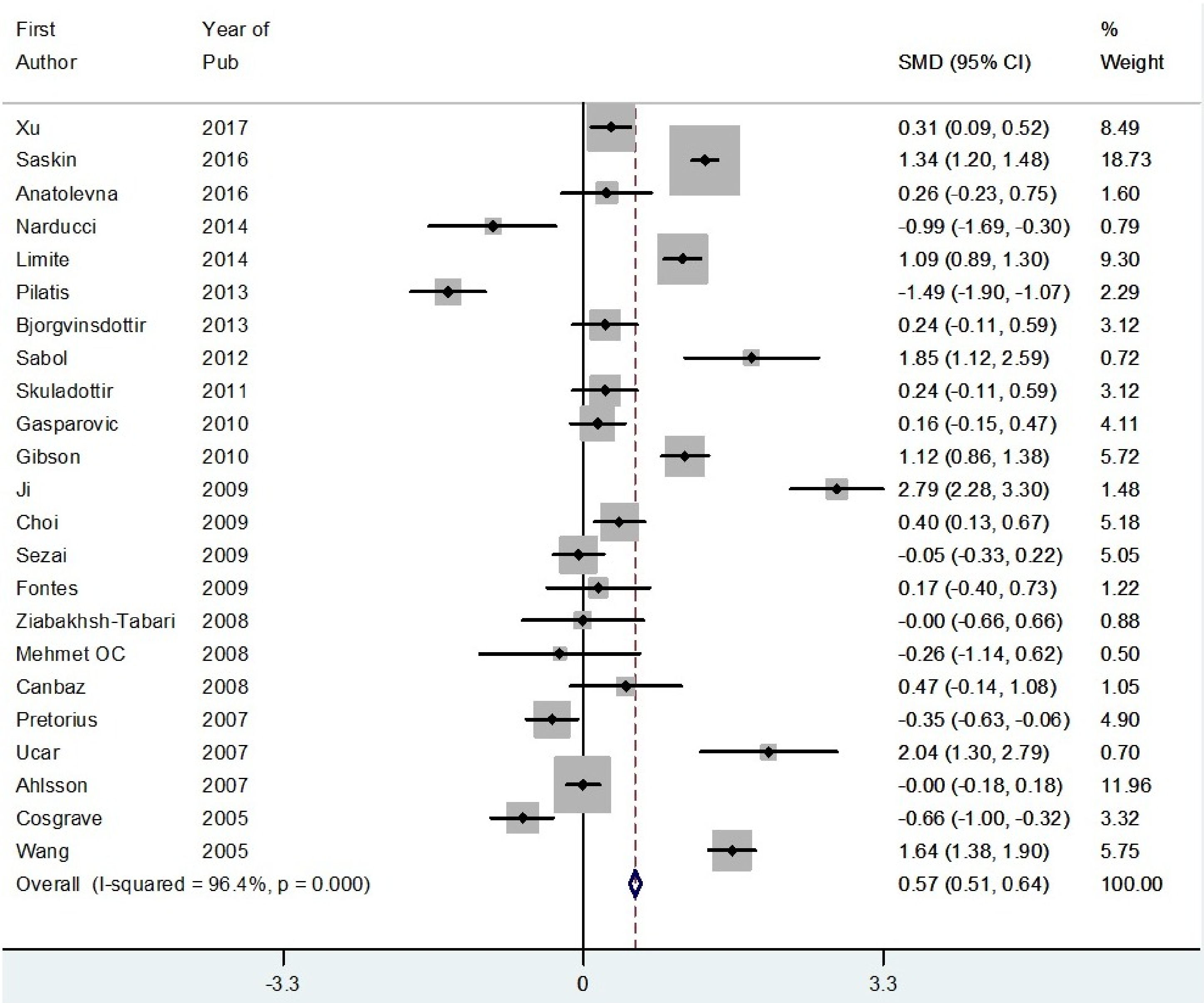
Supplemental Figure 10. Funnel plot for publication bias of studies investigating of postoperative level of IL-6

Supplemental Figure 11. Funnel plot for publication bias of studies investigating of postoperative level of IL-8

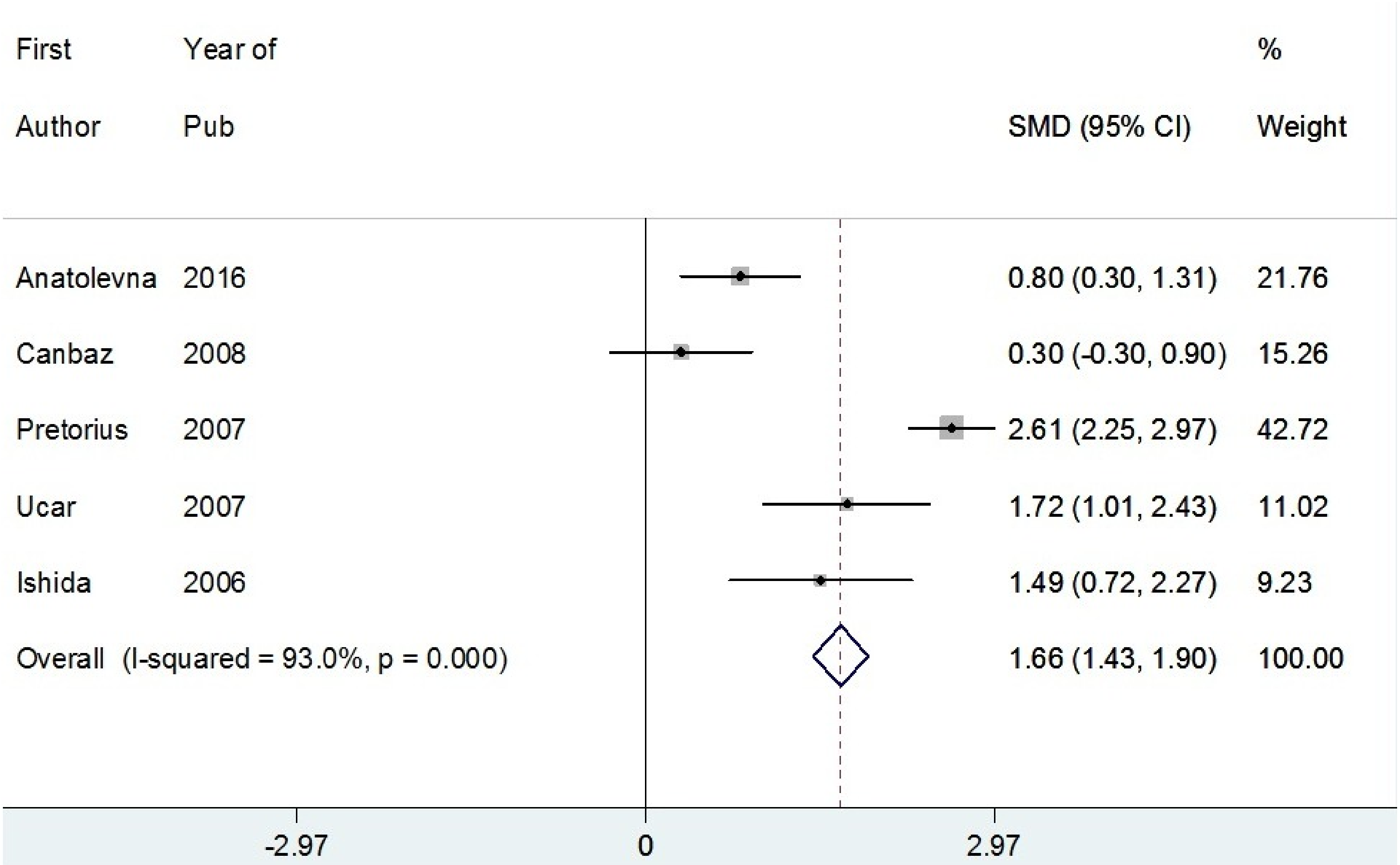
Supplemental Figure 12. Funnel plot for publication bias of studies investigating of postoperative level of IL-10

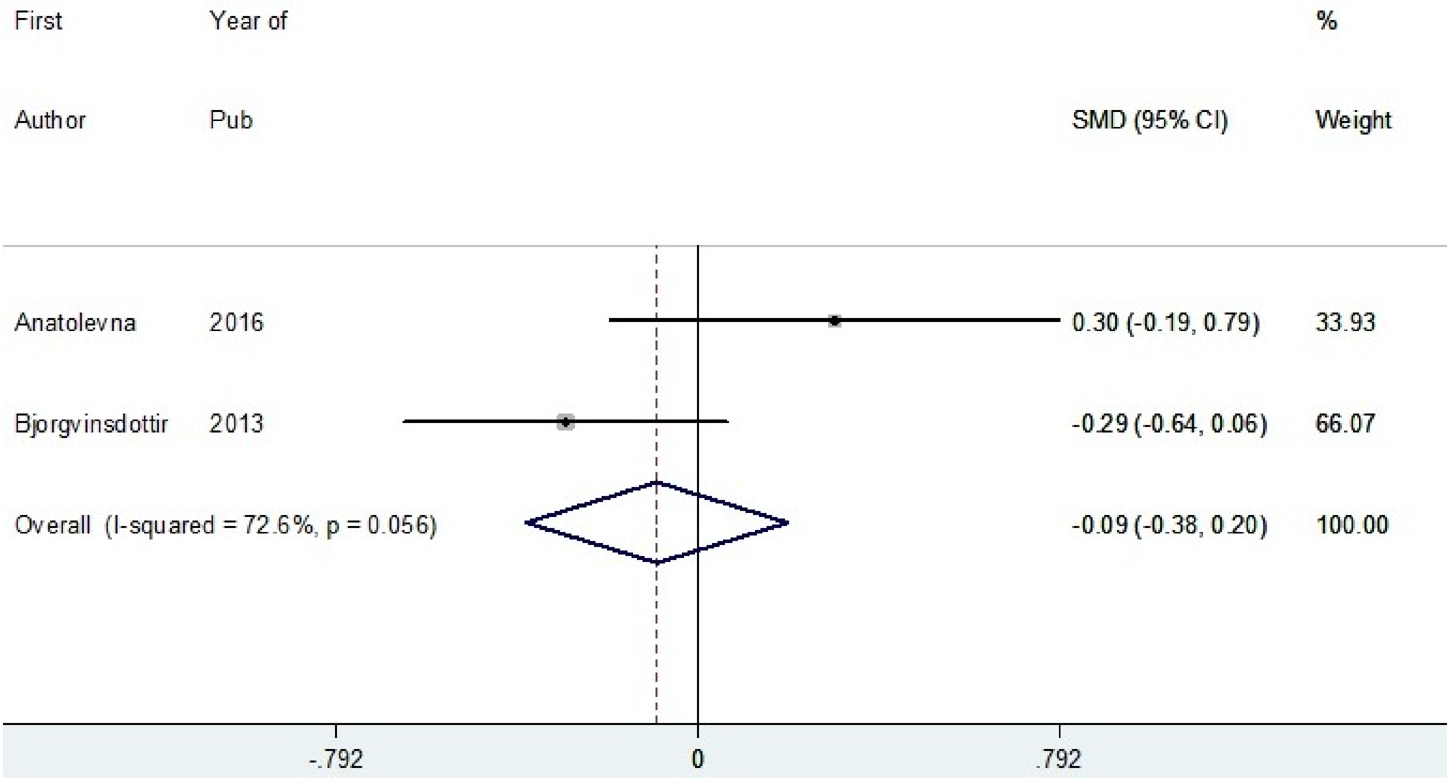

First Author
Year of Pub
SMD (95% CI)
% Weight
Xu 2017 0.16 (-0.06, 0.37) 5.94
Saskin 2017 1.66 (1.46, 1.86) 6.62
Saskin 2016 1.00 (0.86, 1.14) 13.93
Cerit 2016 0.41 (0.00, 0.81) 1.63
Anatolevna 2016 0.19 (-0.30, 0.68) 1.12
Gecmen 2016 0.26 (-0.17, 0.69) 1.44
Korantzopoulos 2015 1.25 (0.83, 1.67) 1.54
Erdem 2014 0.70 (0.32, 1.07) 1.95
Narducci 2014 1.42 (0.68, 2.16) 0.50
Limite 2014 -0.10 (-0.29, 0.09) 7.39
Erdem 2014 0.30 (-0.07, 0.66) 2.03
Pilatis 2013 0.90 (0.52, 1.29) 1.82
Cao 2013 2.43 (2.00, 2.85) 1.51
Garcia 2012 -0.04 (-0.40, 0.32) 2.10
Gabrielli 2011 0.88 (0.32, 1.43) 0.87
Kaireviciute 2010 2.38 (1.84, 2.92) 0.92
Gasparovic 2010 0.00 (-0.31, 0.31) 2.87
Gibson 2010 0.91 (0.66, 1.17) 4.16
Girerd 2009 0.17 (-0.06, 0.40) 5.13
Choi 2009 0.16 (-0.11, 0.43) 3.65
Antoniades 2009 -0.26 (-0.62, 0.10) 2.10
Sezai 2009 -0.20 (-0.48, 0.08) 3.50
Fontes 2009 -0.05 (-0.61, 0.51) 0.85
Ziabakhsh-Tabari 2008 0.33 (-0.33, 1.00) 0.61
Mehmet OC 2008 -0.29 (-1.17, 0.59) 0.35
Canbaz 2008 0.41 (-0.19, 1.02) 0.73
Qian 2008 0.24 (-0.34, 0.81) 0.82
Ucar 2007 1.50 (0.81, 2.19) 0.57
Ahlsson 2007 0.08 (-0.10, 0.26) 8.31
Houge JR 2006 0.86 (0.48, 1.23) 1.92
Lo 2005 2.86 (2.36, 3.36) 1.09
Cosgrave 2005 -1.29 (-1.65, -0.93) 2.03
Mandal 2005 0.41 (-0.32, 1.13) 0.51
Fontes 2005 0.16 (-0.32, 0.64) 1.16
Wang 2005 0.11 (-0.12, 0.34) 4.97
Mandal 2004 -0.77 (-1.05, -0.48) 3.37
Overall (I-squared = 95.5%, p = 0.000) 0.46 (0.40, 0.51) 100.00
-3.36
0
3.36

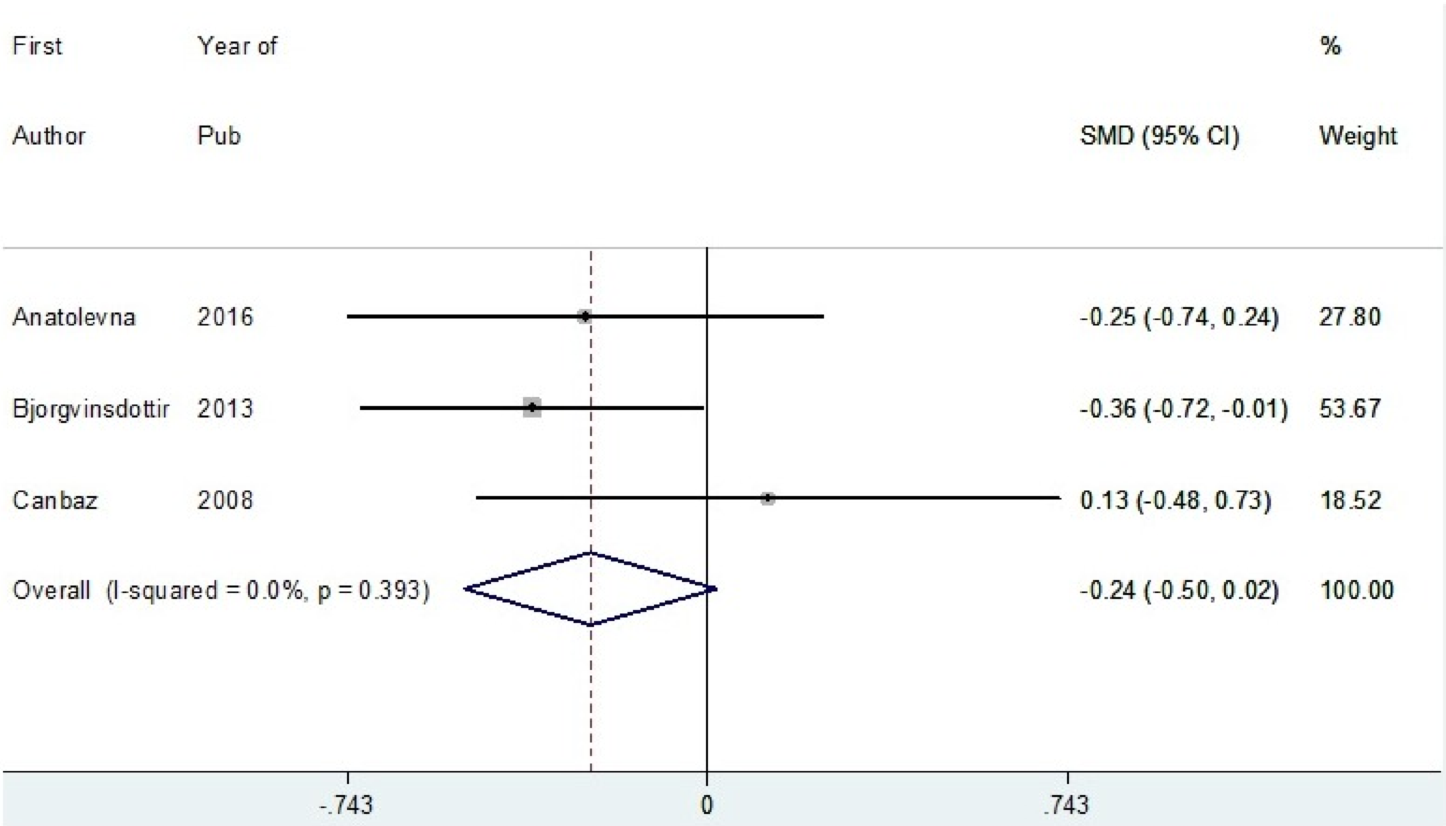

First
Year of
%
Author
Pub
SMD (95% CI)
Weight
Anatolevna
2016
0.25 (-0.24, 0.74)
12.07
Kaireviciute
2010
1.38 (0.91, 1.85)
13.20
Girerd
2009
0.05 (-0.18, 0.28)
55.67
Ziabakhsh-Tabari
2008
3.20 (2.30, 4.10)
3.56
Canbaz
2008
0.16 (-0.45, 0.76)
8.03
Ucar
2007
0.39 (-0.24, 1.01)
7.46
Overall (I-squared = 92.1%, p = 0.000)
0.40 (0.23, 0.57)
100.00
-4.1
0
4.1

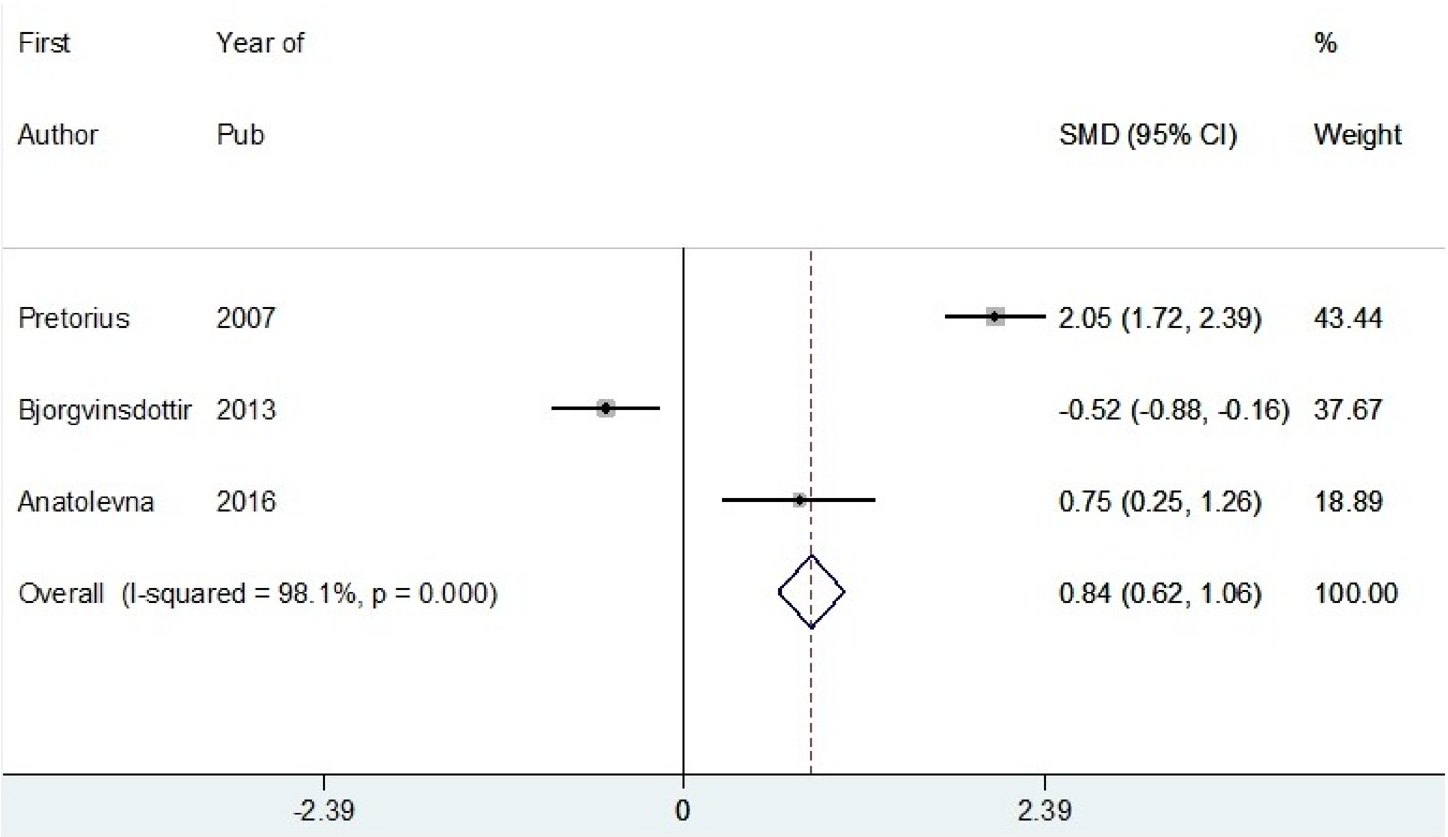


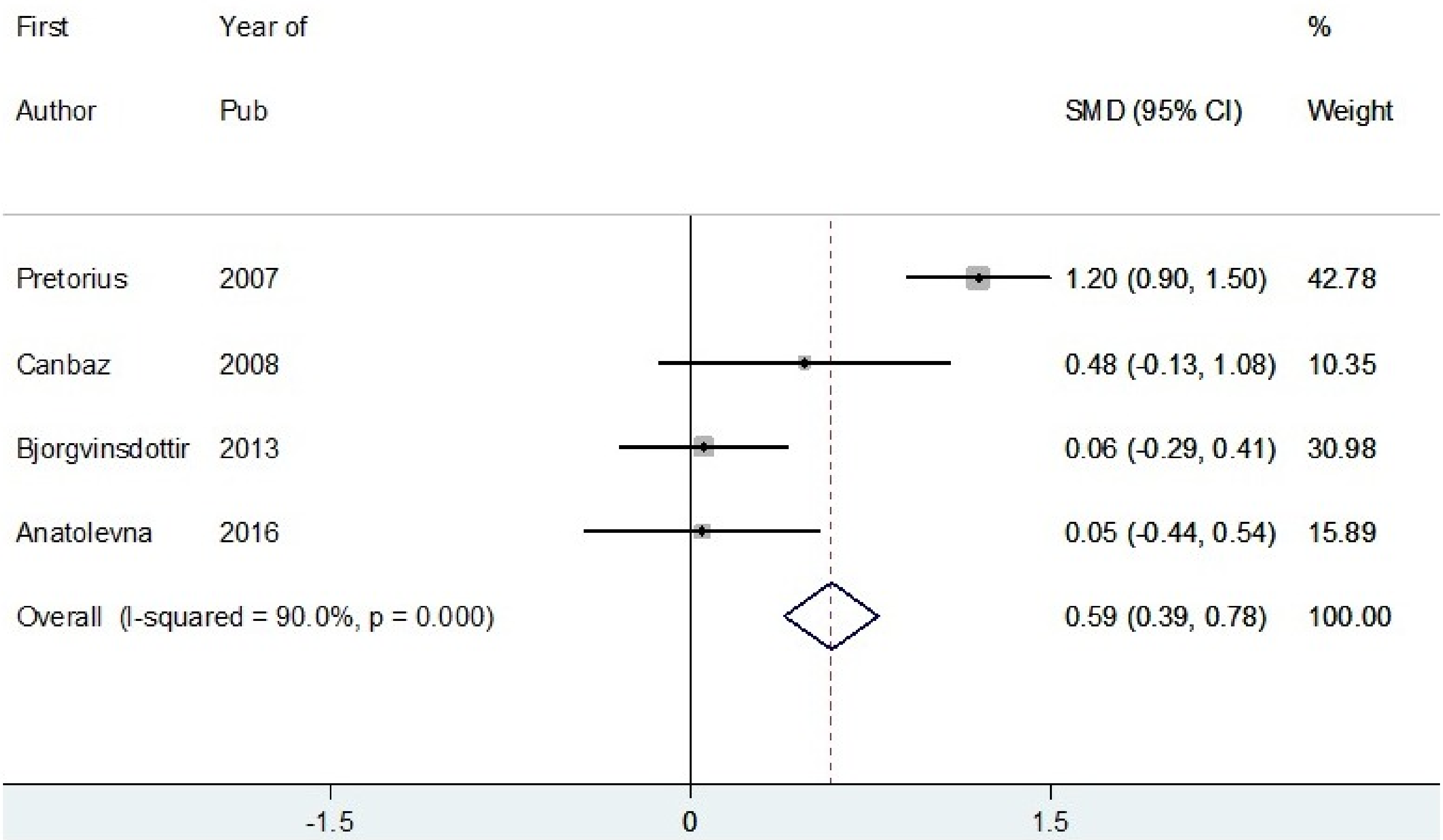
First Author
Year of Pub
SMD (95% CI)
% Weight
Xu 2017 0.31 (0.09, 0.52) 8.49
Saskin 2016 1.34 (1.20, 1.48) 18.73
Anatolevna 2016 0.26 (-0.23, 0.75) 1.60
Narducci 2014 -0.99 (-1.69, -0.30) 0.79
Limite 2014 1.09 (0.89, 1.30) 9.30
Pilatis 2013 -1.49 (-1.90, -1.07) 2.29
Bjorgvinsdottir 2013 0.24 (-0.11, 0.59) 3.12
Sabol 2012 1.85 (1.12, 2.59) 0.72
Skuladottir 2011 0.24 (-0.11, 0.59) 3.12
Gasparovic 2010 0.16 (-0.15, 0.47) 4.11
Gibson 2010 1.12 (0.86, 1.38) 5.72
Ji 2009 2.79 (2.28, 3.30) 1.48
Choi 2009 0.40 (0.13, 0.67) 5.18
Sezai 2009 -0.05 (-0.33, 0.22) 5.05
Fontes 2009 0.17 (-0.40, 0.73) 1.22
Ziabakhsh-Tabari 2008 -0.00 (-0.66, 0.66) 0.88
Mehmet OC 2008 -0.26 (-1.14, 0.62) 0.50
Canbaz 2008 0.47 (-0.14, 1.08) 1.05
Pretorius 2007 -0.35 (-0.63, -0.06) 4.90
Ucar 2007 2.04 (1.30, 2.79) 0.70
Ahlsson 2007 -0.00 (-0.18, 0.18) 11.96
Cosgrave 2005 -0.66 (-1.00, -0.32) 3.32
Wang 2005 1.64 (1.38, 1.90) 5.75
Overall (I-squared = 96.4%, p = 0.000) 0.57 (0.51, 0.64) 100.00
-3.3
0
3.3


First Author
Year of Pub
SMD (95% CI)
% Weight
Anatolevna 2016 0.80 (0.30, 1.31) 21.76
Canbaz 2008 0.30 (-0.30, 0.90) 15.26
Pretorius 2007 2.61 (2.25, 2.97) 42.72
Ucar 2007 1.72 (1.01, 2.43) 11.02
Ishida 2006 1.49 (0.72, 2.27) 9.23
Overall (I-squared = 93.0%, p = 0.000) 1.66 (1.43, 1.90) 100.00
-2.97
0
2.97


First
Year of
%
Author
Pub
SMD (95% CI)
Weight
Anatolevna
2016
0.30 (-0.19, 0.79)
33.93
Bjorgvinsdottir
2013
-0.29 (-0.64, 0.06)
66.07
Overall (I-squared = 72.6%, p = 0.056)
-0.09 (-0.38, 0.20)
100.00
-.792
0
.792

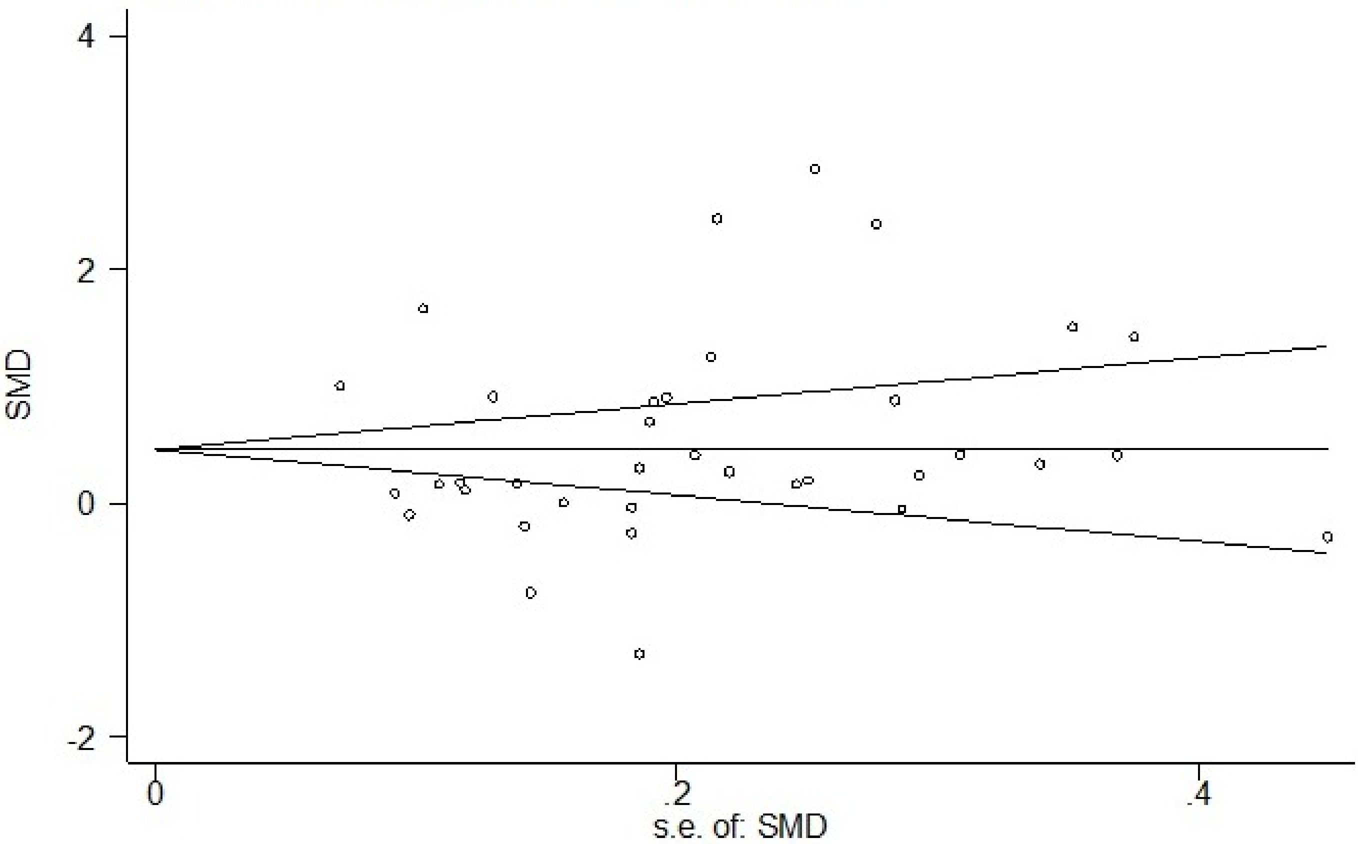

First
Year of
%
Author
Pub
SMD (95% CI)
Weight
Anatolevna
2016
-0.25 (-0.74, 0.24)
27.80
Bjorgvinsdottir
2013
-0.36 (-0.72, -0.01)
53.67
Canbaz
2008
0.13 (-0.48, 0.73)
18.52
Overall (I-squared = 0.0%, p = 0.393)
-0.24 (-0.50, 0.02)
100.00
-.743
0
.743


First
Year of
%
Author
Pub
SMD (95% CI)
Weight
Pretorius
2007
2.05 (1.72, 2.39)
43.44
Bjorgvinsdottir
2013
-0.52 (-0.88, -0.16)
37.67
Anatolevna
2016
0.75 (0.25, 1.26)
18.89
Overall (I-squared = 98.1%, p = 0.000)
0.84 (0.62, 1.06)
100.00
-2.39
0
2.39



First
Year of
%
Author
Pub
SMD (95% CI)
Weight
Pretorius
2007
1.20 (0.90, 1.50)
42.78
Canbaz
2008
0.48 (-0.13, 1.08)
10.35
Bjorgvinsdottir
2013
0.06 (-0.29, 0.41)
30.98
Anatolevna
2016
0.05 (-0.44, 0.54)
15.89
Overall (I-squared = 90.0%, p = 0.000)
0.59 (0.39, 0.78)
100.00
-1.5
0
1.5

Begg's funnel plot with pseudo 95% confidence limits



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.3793409	.2963198	1.28	0.209	-.2228534	.9815353
bias	.5393895	1.866237	0.29	0.774	-3.25326	4.332039

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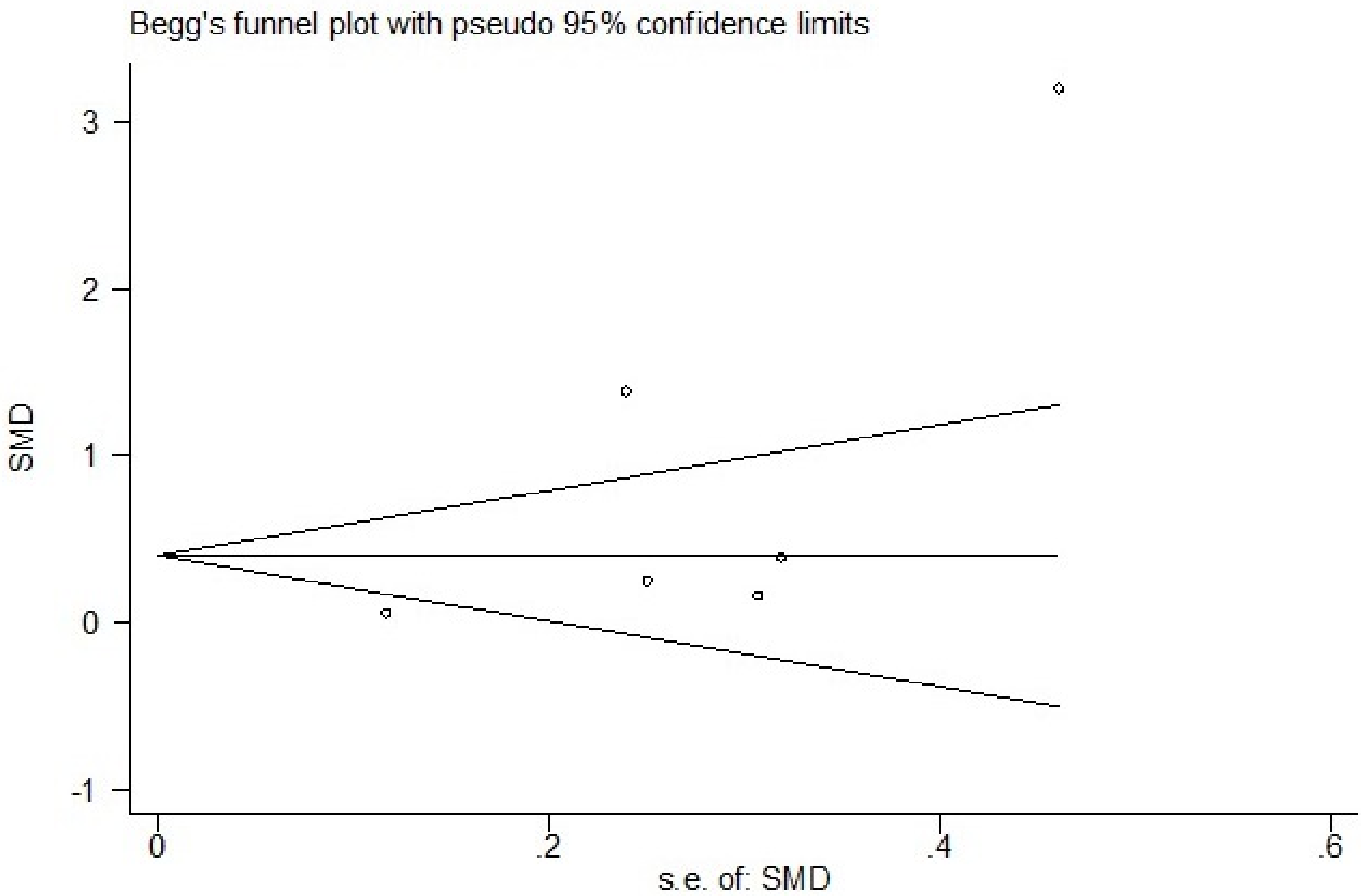
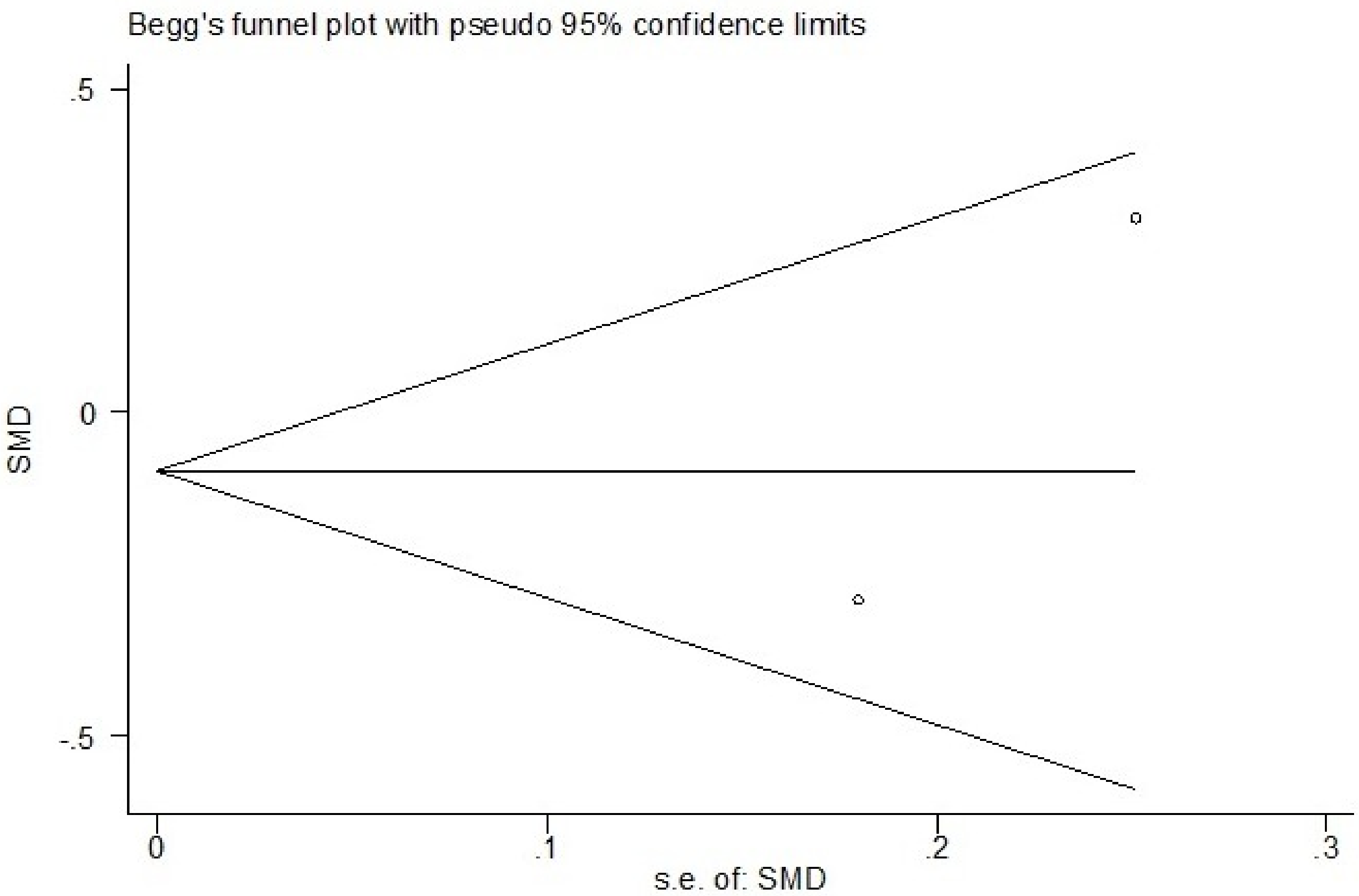


Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.5721597	.5805241	-0.99	0.380	-2.183953	1.039634
bias	5.06043	2.722577	1.86	0.137	-2.498656	12.61952

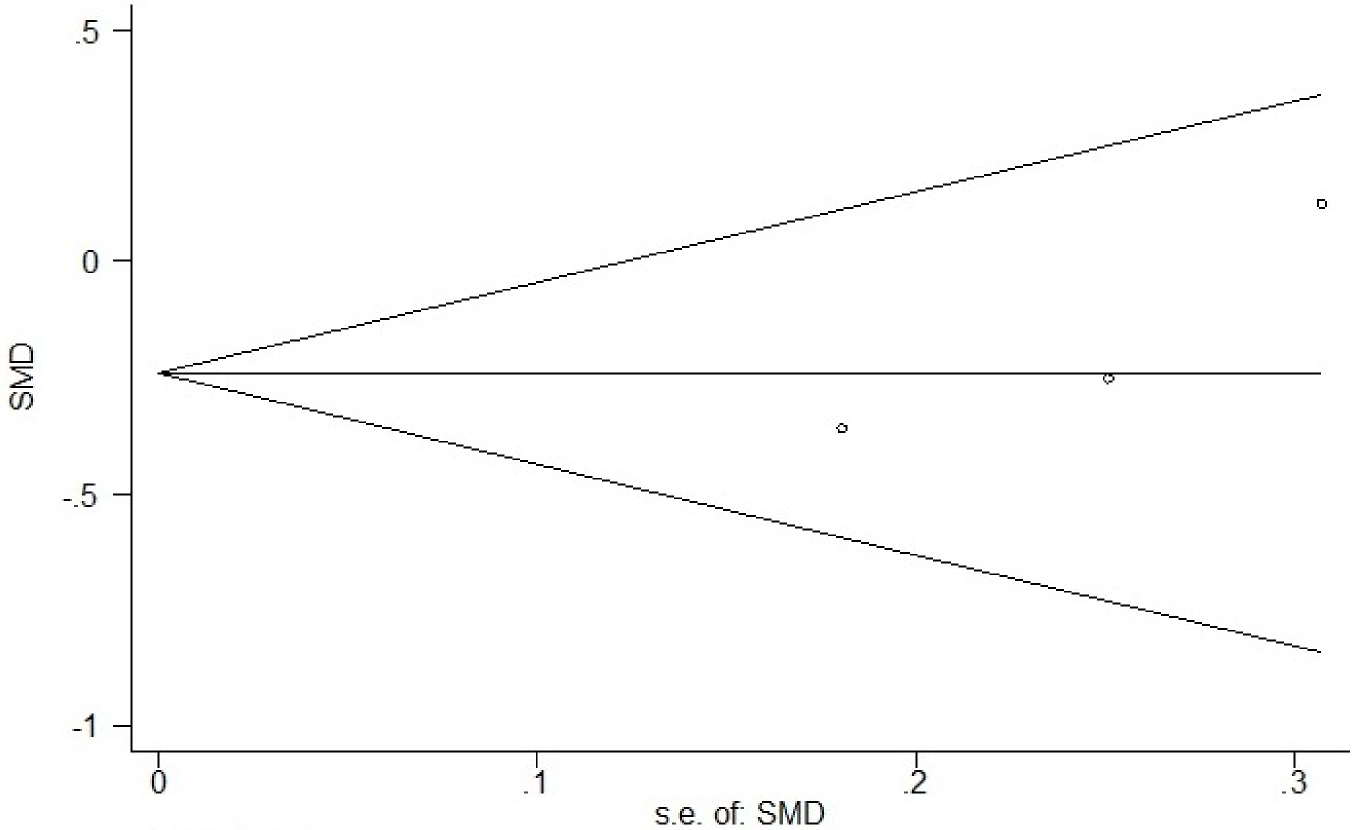
.



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-1.782708	.	.	.	.	.
bias	8.30065	.	.	.	.	.

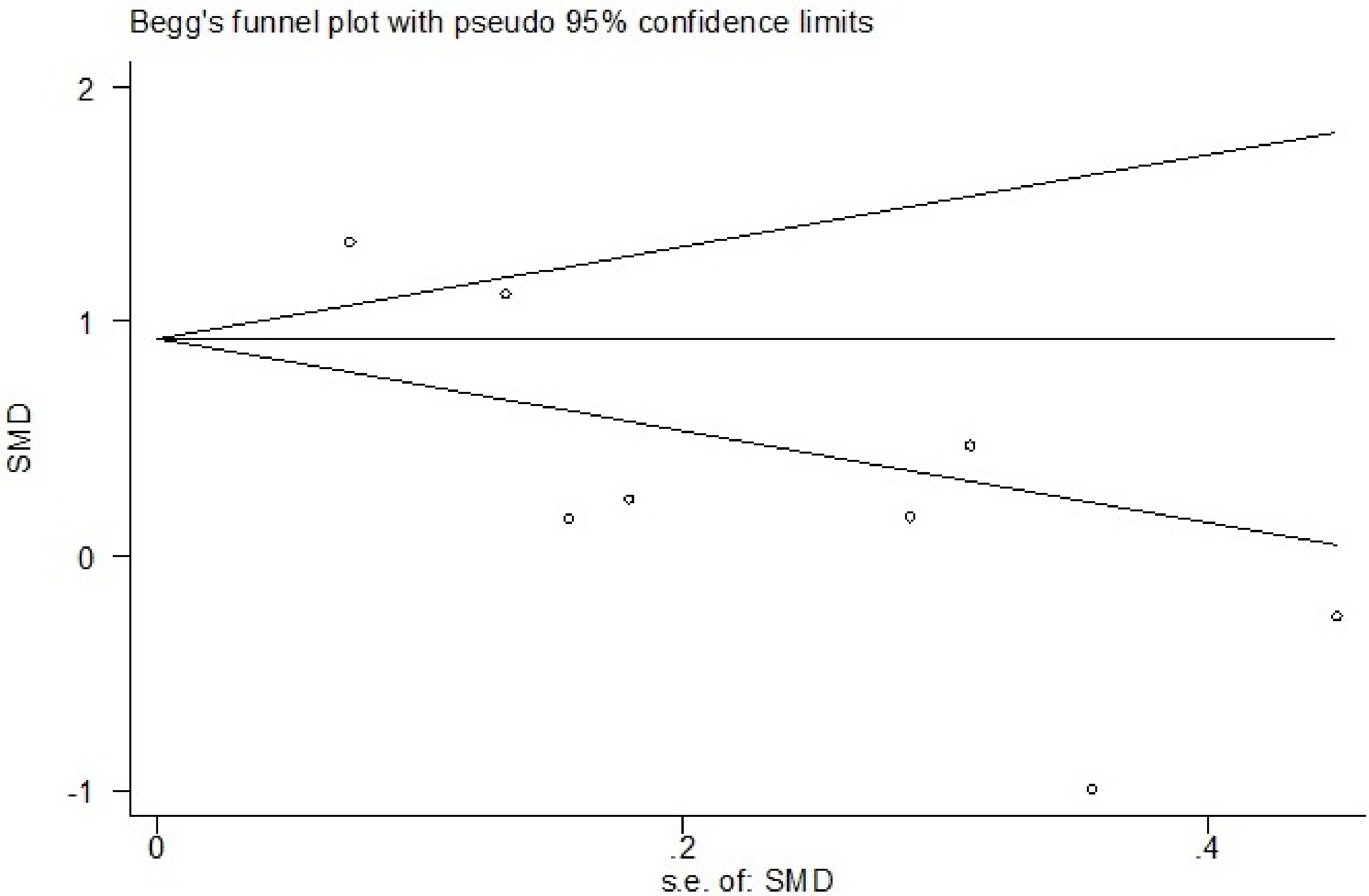
Begg's funnel plot with pseudo 95% confidence limits



Egger's test

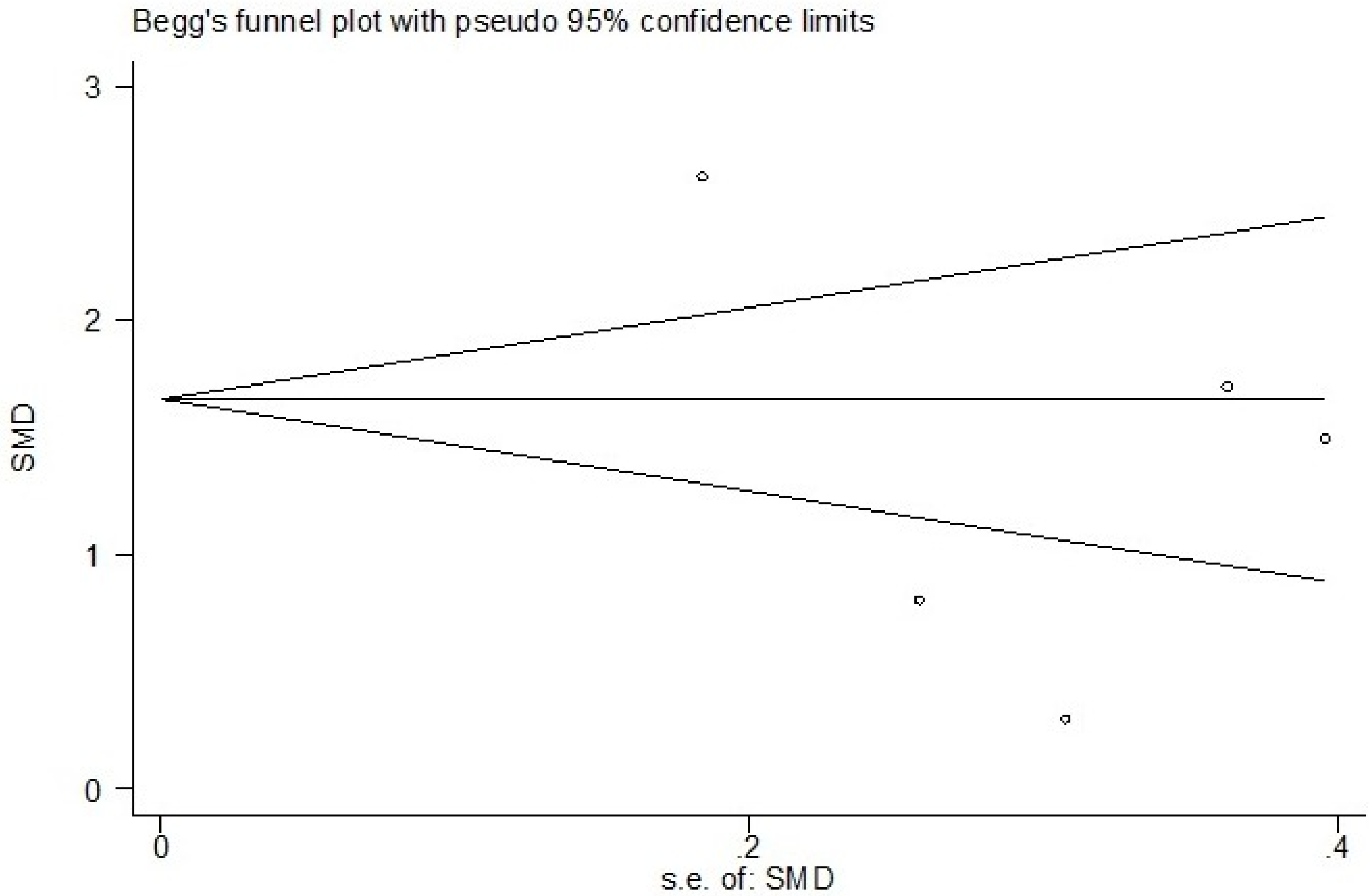
Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.9905236	.3086985	-3.21	0.192	-4.912911	2.931863
bias	3.356137	1.348733	2.49	0.243	-13.78113	20.49341

.



Egger's test

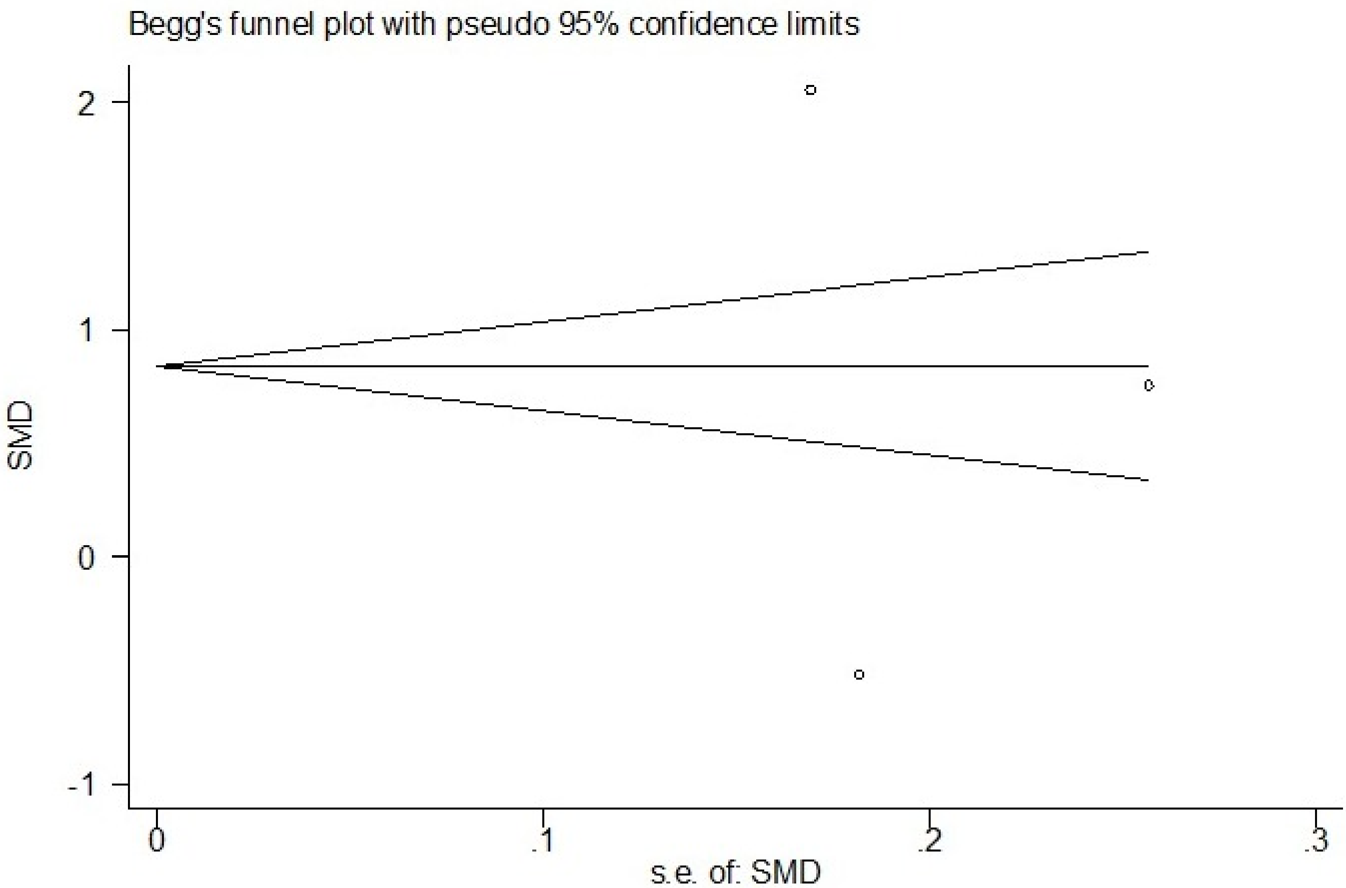
Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.714752	.2350099	7.30	0.000	1.139704	2.289801
bias	-6.14611	1.554831	-3.95	0.008	-9.950645	-2.341574



Egger's test

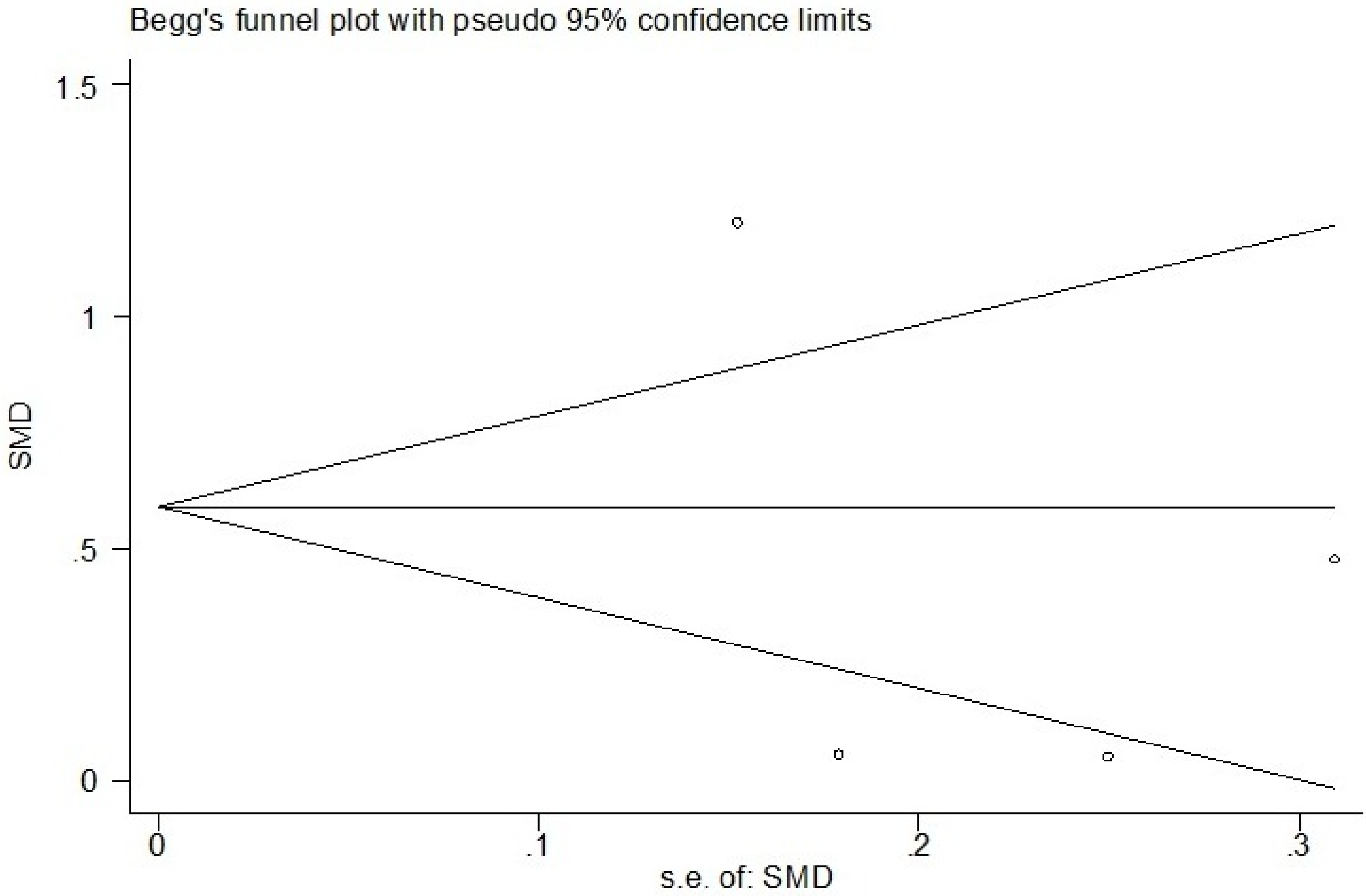
Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	3.568178	1.490597	2.39	0.096	-1.175567	8.311923
bias	-7.377739	5.541134	-1.33	0.275	-25.0121	10.25662

.



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	2.250091	6.74896	0.33	0.795	-83.50358	88.00376
bias	-7.40271	34.89176	-0.21	0.867	-450.7446	435.9391



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.633039	1.266007	1.29	0.326	-3.81415	7.080228
bias	-5.424795	6.356008	-0.85	0.483	-32.77249	21.9229