Is There a Relationship Between Smoking and Stricture Recurrence After the Urethroplasty? a Systematic Review and Meta-Analysis

Yu-cheng Ma
Sichuan University West China Hospital Department of Urology
Menghua Wang
Sichuan University West China Hospital Department of Urology
Zhong-Yu Jian
Sichuan University West China Hospital Department of Urology
Hong Li
Sichuan University West China Hospital Department of Urology
Kunjie Wang (wangkj@scu.edu.cn)
Department of Urology, Institute of Urology (Laboratory of Reconstructive Urology), West China Hospital, Sichuan University https://orcid.org/0000-0001-8289-2791

Research article

Keywords: Urethral stricture, urethroplasty, risk factor, smoking, meta-analysis

Posted Date: February 14th, 2020

DOI: https://doi.org/10.21203/rs.2.23580/v1

Abstract

Background

Some retrospective studies have noted that smoking is a possible risk factor for recurrence of restenosis after urethroplasty, but not all of them are consistent. Therefore a meta-analysis is needed.

Method

Pubmed, Web of Science, Embase, Cochrane databases were searched with key words: “urethroplasty”, “buccal mucosa graft urethroplasty”, “oral mucosa graft urethroplasty”, “excision and primary anastomosis urethroplasty”, “urethral stricture recurrence” until Jan 30, 2020. The quality of included studies was assessed by Newcastle-Ottawa Scale (NOS) system. Hazard ratio (HR), odds ratio (OR), relative risk (RR) with 95% confidence interval (CI) were extracted or re-calculated from included studies. Meta-analysis was performed with Stata 15.0 based on univariate and multivariate data separately. Sensitivity analysis was performed to test stability of meta-analysis. I 2 was calculated to evaluate heterogeneity. Publication biases were assessed by egger’s and begg’s tests. Funnel plots of univariate analysis and multivariate analysis were also offered.

Results

12 studies with 3443 patients were involved into this meta-analysis. The analysis results of two stages were consistent. In the univariate meta-analysis stage, 9 studies with 2279 patients were pooled and the result indicated that smoking might promote stricture recurrence (RR=1.46, 95%CI: 1.11-1.93, P=0.008). In the multivariate meta-analysis stage, based on adjusted estimate, 7 studies with 2074 patients were pooled and the result indicated that smoking might promote stricture recurrence (RR=1.39, 95%CI: 1.04-1.85, P=0.026). There was no significant heterogeneity in both univariate and multivariate stage.

Conclusion

This meta-analysis of current evidence indicates that smoking may prompt stricture recurrence after the urethroplasty. Quitting smoking may be a good option for patients undergoing urethroplasty surgery.

Background

When urologists deal with the urethral stricture patients by urethroplasty, one of the most worrying situations is the stricture recurrence. In order to find out the possible causes of postoperative stricture recurrence, many retrospective studies have been conducted, and many risk factors such as length of stricture[1–3], previous urethroplasty history[2, 4–6], direct visual internal urethrotomy (DVIU) history have been reported[2, 3, 7, 8]. However, in addition to these risk factors that have a strong role in promoting stricture recurrence, there are still some risk factors that are relatively mild or need a long time for stricture promotion, which can only be described by a large sample size of clinical research. In 2010, a study pointed out that tobacco consumption may lead to stricture recurrence after urethroplasty[9]. However, in many subsequent retrospective studies, whether in univariate analysis or multivariate analysis, the role of smoking in the stricture recurrence after the urethroplasty has not been uniformly described.

In this study, a meta-analysis based on the univariate and multivariate results was conducted to obtain a stable assessment of the relationship between smoking and stricture recurrence after the urethroplasty.

Method

1.1 Literature search and inclusion criteria

This meta-analysis was carried out according to the principle of preferred reporting items for systematic reviews and meta-analysis (PRISMA). We searched Pubmed, Embase, Web of Science and Cochrane Library to identify relevant studies. The latest search date was February 1, 2020. The searching key words included urethroplasty, smoking, smoker, tobacco consumption and stricture recurrence. Furthermore, reference part of every candidate literature was manually screened to find possible data source.

Detailed inclusion criteria were as follows: Patients were treated with onlay with buccal mucosa or penile fasciocutaneous flap or oral mucosa or any other type of substitution urethroplasty, anastomotic urethroplasty or any combined urethroplasty techniques for anterior or posterior urethral strictures. Odds ratio (OR), hazard ratio (HR) with 95% confidence interval (CI) of risk factors should be offered. Exclusion criteria were complied as follow: Reviews, meta-analysis, letters, comments, case serials and conference abstract were excluded. Studies didn’t contain regression information or enough data which could be used for secondary analysis were excluded.

1.2 Research Quality Evaluation

All included studies were evaluated by Newcastle-Ottawa Scale (NOS) system and the evaluation procedure was performed by two independent reviewers. According to the NOS, 7–9 score studies were thought as high-level quality, 5–6 score studies were thought as moderate-level and < 5 score studies were low-level quality. Low-level quality studies shouldn’t be involved in the meta-analysis.

1.3 Meta-analysis

In this study, based on univariate and multivariate analysis results, the relationship between smoking and stricture recurrence was pooled in meta-analysis. All analysis was powered by Stata 15.0 software (Stata corporation, College Station TX, USA). Statistical significance was defined as $P < 0.05$ in this study. Pooled estimate larger than 1 indicated that smoking would make patients more vulnerable to stricture recurrence. Heterogeneity was evaluated by I^2. When I^2 was larger than 50%, heterogeneity could be significant. If significant heterogeneity was detected, random effect model should be applied. To identity the potential factors which contributed to heterogeneity, meta-regression analysis was performed. Subgroup analysis based on meta-regression was also performed to get detailed information. Furthermore, sensitivity analysis was performed to test stability of meta-analysis results and publication-bias was tested by Egger's and Begg's tests. Funnel plots were used for publication-bias visual identification.

Result

2.1 Study selection

1159 studies were identified from databases in total. After duplicates removement, abstract screening and full text reading, 12 studies were finally involved into this meta-analysis. Detailed screening procedure is displayed in the Fig. 1.There were 9 studies (total 2279 patients) contained smoking-stricture recurrence univariate analysis information[3, 8–15], 7 studies (total 2074 patients) contained multivariable analysis information[6, 7, 11–13, 16, 17]. Out of 12 involved studies, 11 studies are retrospective cohort studies and only 1 study was prospectively designed. Detailed baseline information and research quality evaluation are shown in Table 1 and Table 2 separately.

2.2 Univariate analysis

In terms of univariate analysis, there are 9 studies containing 2279 patients exploring the association between smoking and stricture recurrence after urethroplasty. According to the overall meta-analysis result, smoking can make patients more vulnerable to stricture recurrence (RR = 1.46, 95%CI: 1.11–1.93, P = 0.008) with no significant heterogeneity found (I2 = 28.6%, p = 0.190) (Fig. 2). No significant publication bias was found according to the Egger's test (t = 0.92, P = 0.389) and Begg's test (z = 0.00, P = 1.00) and was showed in funnel plot (Fig. 3). Sensitivity analysis showed that the results were not significantly changed by eliminating the study one by one (Fig. 4).

2.3 Multivariate analysis

Based on multivariate analysis, the the association between smoking and stricture recurrence after urethroplasty was explored in 7 studies containing 2074 studies. According to the overall meta-analysis result, smoking can make patients more vulnerable to stricture recurrence (RR = 1.39, 95%CI: 1.04–1.85, P = 0.026) with no significant heterogeneity found (I2 = 27.5%, p = 0.290) (Fig. 5). No significant publication bias was found according to the Egger's test (t = 0.85, P = 0.427) and Begg's test (z = 0.37, P = 0.711) and was showed in funnel plot (Fig. 3). Sensitivity analysis showed that the results may become non-significant by eliminating Benjamin N. Breyer (2010) or Jared M. Whitson (2007) (Fig. 4).

Discussion

Urethral stricture is a kind of pathological stricture of urethra, which can limit fluid transportation. Since the male urethra is significantly longer than the female urethra, and the posterior urethra is hidden in the pelvis, urethral stricture can always bring many troubles to patients and urologists. Urethral stricture is a common urinary disease for the male. There are 229–627 cases in every 100000 people, and in some susceptible groups, such as elderly men, the prevalence rate is as high as 0.6%[18]. As one of the main methods to treat urethral stricture, there are many ways to implement urethroplasty, including primary anastomosis and substitution implantation. However, although many different surgical methods have been developed for different stricture degree, length and location, the total success rate is still only 72% – 94%[11, 14, 16]. Therefore, it is very important to find out the risk factors of recurrence of urethral stricture after urethroplasty and to prevent them. Some risk factors such as the length of stricture and etiology have attracted the attention of urologists, but other factors such as tobacco consumption has not been evaluated carefully [1, 3, 8, 19]

This meta-analysis revealed that tobacco consumption can make the chance of stricture recurrence significantly increased based on both univariate and multivariate analysis. In the multivariate analysis stage, the sensitivity analysis result was not exactly stable, this indicated that more multivariate analysis studies and adjusted estimate between smoking and stricture recurrence were required.

There are many proven relationships between smoking and urinary diseases. Smoking can promote the development of bladder cancer, which has been proved by many studies[20, 21]. The possible reasons why smoking is an independent risk factor for bladder cancer are various and some studies mentioned that the substances produced by tobacco burning, when metabolized into urine, will have a great influence on the DNA of bladder urothelial cells, which will lead to cell death and local inflammation[22]. This procedure may also be implied on urothelial cells. Persistent local inflammation in the epithelium of the urethra at the site of urethroplasty, caused by irritation of substances in the urine, may lead to recurrence of urethral stricture. Furthermore, for patients who receive oral mucosa graft Urethroplasty (OMGU), smoking history will make the general state of oral mucosa worse, leading to poor graft survival after OMGU operation, and ultimately leading to the increase of stenosis recurrence rate[9, 23].

In many current urological guidelines, the effect of smoking on the stricture recurrence after urethroplasty is not mentioned[24]. According to the results of this meta-analysis, urologists should guide urethroplasty patients to quit smoking before and after the operation to improve the overall success rate of the operation.

Some potential limitations of this study should be presented. First, although there were some prospective data involved, all the included studies are retrospective studies. Second, although it was recognized in statistical methodology[25, 26], it is still possible to bring some additional bias by combining HR

and OR to get RR estimates. Third, since smoking can directly damage oral mucosa, so OMGU patients with smoking history may have higher recurrence ratio, however, in this meta-analysis, since many studies didn't offer detailed information about OMGU technique, so OMGU subgroup analysis was not performed, further high-level evidences about smoking's effect on OMGU are needed.

Conclusion

This meta-analysis of current evidence indicates that smoking may prompt stricture recurrence after the urethroplasty. Quitting smoking may be a good option for patients undergoing urethroplasty surgery.

Abbreviations

NOS
Newcastle-Ottawa Scale;
HR
Hazard Ratio;
OR
Odds Ratio;
RR
Relative Risk;
CI
Confidence Interval;
DVIU
Direct Visual Internal Urethrotomy;
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-analysis;
OMGU
Oral Mucosa Graft Urethroplasty;
RCS
Retrospective Cohort Study;
NRPCS
Non-Randomized Prospective Cohort Study
BMG
Buccal Mucosa Graft

Declarations

Acknowledgements

Not applicable.

Declarations

Authors' contributions

YCM and MHW were responsible for the design of the work, the acquisition and analysis of data and manuscript writing. ZYJ carried out the acquisition of data. WKJ and LH revised the manuscript. All authors read and approved the final manuscript.

Funding:

This article is supported by 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZY2016104, ZYGD18011 and ZYJC18015) for data-collecting (availability of database purchased and provided by west china hospital). Chengdu Science and Technology Bureau project 2016-HM02-00020-SF, Science and Technology Department of Sichuan Province project 2015SZ0230-2 for data-analysis.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All analyses were based on previous published studies. Thus, no ethical approval and patient consent are required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

[1] Palminteri E, Lumen N, Berdondini E, Di Pierro GB, Cucchiarale G, Tenti G, et al. Two-sided dorsal plus ventral oral graft bulbar urethroplasty: long-term results and predictive factors. Urology. 2015;85:942-7.

[2] Yalcinkaya F, Kartal I. Critical analysis of urethroplasty for male anterior urethral stricture: a single-center experience. World journal of urology. 2019.

[3] Chapman D, Kinnaird A, Rourke K. Independent Predictors of Stricture Recurrence Following Urethroplasty for Isolated Bulbar Urethral Strictures. The Journal of urology. 2017;198:1107-12.

[4] Kluth LA, Dahlem R, Reiss P, Pfalzgraf D, Becker A, Engel O, et al. Short-term outcome and morbidity of different contemporary urethroplasty techniques–a preliminary comparison. Journal of endourology. 2013;27:925-9.

[5] Barbagli G, Morgia G, Lazzeri M. Dorsal onlay skin graft bulbar urethroplasty: long-term follow-up. European urology. 2008;53:628-33.

[6] Kinnaird AS, Levine MA, Ambati D, Zorn JD, Rourke KF. Stricture length and etiology as preoperative independent predictors of recurrence after urethroplasty: A multivariate analysis of 604 urethroplasties. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2014;8:E296-300.

[7] Breyer BN, McAninch JW, Whitson JM, Eisenberg ML, Mehdizadeh JF, Myers JB, et al. Multivariate analysis of risk factors for long-term urethroplasty outcome. The Journal of urology. 2010;183:613-7.

[8] Viers BR, Pagliara TJ, Shakir NA, Rew CA, Folgosa-Cooley L, Scott JM, et al. Delayed Reconstruction of Bulbar Urethral Strictures is Associated with Multiple Interventions, Longer Strictures and More Complex Repairs. The Journal of urology. 2018;199:515-21.

[9] Sinha RJ, Singh V, Sankhwar SN. Does tobacco consumption influence outcome of oral mucosa graft urethroplasty? Urology journal. 2010;7:45-50.

[10] Breyer BN, McAninch JW, Whitson JM, Eisenberg ML, Master VA, Voelzke BB, et al. Effect of obesity on urethroplasty outcome. Urology. 2009;73:1352-5.

[11] Keith CG, Davenport MT, Kavoussi M, Yi YA, Bergeson RL, Morey AF. Long-term outcomes of anastomotic urethroplasty for radiation-induced strictures. World journal of urology. 2019.

[12] Whitson JM, McAninch JW, Elliott SP, Alsikafi NF. Long-term efficacy of distal penile circular fasciocutaneous flaps for single stage reconstruction of complex anterior urethral stricture disease. The Journal of urology. 2008;179:2259-64.

[13] Han JS, Liu J, Hofer MD, Fuchs A, Chi A, Stein D, et al. Risk of urethral stricture recurrence increases over time after urethroplasty. International journal of urology : official journal of the Japanese Urological Association. 2015;22:695-9.

[14] Kahokehr AA, Granieri MA, Webster GD, Peterson AC. A Critical Analysis of Bulbar Urethroplasty Stricture Recurrence: Characteristics and Management. The Journal of urology. 2018;200:1302-7.

[15] Mathur RK, Nagar M, Mathur R, Khan F, Deshmukh C, Guru N. Single-stage preputial skin flap urethroplasty for long-segment urethral strictures: evaluation and determinants of success. BJU international. 2014;113:120-6.

[16] Liu JS, Han J, Said M, Hofer MD, Fuchs A, Ballek N, et al. Long-term outcomes of urethroplasty with abdominal wall skin grafts. Urology. 2015;85:258-62.

[17] Levy M, Gor RA, Vanni AJ, Stensland K, Erickson BA, Myers JB, et al. The Impact of Age on Urethroplasty Success. Urology. 2017;107:232-8.

[18] Santucci RA, Joyce GF, Wise M. Male urethral stricture disease. The Journal of urology. 2007;177:1667-74.

[19] Barbagli G, Montorsi F, Guazzoni G, Larcher A, Fossati N, Sansalone S, et al. Ventral oral mucosal onlay graft urethroplasty in nontraumatic bulbar urethral strictures: surgical technique and multivariable analysis of results in 214 patients. European urology. 2013;64:440-7.

[20] Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. European urology. 2017;71:96-108.

[21] Sanli O, Dobruch J, Knowles MA, Burger M, Alemozaffar M, Nielsen ME, et al. Bladder cancer. Nature reviews Disease primers. 2017;3:17022.

[22] Jin F, Thaiparambil J, Donepudi SR, Vantaku V, Piyarathna DWB, Maity S, et al. Tobacco-Specific Carcinogens Induce Hypermethylation, DNA Adducts, and DNA Damage in Bladder Cancer. Cancer prevention research (Philadelphia, Pa). 2017;10:588-97.

[23] Ye P, Wang X, Ge S, Chen W, Wang W, Han X. Long-term cigarette smoking suppresses NLRP3 inflammasome activation in oral mucosal epithelium and attenuates host defense against Candida albicans in a rat model. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;113:108597.

[24] Wessells H, Angermeier KW, Elliott S, Gonzalez CM, Kodama R, Peterson AC, et al. Male Urethral Stricture: American Urological Association Guideline. The Journal of urology. 2017;197:182-90.

[25] Yang WS, Va P, Wong MY, Zhang HL, Xiang YB. Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies. The American journal of clinical nutrition. 2011;94:1575-83.

[26] Fon Sing M, Yang WS, Gao S, Gao J, Xiang YB. Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2011;20:157-65.

Tables

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	Country	Disease	Study design	Techniques applied	Median/Mean follow (months)	Sample size	Recu num
Adam S. Kinnaird	2014	Canada	Anterior/posterior urethral stricture	RCS	NR	52	604	56(9
Benjamin N. Breyer	2009	USA	Anterior/posterior urethral stricture/combined stricture	RCS	Anastomotic urethroplasty/ Buccal mucosa graft/ Fasciocutaneous flap/combined techniques	70	443	93(7
Boyd R. Viers	2017	USA	bulbar urethral stricture	RCS	Excision + primary anastomosis/Substitution	64	278	34(8
Christopher G. Keith	2019	USA	bulbomembranous urethra	RCS	Primary anastomosis	30.7	116	22(8
David Chapman	2017	Canada	bulbar stricture	RCS	BMG Onlay/ Flap Onlay/ Augmented Anastomosis/ Anastomotic/ Combined Tissue plasty	65.4	596	40(9
Jared M. Whitson	2007	USA	Anterior Urethral Stricture	RCS	fasciocutaneous flap urethroplasty	87.6	124	32(7
Joceline S. Liu	2015	USA	Fossa navicularis/ Penile/ Bulbomembranous/ Panurethral strictures	RCS	Dorsal onlay/ Ventral onlay/ Staged urethroplasty	59.3	238	66(7
Justin S Han	2015	USA	Posterior urethral stricture	RCS	Excision/primary anastomosis/ Dorsal onlay (including augmented anastomotic)/ Ventral onlay/ Staged/ Combined/flap/miscellaneous	62	227	60(7
Arman A. Kahokehr	2018	USA	bulbar urethral stricture	RCS	Excision + primary anastomosis/ Augmented	28	395	25(9

					anastomotic repair/ Onlay			
Mya Levy	2017	USA	Bulbar/ Meatus/Fossa/ Membranous/ Penile stricture	RCS	Excision + primary anastomosis/BMG dorsal onlay	21.6	322	22(9
Raj Kumar Mathur	2014	India	Anterior (penile+ bulbar)/ Posterior (membranous/bulbomembranous)/ Panurethra strictures	RCS + prospective data	single-stage penile preputial flap urethroplasty	42	58	11(8
Rahul Janak Sinha	2010	India	Penile/Bulbar/ Bulbopenile/ Pananterior stricture	NRPCS	Oral mucosa graft Urethroplasty	18.2	42	11(7

RCS = Retrospective Cohort Study; NRPCS =Non-Randomized Prospective Cohort Study; NR = Not Reported; NOS = Newcastle-Ottawa Scale; BMG = buccal mucosa graft.

Table 2. Newcastle-Ottawa scale score of the reviewed studies

Study	Selection (4 stars)				Comparability (2 stars)	Outcome (3 stars)			Total score
	Representativeness score of the stricture recurrence	Selection of the stricture recurrence	Ascertainment of stricture recurrence	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur?	Adequacy of follow up of cohort	
Adam S. Kinnaird (2014)	/	□	/	□	□	/	□	□	5
Benjamin N. Breyer (2009)	□	□	□	□	□	□	□	□	8
Boyd R. Viers (2017)	/	□	/	□	□	/	□	□	5
Christopher G. Keith (2019)	/	□	□	□	□	□	□	□	7
David Chapman (2017)	/	□	□	□	□	□	□	□	7
Jared M. Whitson (2007)	/	□	/	□	□	/	□	□	5
Joceline S. Liu (2015)	□	□	□	□	□	□	□	□	8
Justin S Han (2015)	/	□	/	□	□	/	□	□	5
Arman A. Kahokehr (2018)	/	□	/	□	□	/	□	□	5
Mya Levy (2017)	□	□	/	□	□	/	/	□	5
Raj Kumar Mathur (2014)	□	□	/	□	/	/	□	□	5
Rahul Janak Sinha (2010)	□	□	/	□	□	/	/	□	5

Figures

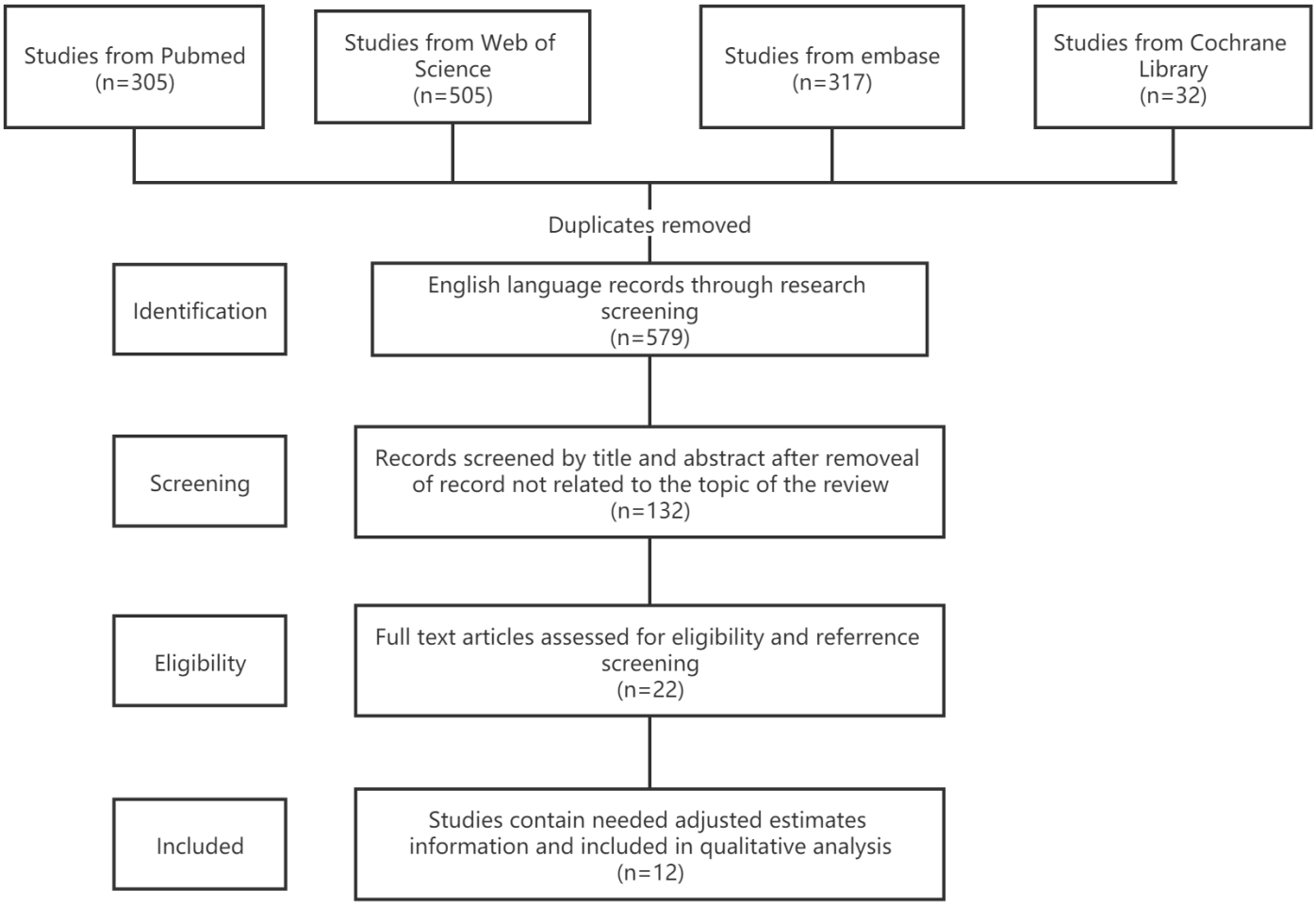

Figure 1

Study selection flowchart

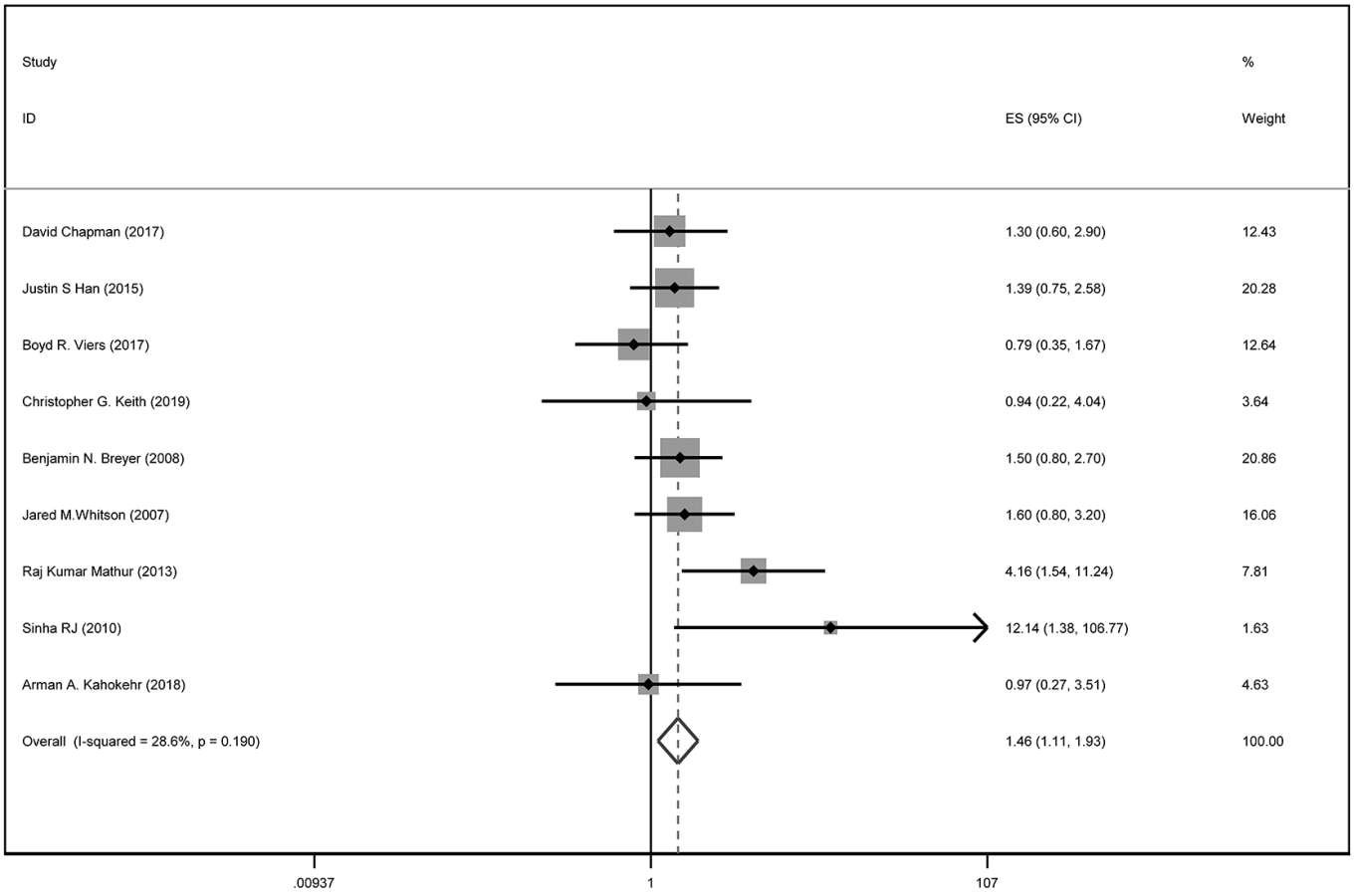

Figure 2

Forest plot of crude estimate meta-analysis between smoking and stricture recurrence.

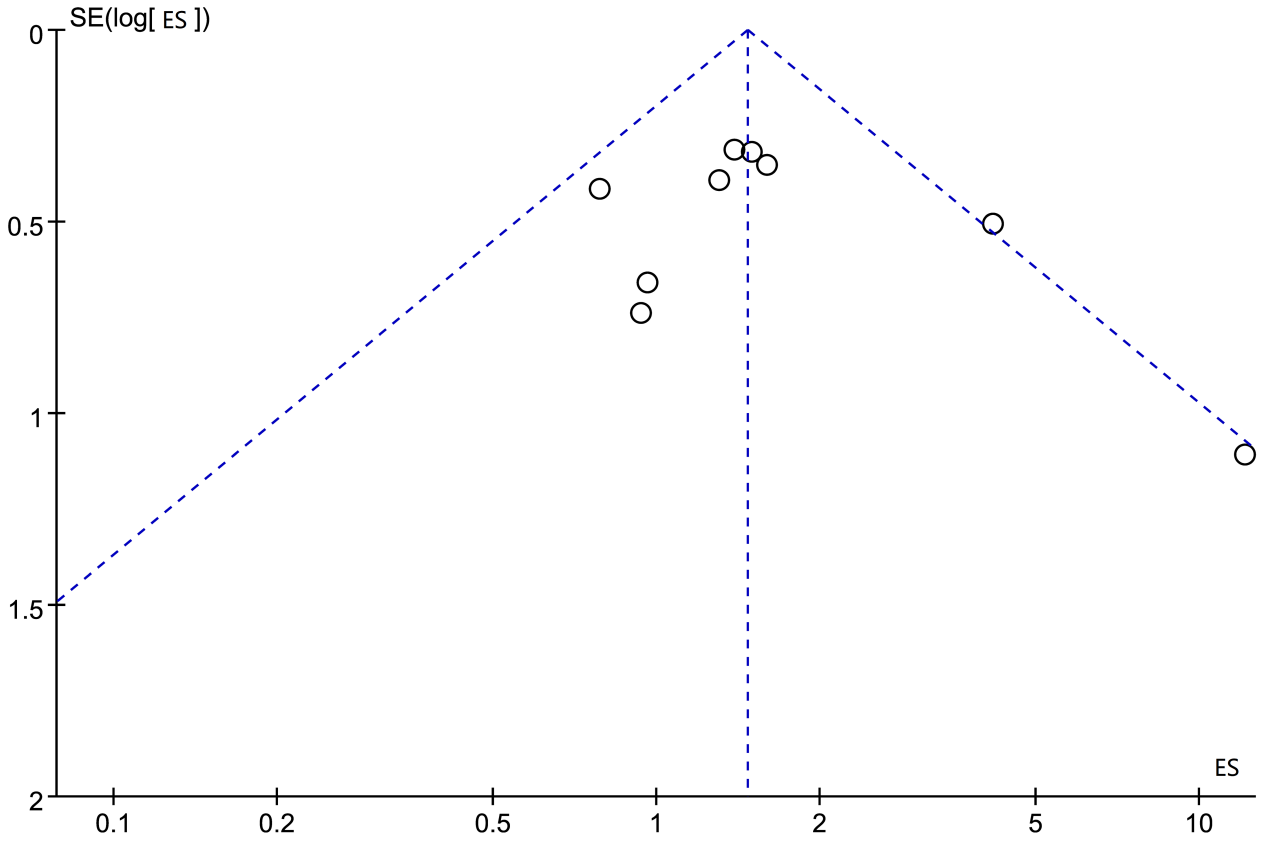

Figure 3

Funnel plot of crude estimate meta-analysis.

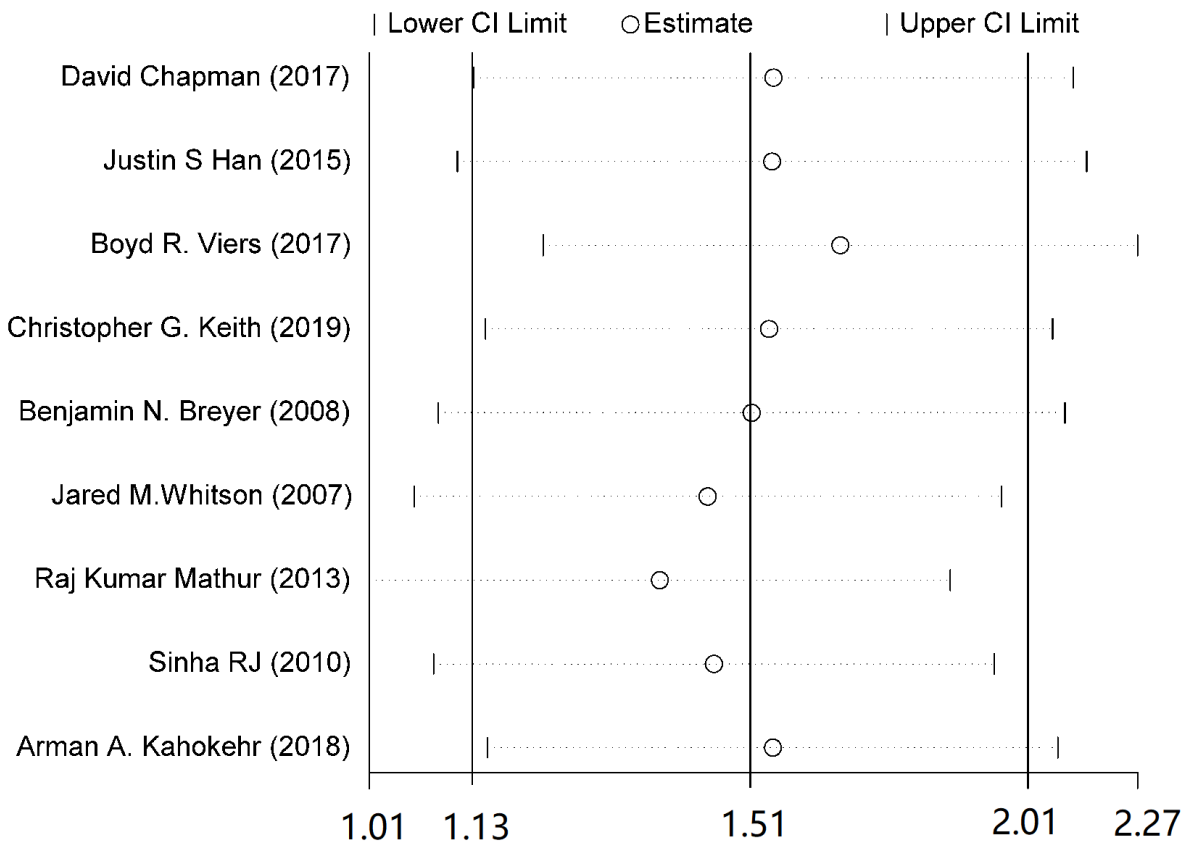

Figure 4

Sensitivity analysis of crude estimate meta-analysis.

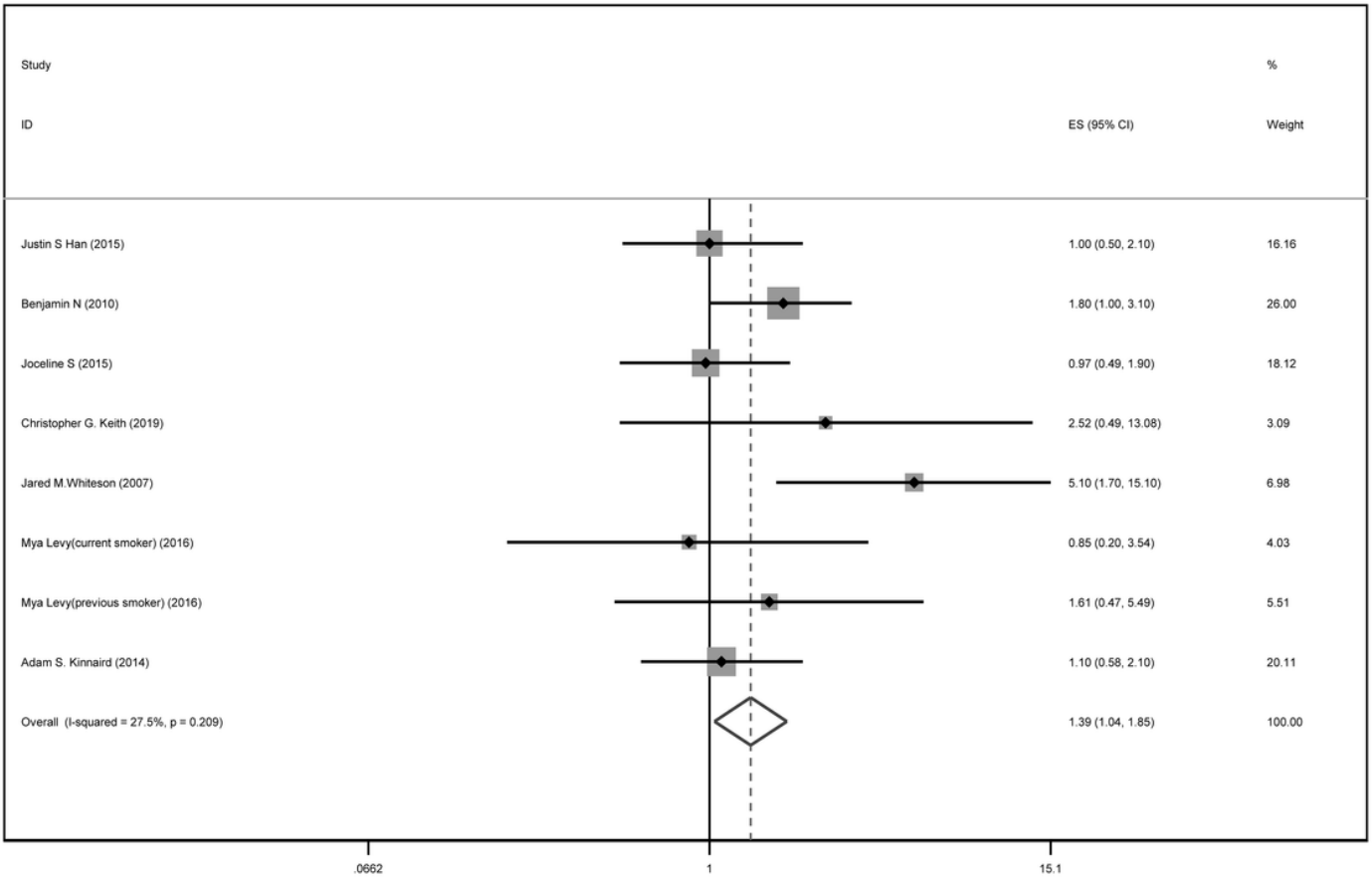

Figure 5

Forest plot of adjusted estimate meta-analysis between smoking and stricture recurrence.

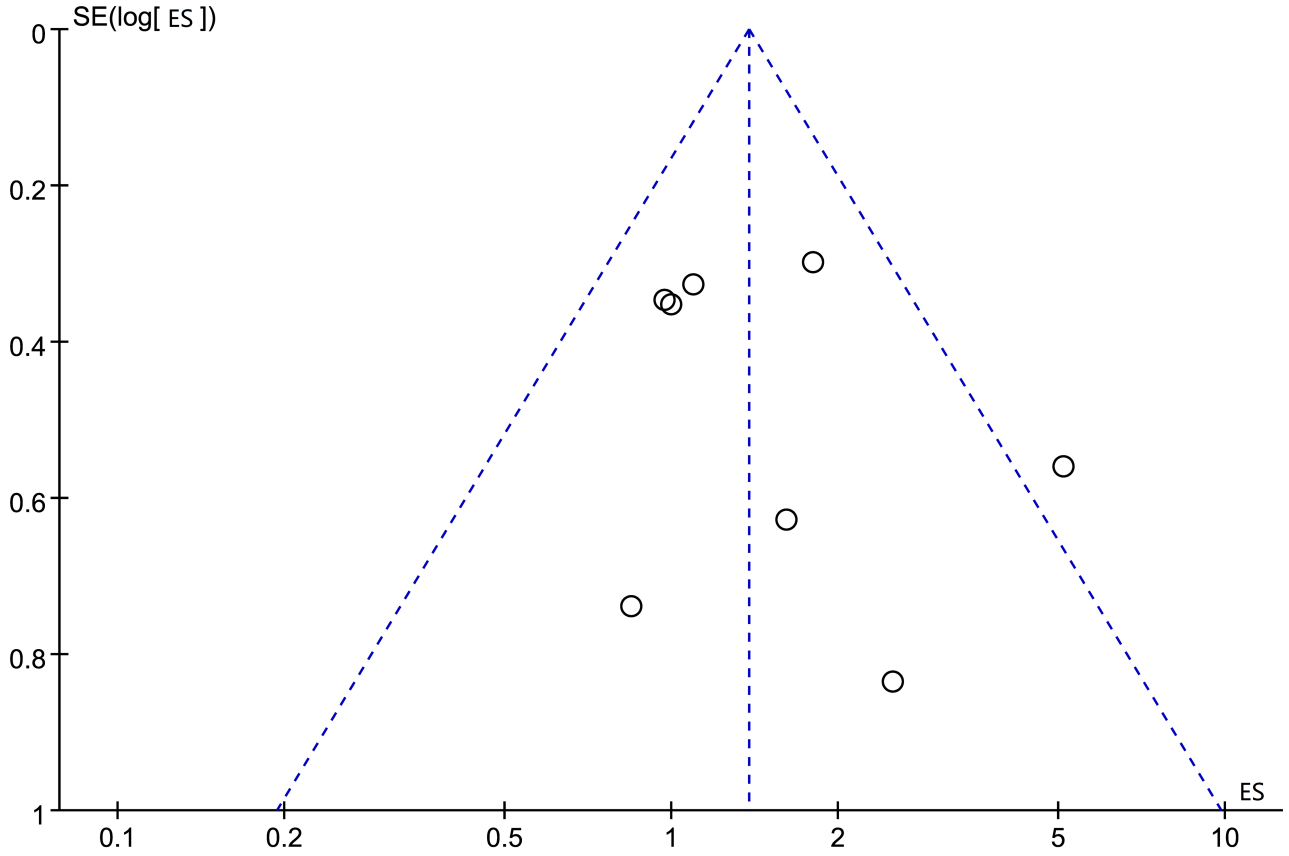

Figure 6

Funnel plot of adjusted estimate meta-analysis.

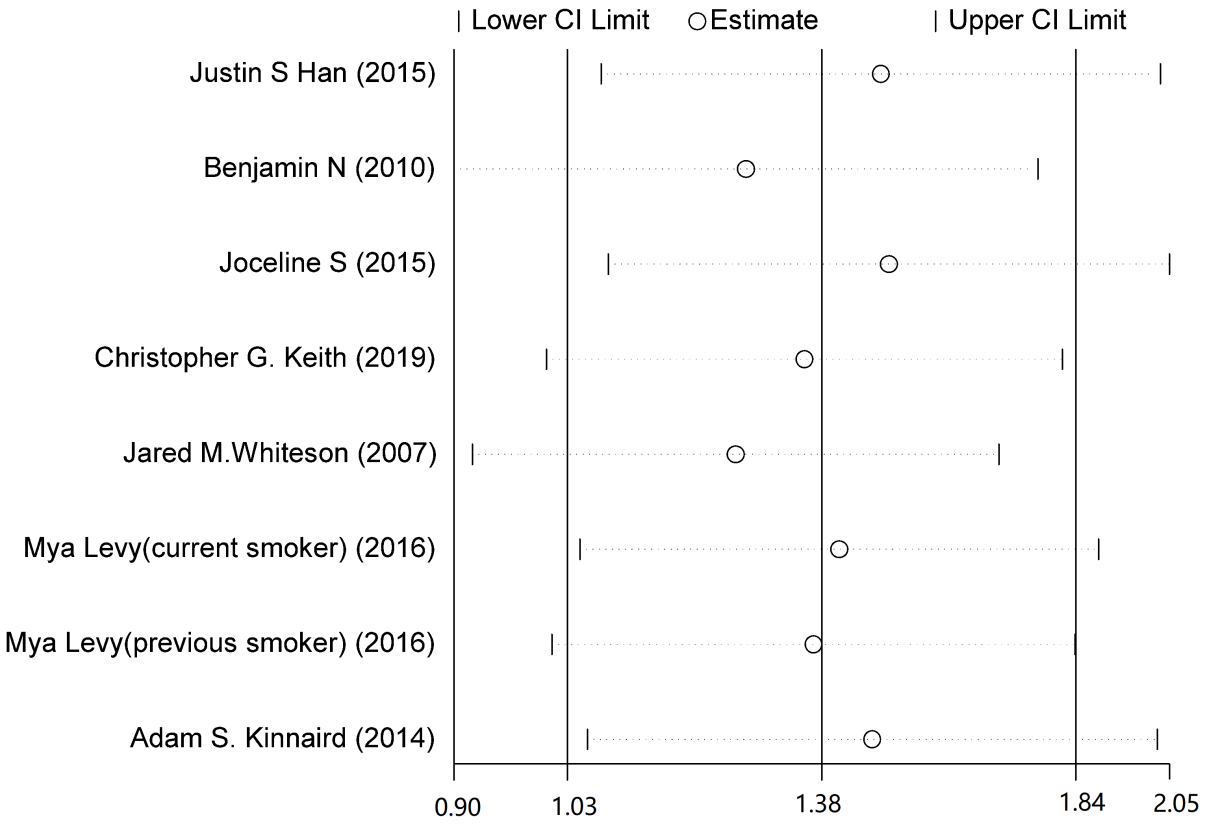

Figure 7

Sensitivity analysis of adjusted estimate meta-analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc