

## **Effectiveness of Pharmacological Intervention among Men with Infertility: A systematic review and network meta-analysis**

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Supplementary material: Contents

Appendix 1 Search strategy

**APPENDIX I: SEARCH STRATEGY**

**Search Term**

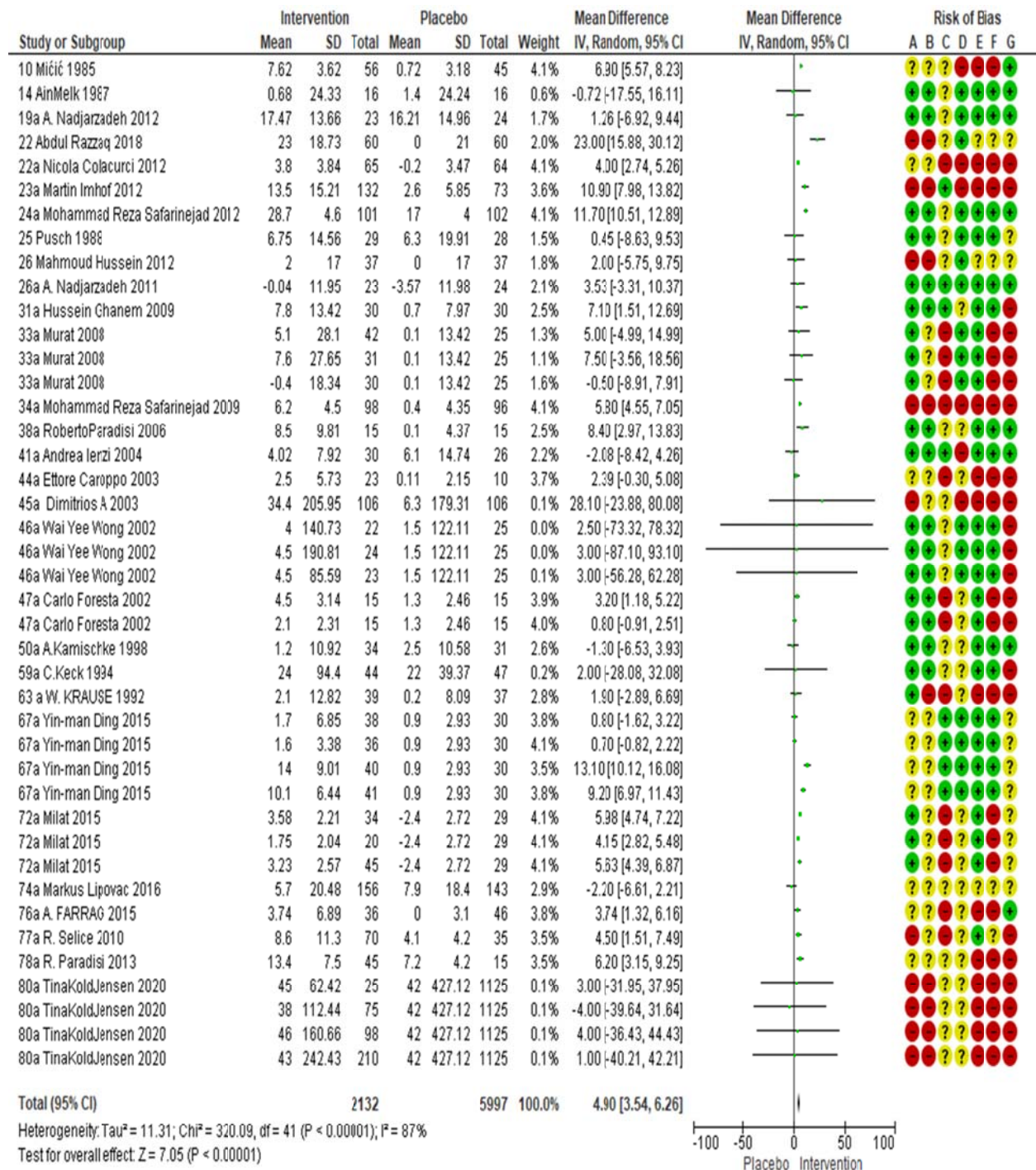
Search Items		Search Engines						
		PubMed	Scopus	Cochrane Library	Embase	EBSCOhost	Ovid Medline	Google Scholar
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	5535	8200	207	4733	3049	4777	15
	Chosen	5499	4786	69	1810	403	4301	11
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("azoospermia"[MeSH Terms] OR "azoospermia"[All Fields] OR "azospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	4709	352	18	6523	3705	8351	80
	Chosen	2352	173	14	2212	641	4375	25
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligozoospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	5992	5288	61	1494	1137	2672	15
	Chosen	236	2316	10	115	51	424	10
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligoasthenoteratozoospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	5677	1241	38	434	271	707	6
	Chosen	99	108	14	82	20	206	4
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) AND "humans"[MeSH Terms]	Result	3312	20352	108	22	1631	74	2
	Chosen	2859	16408	59	7	383	44	1
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("semen"[MeSH Terms] OR "semen"[All Fields]) AND "humans"[MeSH Terms]	Result	10225	41244	876	13428	11509	21294	373
	Chosen	7123	22701	322	4288	1307	12591	257
("infertility"[MeSH Terms] OR "infertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "low"[All Fields] AND "sperm"[All Fields] AND "count"[All Fields]) OR "low sperm count"[All Fields]) AND "humans"[MeSH Terms]	Result	6036	7319	79	143	239	483	3
	Chosen	161	4161	20	33	1	181	2
("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	5521	1224	29	318	135	402	0
	Chosen	0	26	2	28	1	23	0
("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND ("azoospermia"[MeSH Terms] OR "azoospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	4692	9	0	290	86	694	1
	Chosen	23	0	0	29	0	16	1
("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligozoospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	5993	1119	29	93	52	333	3
	Chosen	1	7	0	4	3	2	2
("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields]) AND "humans"[MeSH Terms]	Result	5677	317	1	30	17	95	0
	Chosen	0	2	0	4	0	0	0

("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND (("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]))	Result	4162	1942	15	2	38	10	0
	Chosen	780	273	2	1	3	1	0
("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND ("semen"[MeSH Terms] OR "semen"[All Fields])	Result	11781	6031	119	1110	508	2163	12
	Chosen	1552	463	19	199	17	218	9
("infertility"[MeSH Terms] OR "infertility"[All Fields] OR "subfertility"[All Fields]) AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR ("low"[All Fields] AND "sperm"[All Fields] AND "count"[All Fields]) OR "low sperm count"[All Fields])	Result	6508	1465	16	9	5	76	0
	Chosen	321	76	3	3	0	0	0
Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields])	Result	167	1449	29	242	169	377	0
	Chosen		49	0	20	4	59	0
Subfertile[All Fields] AND ("azoospermia"[MeSH Terms] OR "azoospermia"[All Fields] OR "azospermia"[All Fields])	Result	107	90	0	197	112	653	0
	Chosen	10	0	0	19	1	57	0
Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligozoospermia"[All Fields])	Result	189	1364	11	85	67	345	0
	Chosen	1	23	0	4	0	10	0
Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR "oligoasthenoteratozoospermia"[All Fields])	Result	177	302	1	21	16	106	3
	Chosen	0	2	0	3	0	3	2
Subfertile[All Fields] AND (("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]))	Result	65	1690	15	0	27	6	0
	Chosen	7	268	0	0	0	1	0
Subfertile[All Fields] AND ("semen"[MeSH Terms] OR "semen"[All Fields])	Result	747	6861	119	5078	781	2229	82
	Chosen	131	872	1	120	28	346	60
Subfertile[All Fields] AND ("oligospermia"[MeSH Terms] OR "oligospermia"[All Fields] OR ("low"[All Fields] AND "sperm"[All Fields] AND "count"[All Fields]) OR "low sperm count"[All Fields])	Result	224	1339	17	11	16	76	0
	Chosen	0	78	0	0	1	2	0

**Supplementary Table 1: Reasons for study exclusion after full-text assessment (n=607)**

<b>Database</b>	<b>Number of records</b>
Review articles	<b>203</b>
Irrelevant articles (conference papers/proceedings, letter to the editor and study protocols)	<b>194</b>
Meta-Analysis	<b>19</b>
Surgical intervention articles	<b>30</b>
Systematic reviews	<b>44</b>
Does not meet selection criteria (details are as under)-	<b>75</b>
<i>Not measured male patient data</i>	<i>37</i>
<i>Not measured the selected outcomes</i>	<i>51</i>

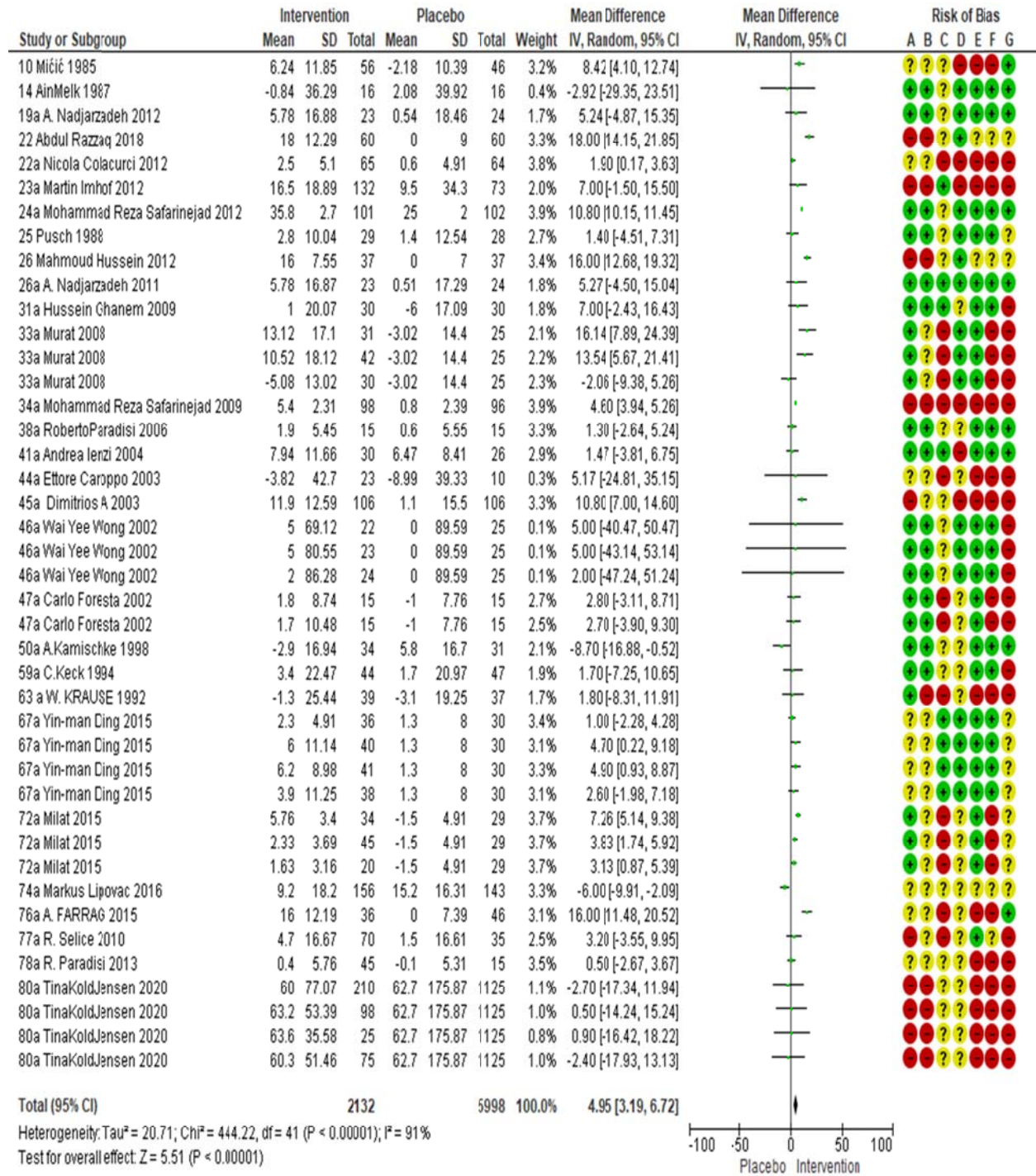
**Supplementary Figure 1:** Overall meta-analysis for sperm concentration of included RCTs (n=29)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)

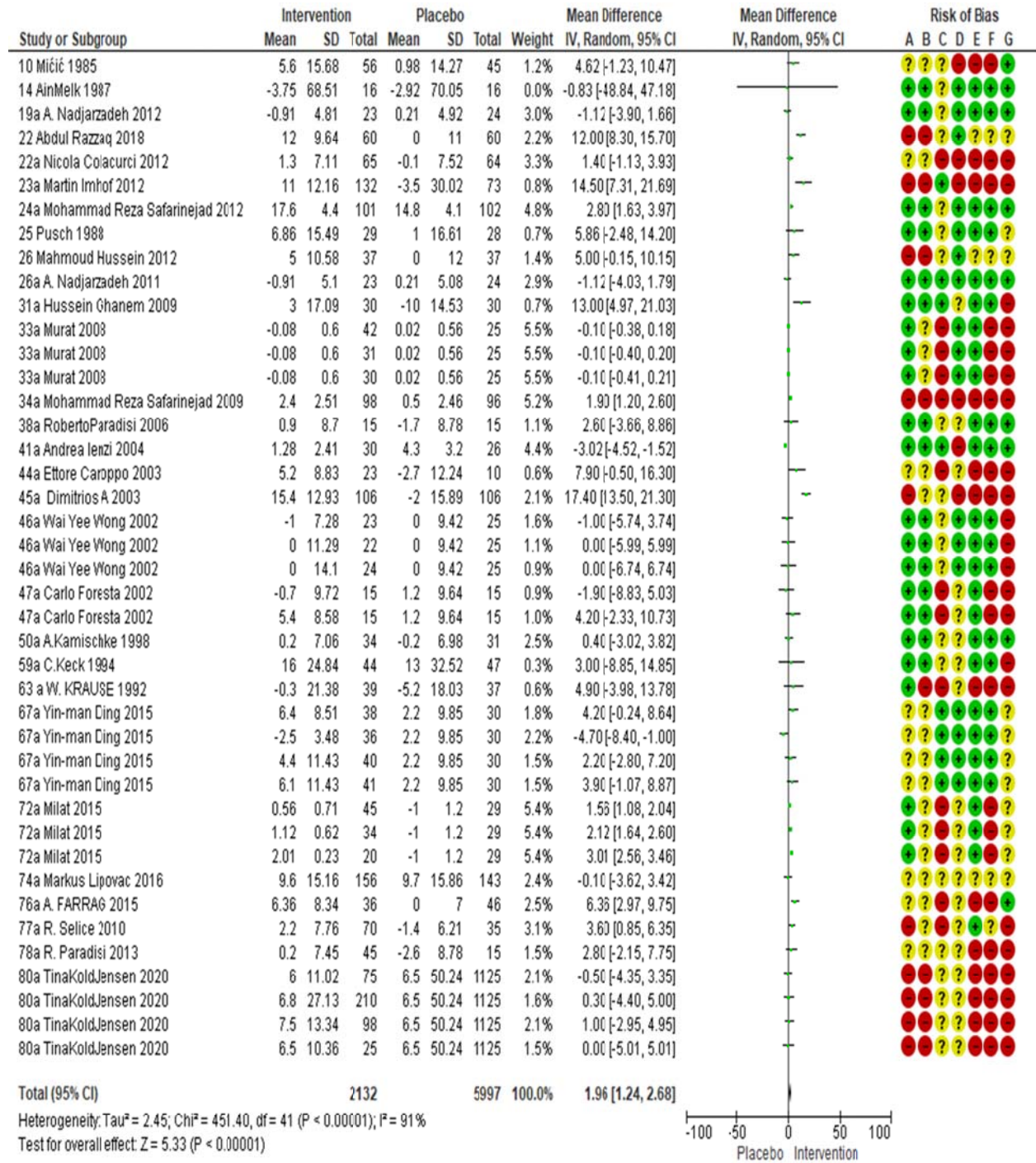
**Supplementary Figure 2:** Overall meta-analysis for sperm motility of included RCTs (n=29)



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)

**Supplementary Figure 3:** Overall meta-analysis for sperm morphology of included RCTs (n=29)

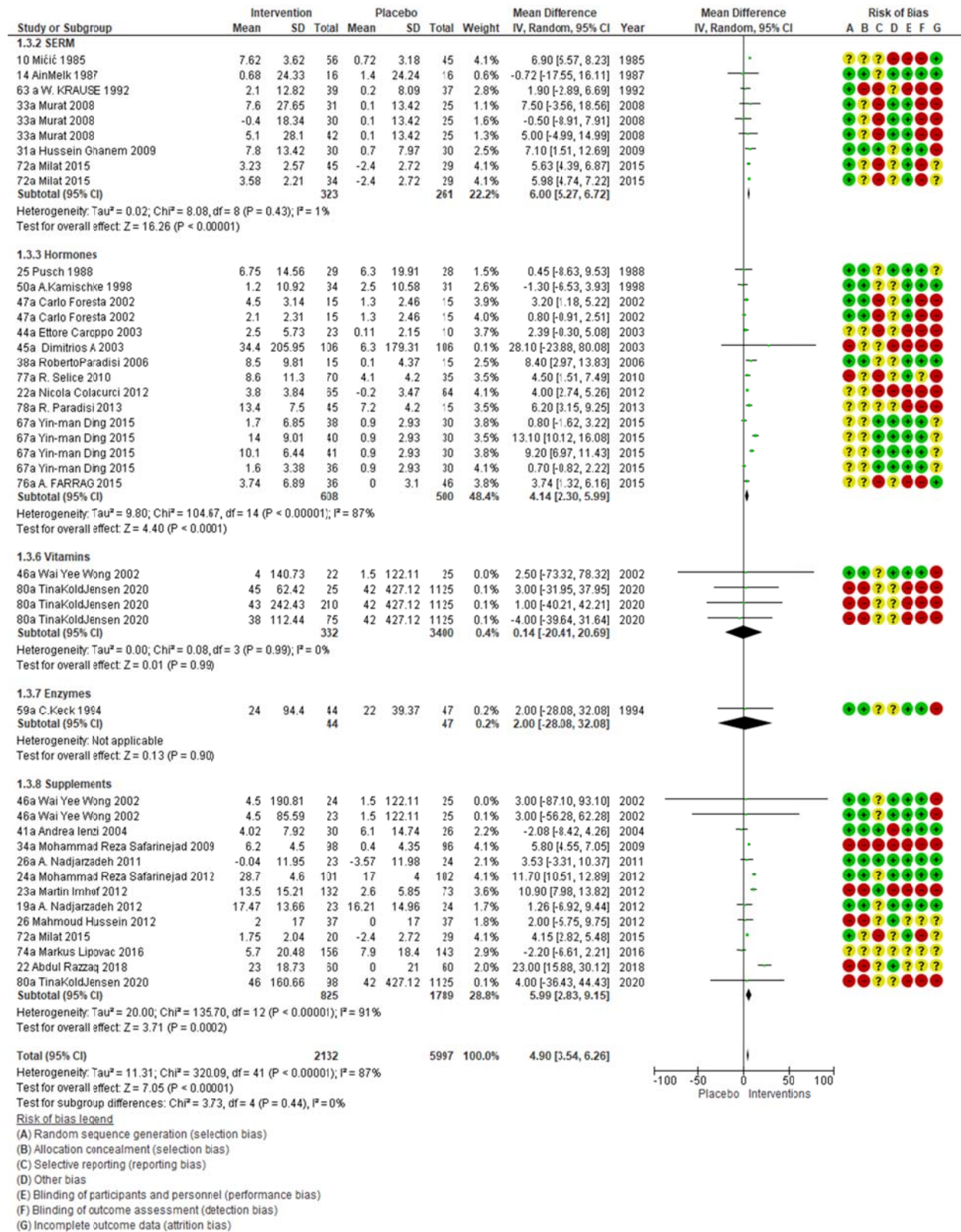


**Risk of bias legend**

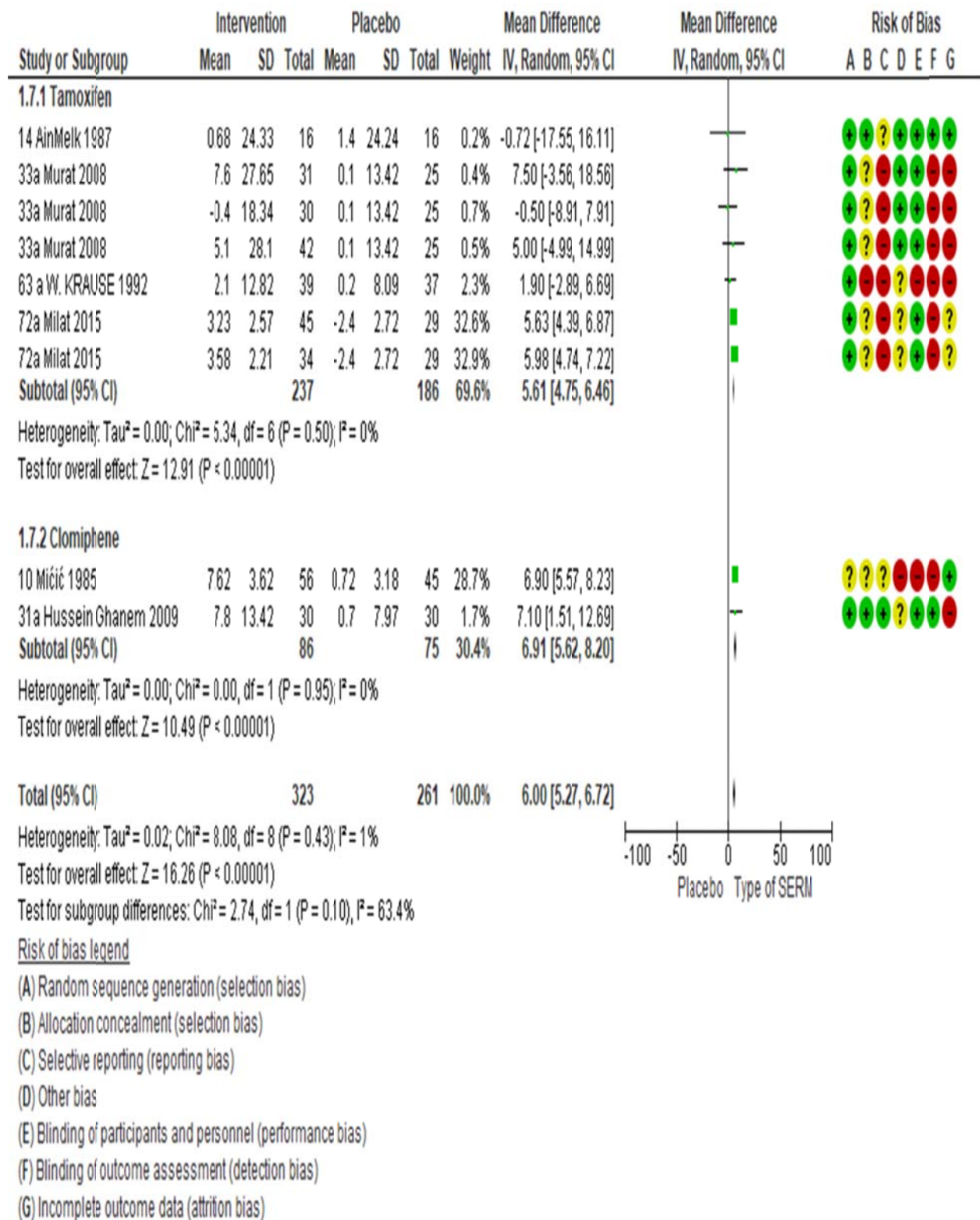
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)



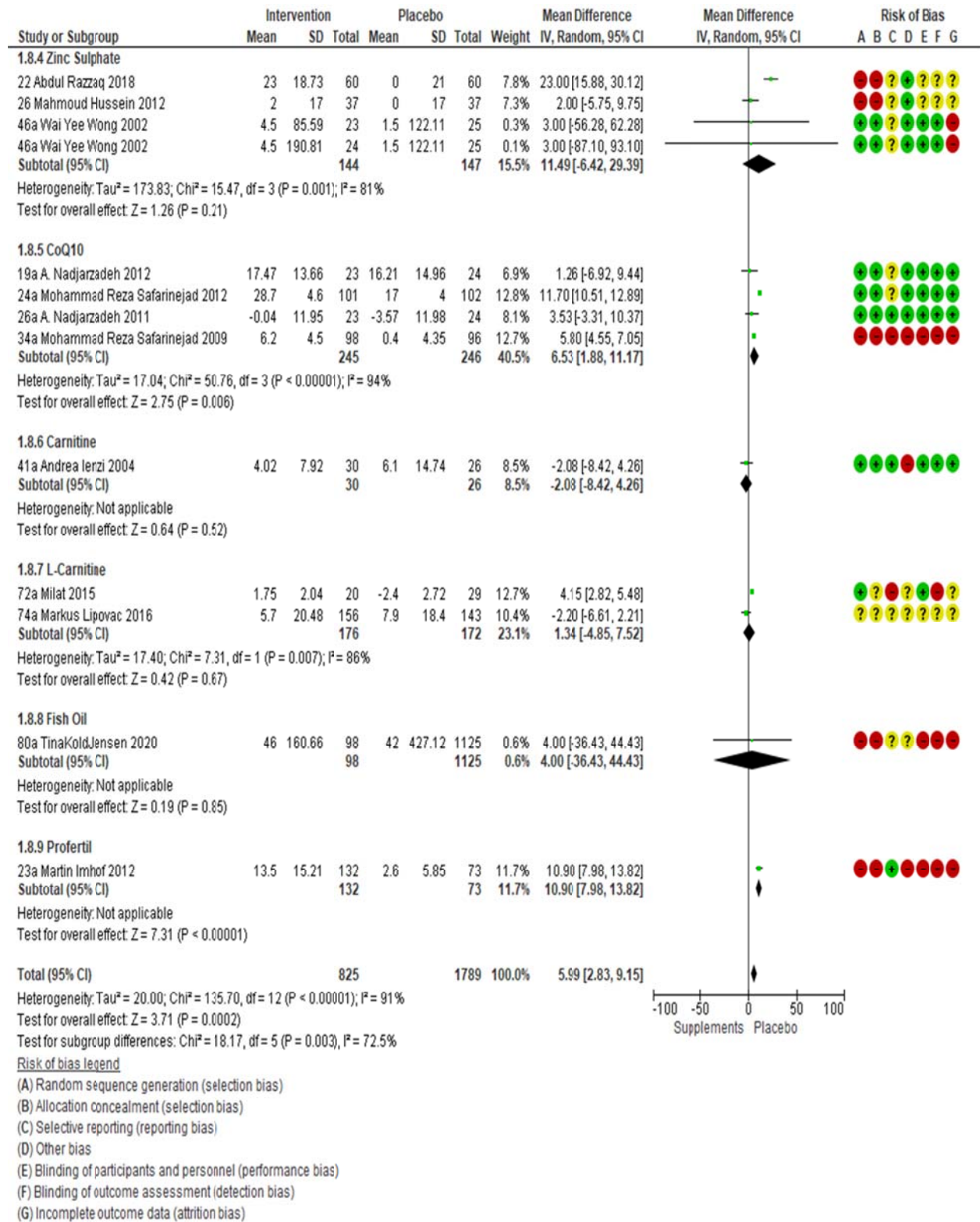
**Supplementary Figure 4: Sub-group meta-analysis (intervention based) for sperm concentration (n=29)**



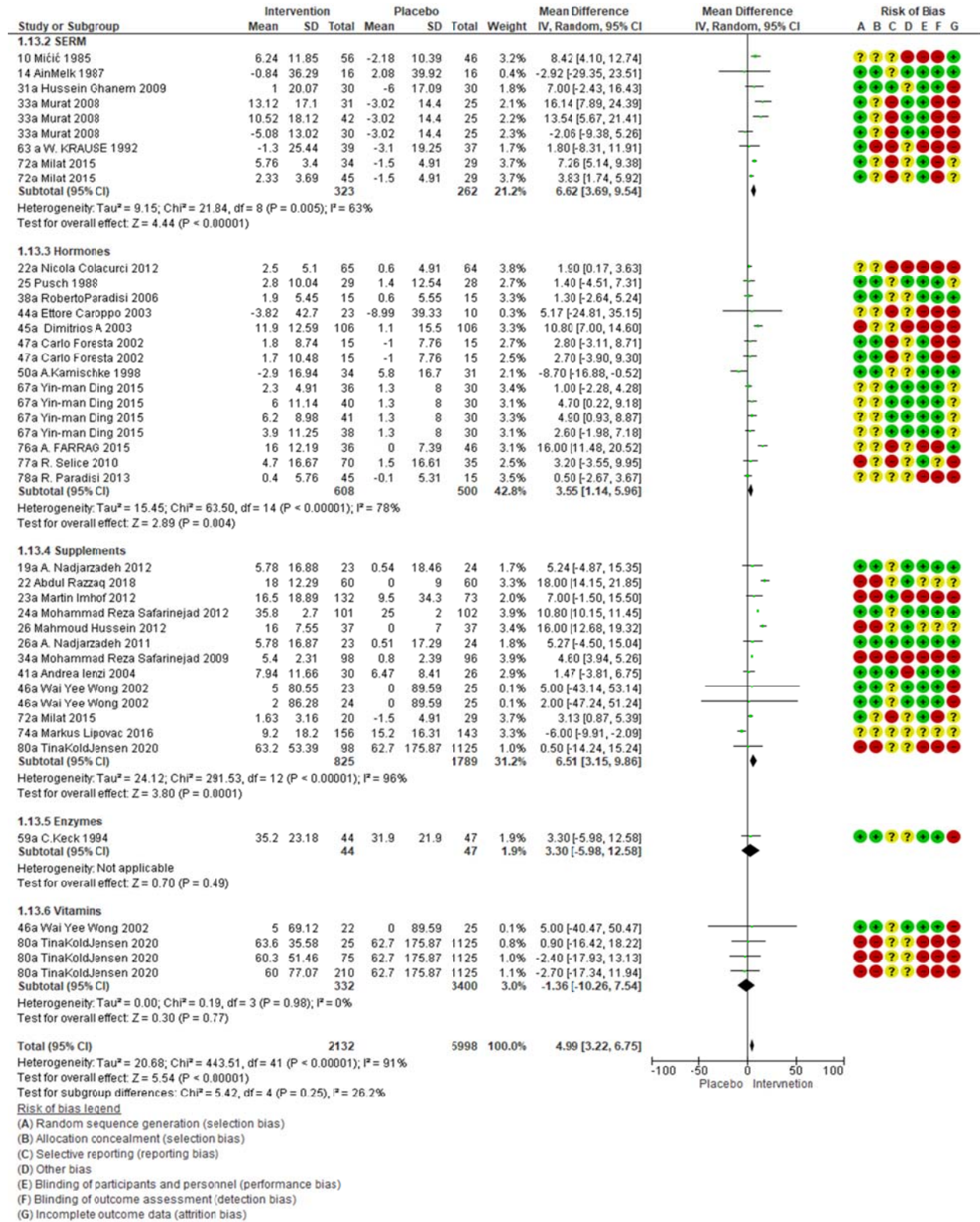
**Supplementary Figure 5:** Sub-group meta-analysis (SERM type based) for sperm concentration (n = 6).



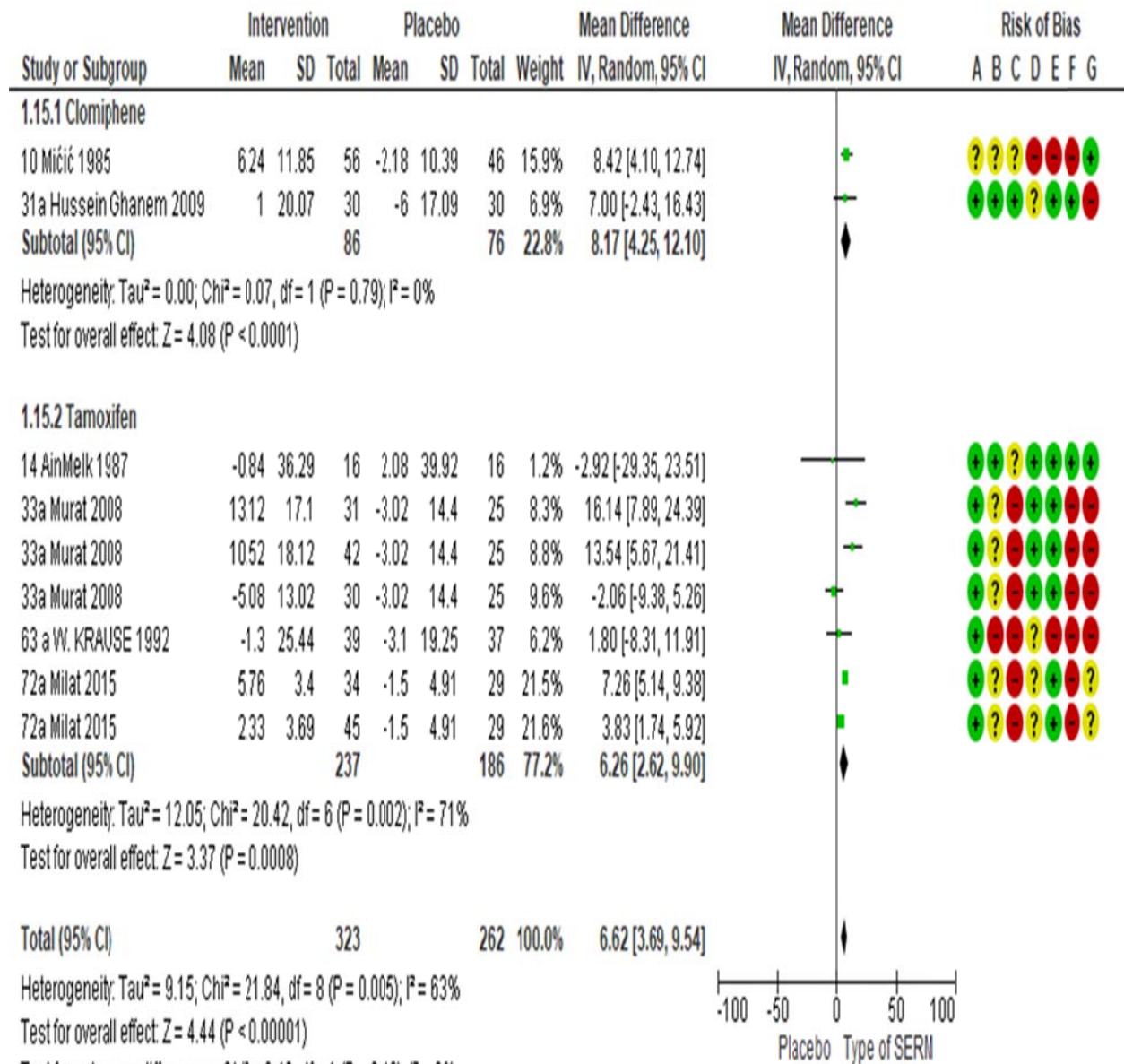
**Supplementary Figure 6:** Sub-group meta-analysis (Supplement type based) for sperm concentration (n = 12)



Supplementary Figure 7: Sub-group meta-analysis (intervention based) for sperm motility (n = 29)



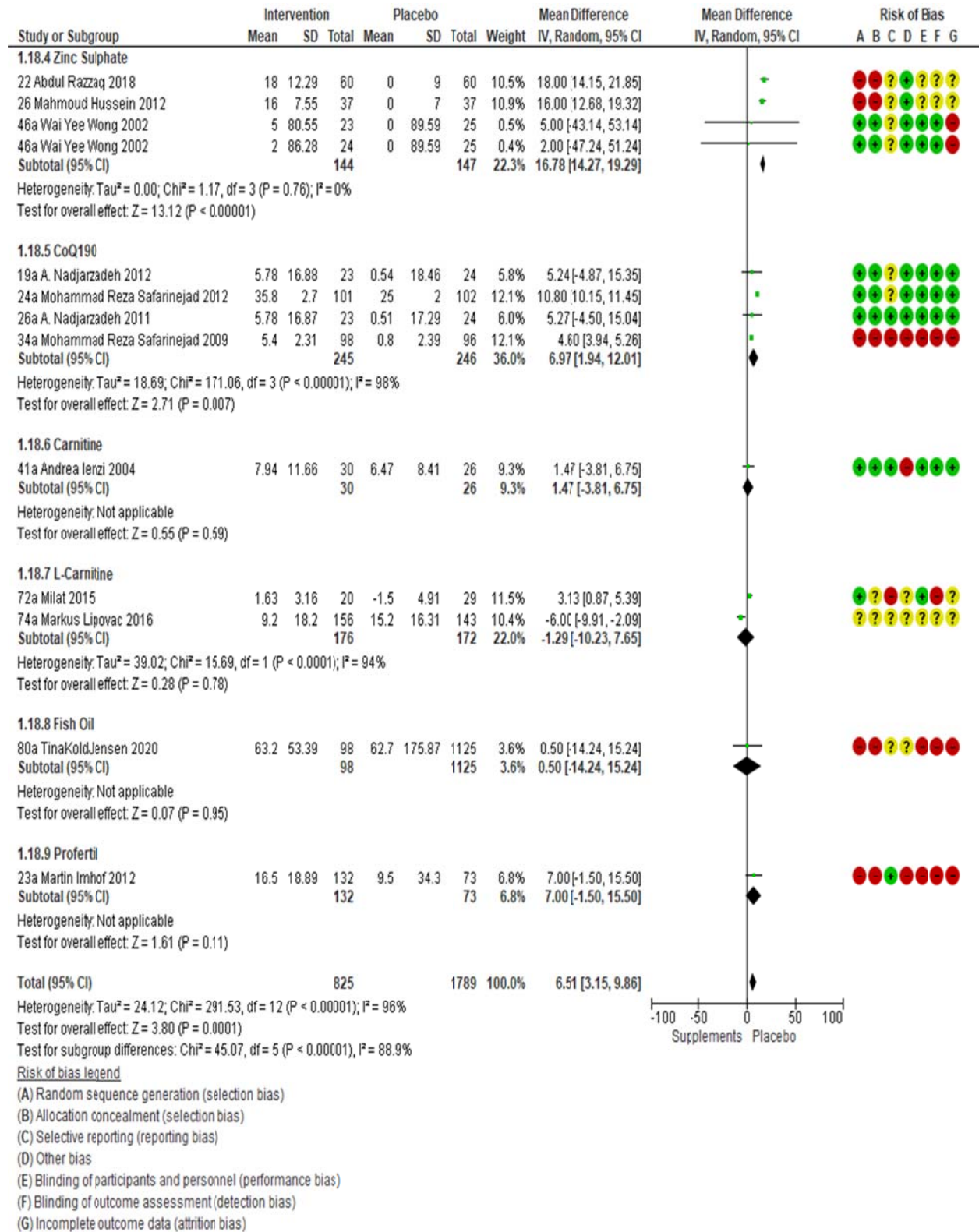
**Supplementary Figure 8:** Sub-group meta-analysis (SERM type based) for sperm motility (n = 6).



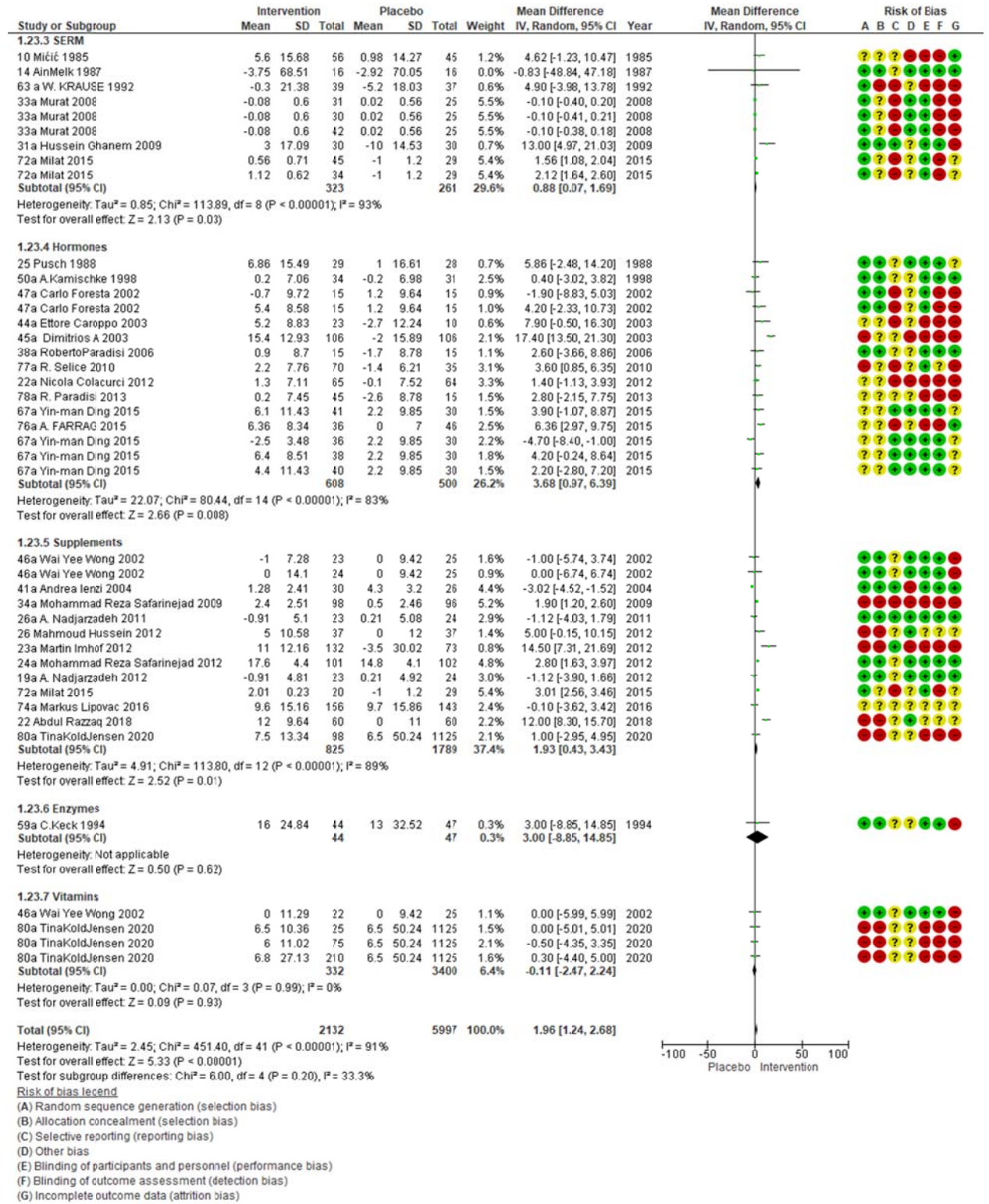
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)

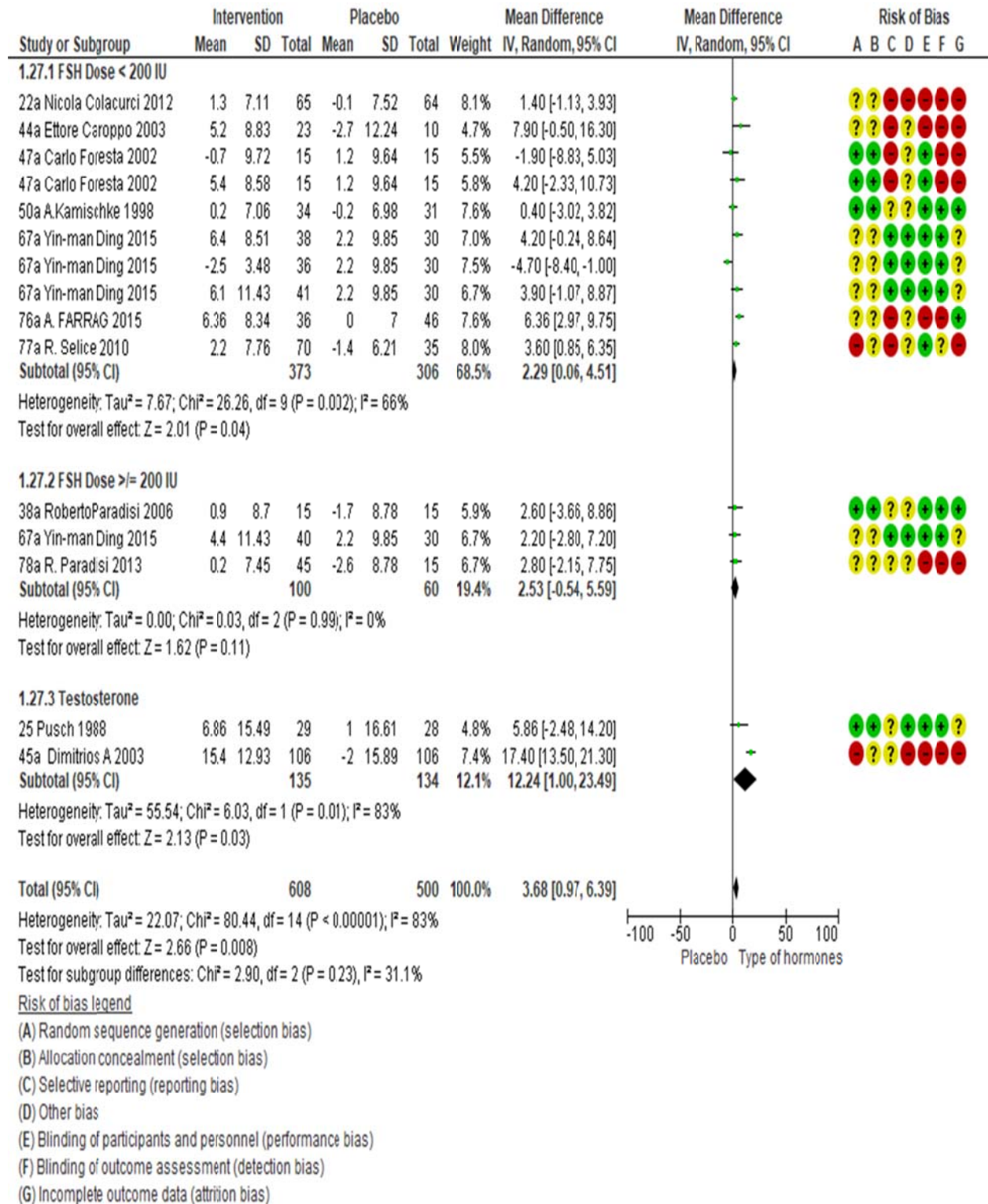
**Supplementary Figure 9:** Sub-group meta-analysis (supplement type based) for sperm motility (n = 12).



**Supplementary Figure 10: Sub-group meta-analysis (intervention based) for sperm morphology (n=29).**

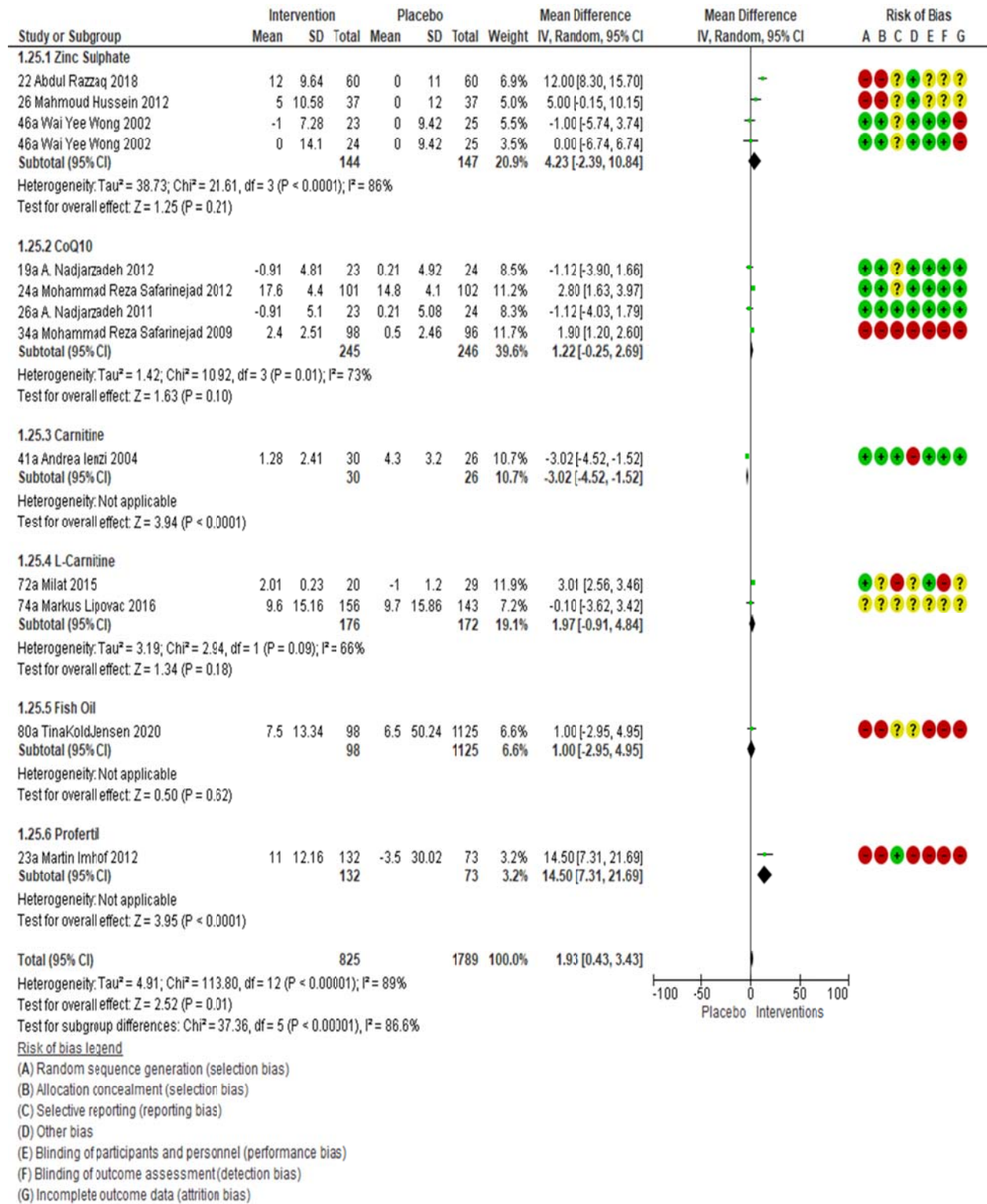


**Supplementary Figure 11: Sub-group meta-analysis (hormone type based) for sperm morphology (n = 12)**

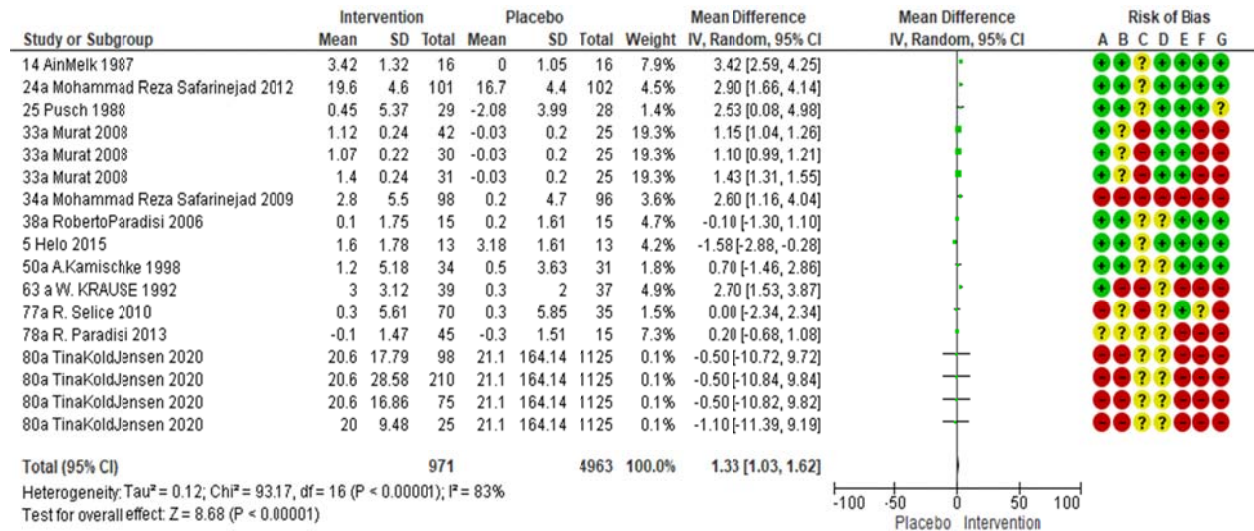




**Supplementary Figure 12: Sub-group meta-analysis (supplement type based) for sperm morphology (n=12)**



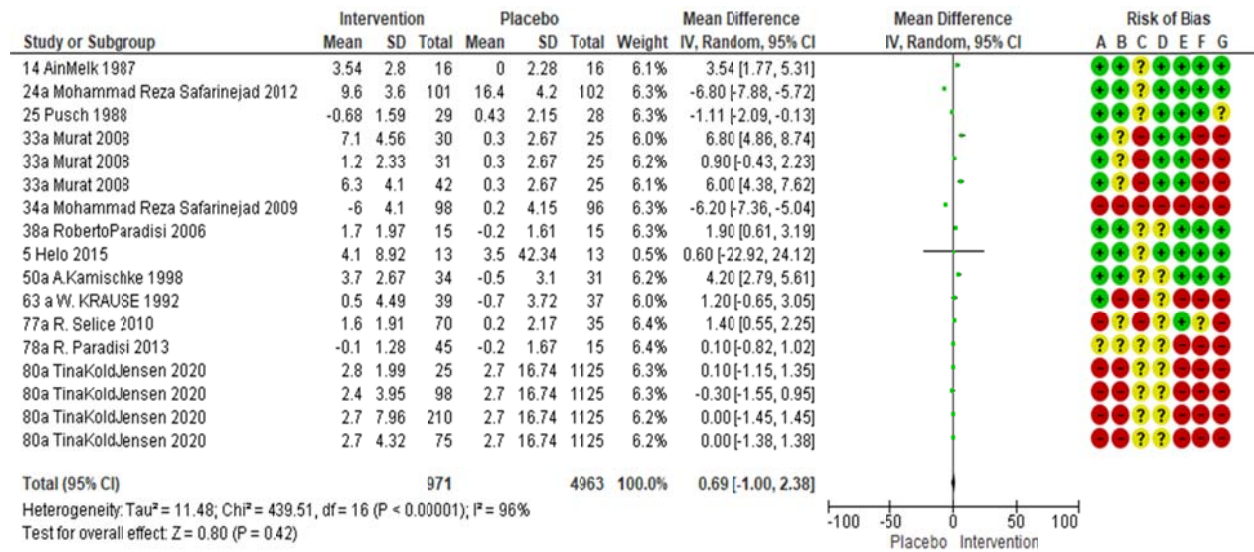
**Supplementary Figure 13:** Overall meta-analysis for total serum testosterone of included RCTs (n=17).



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)

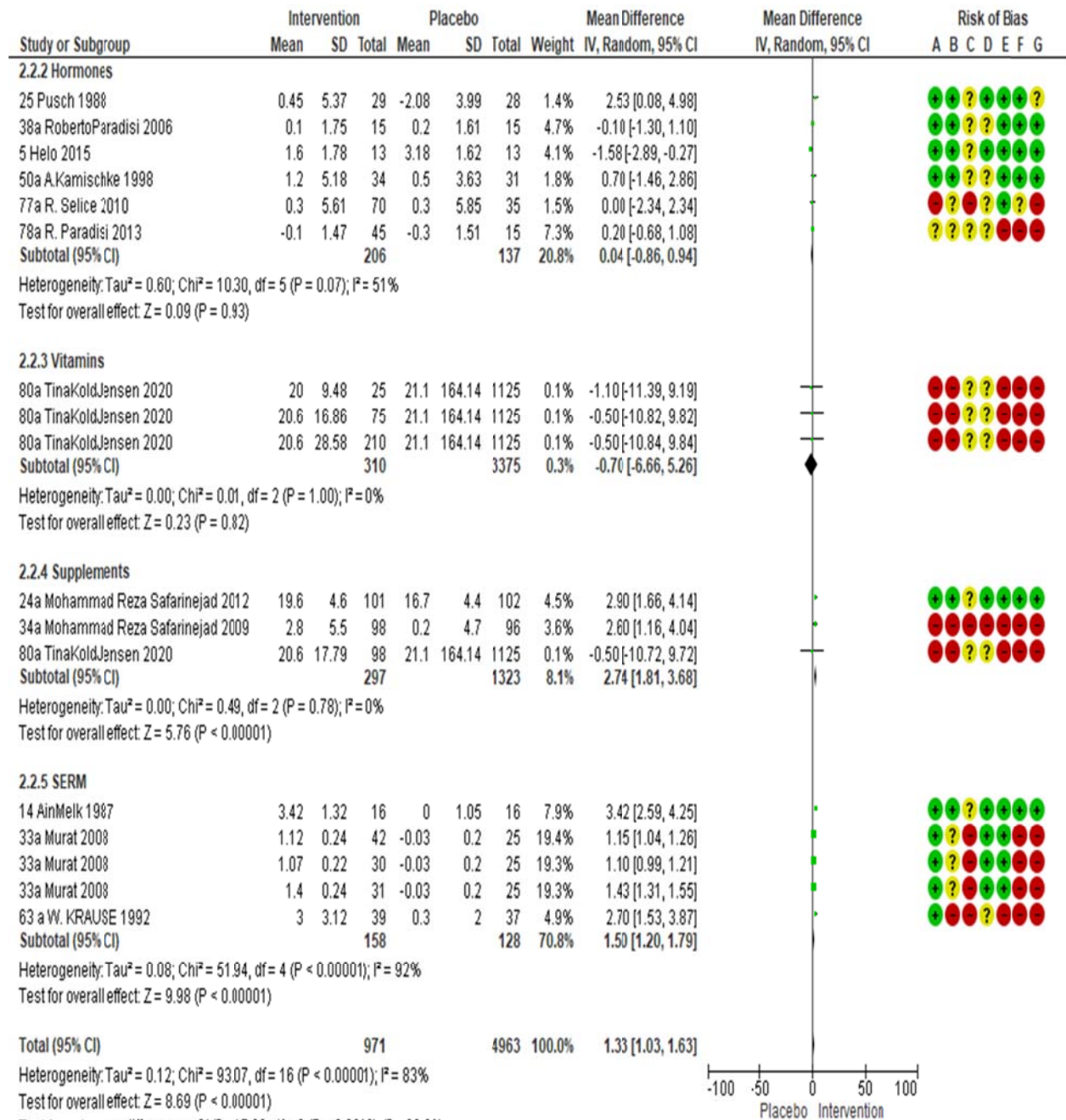
**Supplementary Figure 14:** Overall meta-analysis for total serum FSH of included RCTs (n=17).



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)

**Supplementary Figure 15:** Sub-group meta-analysis (intervention based) for total serum testosterone (n = 12).



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Selective reporting (reporting bias)
- (D) Other bias
- (E) Blinding of participants and personnel (performance bias)
- (F) Blinding of outcome assessment (detection bias)
- (G) Incomplete outcome data (attrition bias)









# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			<b>01</b>
Title	1	Identify the report as a systematic review, meta-analysis, or both.	01
<b>ABSTRACT</b>			<b>03-04</b>
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	03-04
<b>INTRODUCTION</b>			<b>03-06</b>
Rationale	3	Describe the rationale for the review in the context of what is already known.	03-05
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	06
<b>METHODS</b>			<b>06-08</b>
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	08
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	07
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	06
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	06
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	07
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	07
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	07
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	07
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	07
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	07



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	07
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	07
<b>RESULTS</b>			<b>08-15</b>
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	08
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	08
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	09
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	09
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	09-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	09
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	09-13
<b>DISCUSSION</b>			<b>15-18</b>
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
<b>FUNDING</b>			<b>18</b>
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).