APPENDIX

APPENDIX 1. Search Strategy

Date: 8/22/2019

Database (including vendor/platform): MEDLINE (via PubMed)

Set #		Results
1 ACL	"Anterior Cruciate Ligament"[Mesh] OR "Anterior Cruciate Ligament Injuries"[Mesh] OR "anterior cruciate"[tiab] OR ACL[tiab]	24,115
2 Surgery	"Anterior Cruciate Ligament Reconstruction"[Mesh] OR autograft[tiab] OR "auto-graft"[tiab] OR HTA[tiab] OR ACLR[tiab] OR surgery[tiab] OR surgeries[tiab] OR procedure[tiab] OR procedures[tiab] OR reconstruction[tiab] OR reconstructions[tiab] OR reconstructed[tiab]	2,204,124
3 Reinjury	"Recurrence"[Mesh] OR reinjury[tiab] OR "re-injury"[tiab] OR reinjured[tiab] OR "re-injured"[tiab] OR reinjuries[tiab] OR "re-injuries"[tiab] OR recurrence[tiab] OR recurring[tiab] OR recurrent[tiab] OR ((subsequent[tiab] OR second[tiab] OR secondary[tiab] OR multiple[tiab]) AND (injury[tiab] OR injuries[tiab]))	716,976
4	1 AND 2 AND 3	1,505
5	4 NOT (Editorial[ptyp] OR Comment[ptyp])	1,496
6	5 NOT (animals[mh] NOT humans[mh])	1,464

26 Database (including vendor/platform): EMBASE (via Elsevier)

Set #		Results
1 ACL	'anterior cruciate ligament'/exp OR 'anterior cruciate ligament injury'/exp OR 'anterior cruciate':ti,ab OR ACL:ti,ab	30,985
2 Surgery	'anterior cruciate ligament reconstruction'/exp OR autograft:ti,ab OR 'auto-graft':ti,ab OR HTA:ti,ab OR ACLR:ti,ab OR surgery:ti,ab OR surgeries:ti,ab OR procedure:ti,ab OR procedures:ti,ab OR reconstruction:ti,ab OR reconstructions:ti,ab OR reconstructed:ti,ab	2,991,980
3 Reinjury	'recurrence risk'/exp OR reinjury:ti,ab OR 're-injury':ti,ab OR reinjured:ti,ab OR 're-injured':ti,ab OR reinjuries:ti,ab OR 're-injuries':ti,ab OR recurrence:ti,ab OR recurring:ti,ab OR recurrent:ti,ab OR ((subsequent:ti,ab OR second:ti,ab OR secondary:ti,ab OR multiple:ti,ab) AND (injury:ti,ab OR injuries:ti,ab))	958,579
4	1 AND 2 AND 3	1,955
5	4 AND ([article]/lim OR [article in press]/lim OR [letter]/lim OR [review]/lim)	1,420
6	5 AND [humans]/lim	1,354

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51 Database (including vendor/platform): CINAHL (via EBSCO)

Set #		Results
1 ACL	(MH "Anterior Cruciate Ligament" OR MH "Anterior Cruciate Ligament Injuries") OR TI ("anterior cruciate" OR ACL) OR AB ("anterior cruciate" OR ACL)	11,829
2 Surgery	(MH "Anterior Cruciate Ligament Reconstruction") OR TI (autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed) OR AB (autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed)	356,241
3 Reinjury	(MH "Recurrence" OR MH "Reinjury") OR TI (reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR recurrent OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries))) OR AB (reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries)))	113,076
4	1 AND 2 AND 3	839
5	4 AND Limiters - Publication Type: Clinical Trial, Journal Article, Letter, Meta Analysis, Meta Synthesis, Practice Guidelines, Randomized Controlled Trial, Review, Systematic Review	538

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71 Database (including vendor/platform): SPORTDiscus (via EBSCO)

Set #		Results
1 ACL	(DE "ANTERIOR cruciate ligament" OR DE "ANTERIOR cruciate ligament injuries") OR TI("anterior cruciate" OR ACL) OR AB("anterior cruciate" OR ACL)	10,355
2 Surgery	(DE "ANTERIOR cruciate ligament surgery" OR DE "ANTERIOR cruciate ligament transplantation") OR TI(autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed) OR AB(autograft OR "auto-graft" OR HTA OR ACLR OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed)	57,184
3 Reinjury	TI(reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR recurrent OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries))) OR AB(reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries)))	12,955
4	1 AND 2 AND 3	573

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Database (including vendor/platform): Scopus (via Elsevier)

Set #		Results
1 ACL	TITLE-ABS ("anterior cruciate" OR acl)	30,854
2 Surgery	TITLE-ABS (autograft OR "auto-graft" OR hta OR aclr OR surgery OR surgeries OR procedure OR procedures OR reconstruction OR reconstructions OR reconstructed)	4,099,026
3 Reinjury	TITLE-ABS (reinjury OR "re-injury" OR reinjured OR "re-injured" OR reinjuries OR "re-injuries" OR recurrence OR recurring OR recurrent OR ((subsequent OR second OR secondary OR multiple) AND (injury OR injuries)))	857,866
4	1 AND 2 AND 3	1,708
5	4 AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "le"))	1,563

126 **APPENDIX 2.** Studies Contacted for Clarifying Data and Responses Received

Data clarification lead to inclusion		
Authors	Year	Title
Beischer et al	2020	Young athletes who return to sport before 9 months after anterior cruciate ligament reconstruction have a rate of new injury 7 times that of those who delay return
Bourke et al	2012	Survival of the anterior cruciate ligament graft and the contralateral ACL at a minimum of 15 years
Everhart et al	2019	Femoral nerve block at time of ACL reconstruction causes lasting quadriceps strength deficits and may increase short-term risk of re-injury
Fleming et al	2013	The effect of initial graft tension after anterior cruciate ligament reconstruction: a randomized clinical trial with 36-month follow-up
Kamath et al	2014	Anterior cruciate ligament injury, return to play, and reinjury in the elite collegiate athlete: analysis of an NCAA Division I cohort
Webster et al	2019	Clinical Tests Can Be Used to Screen for Second Anterior Cruciate Ligament Injury in Younger Patients Who Return to Sport
Data clarification lead to exclusion		
Authors	Year	Title
Herbst et al	2017	Impact of surgical timing on the outcome of anterior cruciate ligament reconstruction
Leys et al	2012	Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts
McPherson et al	2019	Psychological readiness to return to sport is associated with second anterior cruciate ligament injuries
McRae et al	2013	Ipsilateral versus contralateral hamstring grafts in anterior cruciate ligament reconstruction: a prospective randomized trial
Schmale et al	2014	High satisfaction yet decreased activity 4 years after transphyseal ACL reconstruction
Paterno et al	2010	Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport
Paterno et al	2017	Clinical factors that predict a second ACL injury after ACL reconstruction and return to sport: preliminary development of a clinical decision algorithm
Paterno et al	2018	Self-reported fear predicts functional performance and second ACL injury after ACL reconstruction and return to sport: a pilot study
Webster et al	2014	Younger patients are at increased risk for graft rupture and contralateral injury after anterior cruciate ligament reconstruction
Data could not be clarified		

Authors	Year	Title
Akada et al	2019	Partial meniscectomy adversely affects return-to-sport outcome after anatomical double-bundle anterior cruciate ligament reconstruction
Astur et al	2018	Increased incidence of anterior cruciate ligament revision surgery in paediatric verses adult population
Barrett et al	2010	Allograft anterior cruciate ligament reconstruction in the young, active patient: Tegner activity level and failure rate
Calvo et al	2015	Transphyseal anterior cruciate ligament reconstruction in patients with open physes: 10-year follow-up study
Dekker et al	2017	Return to sport after pediatric anterior cruciate ligament reconstruction and its effect on subsequent anterior cruciate ligament injury
Falciglia et al	2016	Anterior cruciate ligament reconstruction in adolescents (Tanner stages 2 and 3)
Gans et al	2018	Epidemiology of recurrent anterior cruciate ligament injuries in National Collegiate Athletic Association sports: the Injury Surveillance Program, 2004-2014
Geffroy et al	2018	Return to sport and re-tears after anterior cruciate ligament reconstruction in children and adolescents
Granan et al	2015	Associations between inadequate knee function detected by KOOS and prospective graft failure in an anterior cruciate ligament-reconstructed knee
Grindem et al	2012	A pair-matched comparison of return to pivoting sports at 1 year in anterior cruciate ligament–injured patients after a nonoperative versus an operative treatment course
Grindem et al	2014	Nonsurgical or surgical treatment of ACL injuries: knee function, sports participation, and knee reinjury: the Delaware-Oslo ACL Cohort Study
Grindem et al	2016	Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study
Gupta et al	2018	Low re-rupture rate with BPTB autograft and semitendinosus gracilis autograft with preserved insertions in ACL reconstruction surgery in sports persons
Gupta et al	2019	Is anterior cruciate ligament graft rupture (after successful anterior cruciate ligament reconstruction and return to sports
Herbst et al	2017	Impact of surgical timing on the outcome of anterior cruciate ligament reconstruction
Imbert et al	2017	Midterm results of combined intra-and extra-articular ACL reconstruction compared to historical ACL reconstruction data
Ithurburn et al	2019	Knee function, strength, and resumption of preinjury sports participation in young athletes following anterior cruciate ligament reconstruction

Kaeding et al	2015	Risk factors and predictors of subsequent ACL injury in either knee after ACL reconstruction: prospective analysis of 2488 primary ACL reconstructions from the MOON cohort
Koga et al	2015	Effect of posterolateral bundle graft fixation angles on clinical outcomes in double-bundle anterior cruciate ligament reconstruction: a randomized controlled trial
Lebel et al	2008	Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone autograft: a minimum 10-year follow-up
Magnussen et al	2012	Graft size and patient age are predictors of early revision after anterior cruciate ligament reconstruction with hamstring autograft
Magnussen et al	2016	Effect of high-grade preoperative knee laxity on anterior cruciate ligament reconstruction outcomes
Nwachukwu et al	2017	Return to play and patient satisfaction after ACL reconstruction: study with minimum 2-year follow-up
Oates et al	1999	Comparative injury rates of uninjured, anterior cruciate ligament-deficient, and reconstructed knees in a skiing population
Pennock et al	2018	Use of a modified all-epiphyseal technique for anterior cruciate ligament reconstruction in the skeletally immature patient
Rousseau et al	2019	Complications after anterior cruciate ligament reconstruction and their relation to the type of graft: a prospective study of 958 cases
Siebold et al	2016	Anatomical “C”-shaped double-bundle versus single-bundle anterior cruciate ligament reconstruction in pre-adolescent children with open growth plates
Snaebjörnsson et al	2017	Adolescents and female patients are at increased risk for contralateral anterior cruciate ligament reconstruction: a cohort study from the Swedish National Knee Ligament Register
Sousa et al	2017	Return to sport: does excellent 6-month strength and function following ACL reconstruction predict midterm outcomes?
Takazawa et al	2013	ACL reconstruction preserving the ACL remnant achieves good clinical outcomes and can reduce subsequent graft rupture
Takazawa et al	2016	Anterior cruciate ligament injuries in elite and high school rugby players: a 11-year review
Wall et al	2017	Outcomes and complications after all-epiphyseal anterior cruciate ligament reconstruction in skeletally immature patients
Wernecke et al	2017	The diameter of single bundle, hamstring autograft does not significantly influence revision rate or clinical outcomes after anterior cruciate ligament reconstruction

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APPENDIX 3. Summary of Findings and Strength of the Evidence Using GRADE

GRADE Criteria	Total Second ACLI Risk	Justification	Ipsilateral ACLI Risk	Justification	Contralateral ACLI Risk	Justification
Study Design[$]	+2	RCT and non-RCT included	+2	RCT and non-RCT included	+2	RCT and non-RCT included
Risk of Bias*	0	Only low or moderate RoB included	0	Only low or moderate RoB included	0	Only low or moderate RoB included
Inconsistency*	-1	Inconsistency is present, (I^2=50%, p=0.02) and could be meaningful	-1	Inconsistency is present (I^2=52%, p=0.02) and could be meaningful.	0	Inconsistency is not present (I^2=0%, p=0.67)
Indirectness*	0	No concerns for indirectness	0	No concerns for indirectness	0	No concerns for indirectness
Imprecision*	-1	There is concern for imprecision of the estimate due to each end of the confi-dence intervals indicating an opposite effect	0	There is minimal concern for imprecision based on tight confidence intervals despite a null estimate for RR.	0	There is minimal concern for imprecision based on tight confidence intervals despite an estimate that includes the null estimate.
Publication Bias[&]	0	Not detected	0	Not detected	0	Not detected
Upgrading Factors[#]	0	No upgrading factors	0	No upgrading factors	0	No upgrading factors
GRADE Quality of Evidence Score[$$]	Very Low		Very Low		Low	
Summary of Findings	There was no difference in the relative or absolute risk of a second ACLI between males and females.		There was no difference in the relative risk, but females have a 3.5% reduced absolute risk of an ipsilateral ACLI compared to males.		Females were found to have 1.27 times higher relative risk of experiencing a contralateral ACL injury compared to males	

GRADE= Grading of Recommendations, Assessment, Development and Evaluation, RCT= randomized controlled trial, Non-RCT= nonrandomized controlled trail, ACLI= anterior cruciate ligament injury, RoB= Risk of Bias

$ RCT (+4, high quality), Non-RCT (+2, low quality)

*Judged as No (0), Serious (-1), Very Serious (-2)

&Undetected (0), Strongly Suspected (-1)

#Large Effect (+1 or +2), Dose Response (+1 or +2), No Plausible Confounding (+1 or +2)

$$Overall Quality of Evidence Score = sum of rating score given of all GRADE criteria

[†]High quality (score ≥ 4), moderate quality (score = 3), Low quality (score = 2), very low quality (score ≤ 1)

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Question	Criteria Met: Yes/No/Partial Yes	Justification
1	**Yes**	PICO established in research question and selection criteria.
2	**Yes**	Methods were established prior to conducting this review.
3	**Yes**	Explanation provided for inclusion of RCTs and NRSI
4	**Yes**	Searched 5 databases, considered grey literature in search design, provided all searches for reviewers, and searched within 12 months of submission.
5	**Yes**	Two reviewers independently performed study selection.
6	**Yes**	Two reviewers independently performed data extraction.
7	**Partial Yes**	A list of reasons for excluded studies provided, but not a complete list of references.
8	**Yes**	Adequate description of included studies provided.
9	**Yes**	RoB was assessed, reported and used to factor into GRADE scoring.
10	**Yes**	Funding sources of included studies were reported.
11	**Yes**	Appropriate decision to perform statistical analysis provided, methods and justification described in detail. Appropriate weighting performed with meta-regression to determine influence of confounders.
12	**Yes**	High RoB studies were excluded from meta-analysis, and sensitivity analyses reported.
13	**Yes**	RoB was reported for each study, influenced meta-analysis inclusion and considered during GRADE scoring.
14	**Yes**	Yes, heterogeneity was discussed, and limitations were noted that could have contributed.
15	**Yes**	Publication bias was reported, discussed and considered during GRADE scoring.
16	**Yes**	We report that one listed author of the present study (MVP) was the first author of one study included in this review. However, we

		declare no other competing interests.

PICO= Patient/problem, Intervention, Comparison, Outcome; framework for development of research questions, RoB= risk of bias, GRADE= Grading of Recommendations, Assessment, Development and Evaluation, RCTs= Randomized controlled trials, NRSI= Non-randomized studies of healthcare interventions

1=research question and inclusion criteria include PICO? 2= Was review methods/protocol established prior to conduct of review? 3= Explain selection criteria based on study design? 4= Comprehensive literature search? 5= Study selection in duplicate? 6= Data extraction in duplicate? 7= List of excluded studies provided? 8= Describe included studies in adequate detail? 9= Satisfactory technique to assess RoB? 10= Report sources of funding for included studies? 11= Appropriate statistical methods used for meta-analysis? 12= Assess for impact of RoB on results of meta-analysis? 13= RoB accounted for when discussing results? 14= Discussion of heterogeneity? 15= Investigation into publication bias? 16= Any conflict of interest report

193 **Potential Sources of Conflict and Sources of Funding for Included Studies**

INCLUDED STUDIES	Potential Sources of Support (if reported in study)
Bak *et al*†(58)	No reported conflict of interest statement or statement of funding provided
Beischer *et al*†*(59)*	The authors report no conflicts of interest. Funding: Grants from the Swedish Research Council for Sport Science, by the Local Research and Development Board of Gothenburg and Sodra Bohuskan, and by the Unit of Physiotherapy, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg.
Bourke *et al*†(60)	**"**One or more of the authors has declared the following potential conflict of interest or source of funding: Dr. Pinczewski has received research funds from Smith & Nephew in the past 5 years. No funding was received for the current study."
Cordasco *et al(51)*	"One or more of the authors has declared the following potential conflict of interest or source of funding: FAC is a consultant for Arthrex and receives royalties from Conmed Linvatec and Arthrex. DWG is a consultant for and receives royalties from Arthrex."
Dekker *et al*†(61)	The authors report no conflicts of interest or external sources of funding for this study.
Demange *et al*(52)	"The authors declared that they have no conflicts of interest in the authorship and publication of this contribution."
Everhart *et al*†(62)	The authors report no funding for this study and declare no conflicts of interest
Fleming *et al*(53)	Funding: This study was funded by grants from the National Institues of Health (RO1-AR047910; RO1-AR047910S1. No conflict of interest statement provided.
Geffroy *et al*(54)	Funding: None Conflicts of Interest: NL is a consultant for developing logicielwebsurvey.fr® software.
Graziano *et al*(55)	The authors declare no conflicts of interest
Gupta *et al*(56)	The authors declare no conflicts of interest or funding for this study
Heath *et al*† (63)	The authors declare no conflicts of interest. "AOSSM has not conducted an independent investigation on the Open Payments Database (OPD) and disclaims any liability or responsibility relating therto."
Heijne *et al*†(64)	No conflict of interest statement or statement of funding provided
Kamath *et al*†(65)	"One or more of the authors has declared the following potential conflict of interest or source of funding: This study was paid for by the University of North Carolina at Chapel Hill, Department of Orthopaedic Surgery, Sports Medicine Research Fund."
Laboute *et al*(57)	Authors declare no conflicts of interest. Funding statement not provided.
Mohtadi *et al*†(66)	"NM and DC are currently receiving a research grant to support this trial, from the Workers' Compensation Board, Alberta, and received prior funding from the Calgary Orthopaedic Research and Education Fund (COREF). The remaining authors report no conflicts of interest."
Paterno *et al*†(31)	"One or more of the authors has declared the following potential conflicts of interest or source of funding: The study was supported by the National Football League Charities and the National Institute of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grants RO1-AR049735, RO1-AR049735, RO1-AR056259, and F32-AR055844."
Shelbourne *et al*†(36)	No potential conflicts of interest declared.
Webster *et al*†(67)	The authors declare no conflicts of interest. "AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating therto."

194 †Included in meta-analysis

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197 **APPENDIX 5**. Incidence Numbers by Sex and Laterality

Source	Whole Cohort			Second ACL Injuries			Ipsilateral Injuries			Contralateral Injuries		
	Total	*Females*	*Males*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*
Bak *et al*†(61)	132	15	117	13*	3	1	4	3	1	9*	-	-
Beischer *et al*†*(62)*	159	102	57	18	11	7	10	5	5	8	6	2
Bourke *et al*†(63)	673	241	432	156	48	108	71	15	56	85	33	52
Cordasco *et al(51)*	23	6	17	1	0	1	1	0	1	0	0	0
Dekker *et al*†(64)	85	51	34	27	14	13	16	-	-	11	-	-
Demange *et al*(52)	12	5	7	3	1	2	3	1	2	-	-	-
Everhart *et al*†(65)	360	215	145	27	10	17	16	6	10	11	4	7
Fleming *et al*(53)	85	48	42	7	5	2	4	3	1	3	2	1
Geffroy *et al*(54)	278	123	155	29*	10	13	14	3	11	15*	7	2
Graziano *et al*(55)	42	12	30	6	2	4	4	1	3	2	1	1
Gupta *et al*(56)	340	26	314	25	4	21	7	1	6	18	3	15
Heath *et al*† (67)	247	82	165	81	25	56	53	14	39	30	11	19
Heijne *et al*†(68)**	68	32	36	11	9	2	7	6	1	4	3	1
Kamath *et al*†(69)	89	47	42	20	11	9	7	3	4	13	8	5
Laboute *et al*(57)	298	64	234	26	5	21	26	5	21	0	-	-
Mohtadi *et al*†(72)	322	139	183	96	43	53	79	33	46	17	10	7
Paterno *et al*†(36)	78	59	19	23	19	4	7	5	2	16	14	2
Shelbourne *et al*†(38)	402	319	83	104	81	23	41	27	14	63	54	9
Webster *et al*†(74)	329	129	200	95	36	59	50	16	34	45	20	25
Totals	4027	1715	2312	771	337	418	420	147	257	351	176	148

198 †Included in meta-analysis; *Contralateral injuries were not classified by sex. **2 participants (1 male, 1 female)
199 experienced 2 subsequent ACL injuries (1 ipsilateral and 1 contralateral injury each) that could not be clarified
200 which occurred first and are still included
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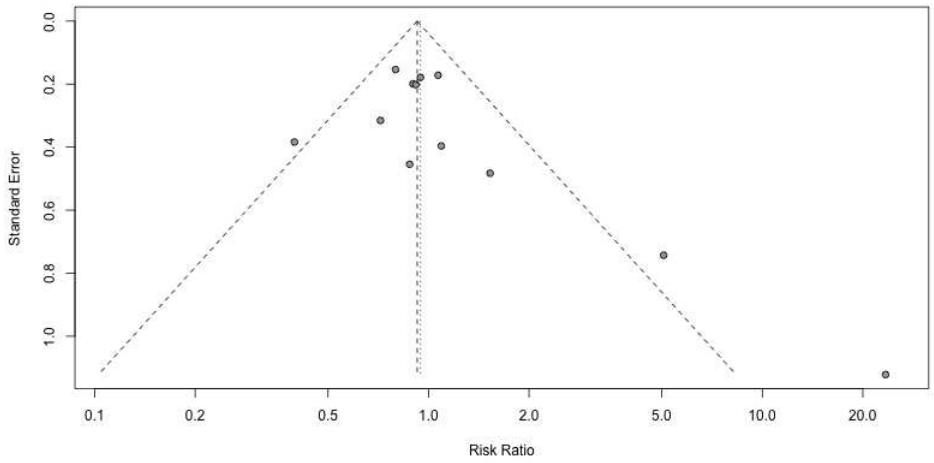
205 **APPENDIX 6**. Funnel Plot



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