ASSOCIATION BETWEEN CIGARETTE SMOKING AND SYSTEMIC LUPUS ERYTHEMATOSUS - AN UPDATED MULTIVARIATE BAYESIAN META-ANALYSIS

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ABSTRACT

Objective

The association between cigarette smoking and the risk of systemic lupus erythematosus (SLE) remains controversial. Additionally, the impact of the change of smokers' demographics on the risk of development of SLE over time was not formally addressed. We aimed to examine the association between cigarette smoking and the risk of SLE by performing an updated meta-analysis.

Methods

A literature search using the keywords including "lupus', "smoking", "cigarette", "environmental", "autoimmune" and "connective tissue disease" was performed in computerized databases to identify studies addressing the relationship between cigarette smoking and SLE occurrence. A Bayesian meta-analysis was conducted by computing the log odds ratios (OR) between current and never smokers, and between former and never smokers. The average log ORs (subsequently converted to ORs) and their corresponding 95% credible intervals (CI) were calculated. The impact of publication time, gender and age of SLE patients on the effect sizes was examined by multivariate meta-regression.

Results

Data aggregation of 12 eligible studies comprising 3,234 individuals who developed SLE and 288,336 control subjects revealed a significant association between SLE occurrence and current-smoking status (OR 1.54, 95% CI [1.06, 2.25]), while only a non-significant trend was demonstrated between SLE occurrence and former-smoking status (OR 1.39, 95% CI [0.95, 2.08]). Publication time, gender and the mean age of SLE patients did not explain the heterogeneity of the effect sizes.

Conclusions

Current-smoking status is associated with the risk of SLE. Gender and the age of SLE patients had no significant impact on the risk of SLE over time.

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Introduction

Systemic lupus erythematosus (SLE) is a complex and aetiologically multifactorial autoimmune disease. While genetic susceptibility and environmental factors play a pathophysiologically important role in the development of SLE [1], studies addressing as to how these factors are related to the occurrence and flare of the disease have yielded interesting yet inconsistent results. Differences in study populations, timing and duration of study, ethical issues and research methodology among various studies often contribute to such discrepancies [2].

Amongst various environmental factors, cigarette smoking has been implicated to be associated with the development of autoimmune conditions such as Grave's disease, rheumatoid arthritis and primary biliary cirrhosis [3-7]. In the National Institute of Environmental Health Sciences (NIEHS) Expert Panel which was convened in 2014, cigarette smoking was considered to contribute a risk for the development of SLE [8]. Cigarette smoke contains a number of toxic substances that are capable of inducing myeloperoxidase activity, activating macrophages and producing free radicals [9]. Mechanistically, these toxic substances can induce pro-inflammatory responses and potentially trigger the onset of SLE in genetically susceptible individuals and disease flares in patients with established SLE [10, 11].

Despite the theoretical relationship between cigarette smoke and the development of SLE, methodological issues intrinsic to observational studies often mitigate the ability in discerning the genuine association between cigarette smoking and SLE. For example, the global change of smokers' demographics over the past few decades leads to potential confounders in answering the research question with observational studies [12]. In the 2015 National Health Interview Survey (NHIS), the proportion of adults in the United States (US) who smoked cigarettes declined from 20.9% in 2005 to 15.1% in 2015, and the proportion of daily smokers

declined from 16.9% to 11.4% [13]. In addition, as for age and gender, most of the smokers were male and aged between 25 and 44 years [13]. Compared to the US, disparities in the trend of cigarette smoking have been observed in European countries where the prevalence of female smokers has been increasing over the past two decades. In a Swedish study, the point prevalence of cigarette smoking among women was reported to be as high as around 23.5%, as compared to that of 19.5% in men [14]. In addition, the prevalence of cigarette smoking was on the rise amongst younger women, for which daily smoking increased from 10% in 2009 to 13% in 2011 in those between 16 and 29 years of age [15]. Similarly, in France, an increase in the number of female smokers was observed between 2005 and 2010 [16]. In Asia, the Japan National Health and Wellness Survey which examined smoking trends among adults in Japan from 2008 to 2017 revealed that lifetime smoking prevalence declined from 49.1% in 2008 to 38.9% in 2018, and such trend was consistent in both women and men. Lifetime smoking prevalence among males declined from 65.6% in 2008 to 54.8% in 2017, and from 33.6% in 2008 to 24.3% in 2017 among females [17]. As such, since SLE predominantly affects women during their prime years, gender potentially confounds the interpretation of the relationship between cigarette smoking and the occurrence of SLE when relevant data over the past 20 years are to be analyzed.

Aside from these confounders, since the absolute risk of the development of SLE is very small in general population, cohorts with very large numbers of patients and healthy subjects are required to address the relationship between cigarette smoking and the risk of development of SLE. Owing to the fact that the sample sizes of published observational studies which investigated the association between SLE and smoking are generally small, statistical aggregation of data with the use of meta-analysis is one of the reasonable methodological approaches to increase the statistical power for examining the relationship. In keeping with the

findings of the first meta-analysis published in 2004 by Costenbader *et al* [18], the second and latest meta-analysis to date in the literature which comprises 12 studies authored by Jiang *et al* in 2015 demonstrated a significantly increased risk of SLE in current smokers as compared to never smokers (OR 1.56, 95% CI of 1.26–1.95), and only a trend of increased risk of SLE amongst former smokers was demonstrated [19]. Apart from the substantial heterogeneity among the studies, involvement of studies with relatively small sample sizes and the direct combination of cross-sectional and prospective studies for synthesizing a common effect size may not be statistically favorable to draw a sound conclusion based on these meta-analyses.

In addition to the three issues related to the limitations intrinsic to the previous meta-analyses, the presence of the confounding impact of the global increase in young female smokers on SLE over time and the potential implications by a recent publication from the prospective Nurses' Health Study (NHS) cohorts [20, 21] warrants a scientific update which re-addresses the association between cigarette smoking and SLE, with an aim to capture a clearer perspective regarding the impact of cigarette smoking and its confounders on the risk of development of SLE.

We aimed to examine the association between cigarette smoking and the risk of the development of SLE by performing an updated meta-analysis with the Bayesian approach. The choice of the Bayesian approach allows the generation of a reliable effect size resulted from aggregating a mixture of case-control and cohort studies of studies. In addition, the multivariate meta-regression approach adopted in the current study offers a platform to identify demographic factors which are potentially associated with the relationship between cigarette smoking and the risk of SLE.

Materials and Methods

Literature search

The first and second authors (M.H.Y.C and I.A.T.N) performed an extensive literature search using the relevant keywords including "lupus'; "smoking"; "cigarette"; "environmental"; "autoimmune" and "connective tissue disease" in various combinations to identify potential case-control and cohort studies addressing the relationship between the occurrence of SLE and cigarette smoking. These studies were published in English in computerized databases accessible to the study investigators, including PubMed (from 1966 to Jan 2018), Embase (1980 to Jan 2018) and Cochrane Central Register of Control Trials (last quarter of 2017). The last author (A.M.) supervised the overall literature search and resolved the conflicts as to whether articles with potentially eligibility issues should have been included or excluded, and ensured the accuracy of the data extracted for subsequent meta-analyses.

Selection of studies and data extraction

The meta-analysis was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the statistical synthesis of observational data [22]. Observational case-control and cohort studies which examined the relationship between the risk of the occurrence of SLE with reference to healthy subjects and the various cigarette smoking statuses were included. Meta-analyses, review articles, case-reports and studies without a comparative smoking (and non-smoking) or a healthy control group were excluded. Studies would also be excluded if they (1) did not examine the occurrence of SLE as an outcome, (2) did not study smoking as a risk factor for SLE, (3) were animal studies or (4) had insufficient data on smoking statuses such as ill-defined categories between former smokers and current smokers. A consensus regarding the eligibility studies was reached amongst the first, second and the last authors (A.M.) before data were extracted from the eligible articles

into an electronic data spreadsheet which facilitated subsequent analyses by statistical programs.

Data analyses

Data analyses were performed by the meta-analyst (M.W.L.C) and the last author with the use of the Bayesian multivariate approach [23, 23, 24, 26]. The log- odds ratios (ORs) of the current smokers versus never smokers and the former smokers versus never smokers were calculated as the effect sizes, with each study contributing two effect sizes. As the 'never smokers' status was in both studies, the two effect sizes were not independent. Most meta-analytic methods assume that the effect sizes are independent, and thus a multivariate approach to handle the dependence of the effect sizes was adopted in this study [27, 28]. The sampling variances and covariances of the effect sizes were calculated based on the methods suggested by Gleser and Olkin [29, 30]. The summary statistics of the eligible studies are shown in Table 1.

Non-informative priors were used in the analyses. Specifically, the priors for the average effect and the heterogeneity were mu~normal(0, 1e3) and standard deviation (SD) ~ uniform(0, 10), respectively. The use of non-informative prior indicates that we do not have a strong belief in the values of the pooled effect size in the meta-analysis. As a sensitivity analysis, we also ran several analyses with different priors of mu~normal(0, 1e5) and SD ~ uniform(0, 20), mu~normal(0, 1e3) with SD ~ exponential(0.1), SD ~ half-Cauchy(0, 5), or SD ~ half-normal(0, 10). The results were similar. The largest difference on the parameter estimates is 0.01. Therefore, the findings were robust to the use of priors.

Since there were only two cohort studies included in this meta-analysis, we assumed that the heterogeneity variances of the case-control and cohort studies were the same. The number of

iterations and warm-ups were one hundred thousand iterations and three thousand iterations, respectively. The generated data in the warm-up period were discarded from the analysis. During the warm-up period, the program would tune the settings so that the generated data would be closer to the mass of the distribution. The reported Rhat and graphical plots were used to monitor the convergence. When Rhat was above 1.00, it suggested that the chain had not yet converged, and the results would not be reliable . All the reported Rhats were 1, indicating that there was no evidence of non-convergent. The average log-ORs and the heterogeneity in standard deviations (SDs) and their corresponding 95% credible intervals (CIs) of the posterior distributions were reported. We transformed the ORs into log-OR so that the effect size (log-OR) is approximately normally distributed in the meta-analysis. After the meta-analysis, we converted log-OR back to OR for ease of interpretations. In contrast to ORs which range from 0 to positive infinity with 1 as the point of equal chance, log-ORs range from negative infinity to positive infinity with 0 as the point of equal chance.

Since there have been demographic changes of smoking behavior, particularly with regard to gender and age over time as described, the year of publication of the studies, the mean age (at the start of study if cohort study) of the patients and the percentage of female patients in the studies were used as moderators in the multivariate models. Publication bias was assessed by funnel plot. All statistical analyses in this meta-analysis were performed using the Stan [31], R [32], and the brms [33], metafor [34] and metaSEM [35] packages.

Results

Results of literature search

We initially identified 3,636 articles through database searches. Amongst these studies, 3,597 studies were excluded during our first-stage assessment because they (1) did not appear to

address the occurrence of SLE as an outcome (n=2,959), (2) did not study smoking as a risk factor of SLE (n=447), (3) did not have a comparator (n=11) and (4) were animal or *in vitro* studies (n=55), (5) were review articles (n=89), case reports and/or meta-analyses (n=36). Thirty nine papers were then subjected to the second-stage evaluation, of which 27 were excluded as they (1) were review articles (n=12), (2) were studies with data duplication (n=3), (3) were studies without stating clearly on smoking status (n=3), (4) were study which only examined the pathogenesis of cigarette smoking in SLE (n=3), (5) were studies which examined the relationship between smoking and autoimmune conditions other than SLE (n=3). For the rest of the 3 studies, one of each was a small study on pregnant woman with SLE only, a study which investigated the relationship of smoking and the risk of autoimmune conditions other than SLE, a study which did not follow the ACR criteria for diagnosis of SLE and a study which mainly analyzed the impact of C2/4 deficiency on the risk of SLE in smokers. Thus, after the second round of exclusion, 12 full papers [21, 36-45, 51] were finally included for meta-analysis. These 12 studies comprise 10 retrospective case-control and 2 cohort studies. In these 12 studies, half of them studied SLE in women only, while 5 studies combined the data for both men and women subjects, and only 1 study had separate data for the two genders and reported the combined data [42]. Figure 1 summarizes the process and results of the literature search.

Synthesis of effect sizes

To test the effect between the case-control and cohort studies, the log-ORs of the current smokers versus never smokers were first computed, and the difference between these two ORs was subsequently calculated. The difference between the case-control and cohort studies in log-ORs was 0.42, 95% CI [-0.60, 1.43] (OR: 1.52, 95% CI [0.55, 4.18]). Similarly, the log-ORs of former smokers versus never smokers in the case-control and cohort studies were

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calculated, and the difference between them was -0.31, 95% CI [-1.31, 0.71] (OR: 0.73, 95% CI [0.27, 2.03]). As there were only two cohort studies included in this meta-analysis, the calculated 95% CIs were quite wide (refer to Supplementary Figure 1 for the posterior distributions). In the subsequent analyses, the combined effect sizes of both case-control and cohort studies are presented.

The posterior means of the log-ORs of the current and former smokers against never smokers were 0.43, 95% CI [0.08, 0.80] (OR: 1.54, 95% CI [1.06, 2.25]) and 0.33, 95% CI [-0.04, 0.73] (OR: 1.39, 95% CI [0.95, 2.08]), respectively. The results suggest that current smokers are more likely to have SLE compared to never smokers, which reached statistical significance, whereas the effect on the former smokers is mild. The estimated SDs (heterogeneity) in log-OR of the current and former smokers were 0.57 and 0.55, respectively. The computed I^2 in log-OR of the current and former smokers were 89.18% and 87.16%, respectively. The estimated correlation between the population log-ORs of the current smokers and the former smokers was 0.55. Supplementary Figure 2 shows the posterior distributions of the parameters.

Figure 2 displays the forest plots of the studies and the average effects. The estimated difference between log-ORs of the current versus never smokers and the former smokers versus never smokers was 0.10, 95% CI [-0.27, 0.51] (OR: 1.11, 95% CI [0.76, 1.67]), indicating that current smokers are slightly more likely to develop SLE than the former smokers, with statistical significance.

Meta-regression and publication bias

In the multivariate model, the estimated coefficients of year of publications in the log-ORs of the current smokers and the former smokers were -0.00, 95% CI [-0.05, 0.04] and 0.02, 95%

CI [-0.02, 0.07], respectively. When the mean age was used as the moderator, the estimated coefficients in the log-ORs of the current smokers and the former smokers were -0.03, 95% CI [-0.12, 0.07] and 0.01, 95% CI [-0.08, 0.08], respectively. Regarding the proportion of the females followed in the studies, the estimated coefficients in the log-ORs of the current smokers and the former smokers were 1.90, 95% CI [-3.48, 7.38] and 3.07, 95% CI [-2.31, 8.41], respectively. Therefore, all the moderators did not explain the heterogeneity of the effect sizes.

Figure 3 displays the funnel plot of the data, with more studies reporting a positive log-OR than negative log-OR. Since there only twelve studies were involved in this meta-analysis, more studies may be required to verify the patterns. However, there were limitations met in obtaining more than 2 cohort studies.

Discussion

Our current Bayesian meta-analyses showed that current smokers were more likely to develop SLE as compared with lupus patients who had never smoked based on 291,570 subjects observed in 10 case-control and 2 cohort studies, including the recent data of the NHS published in 2018 [21]. On the other hand, only a non-significant trend was found between former-smoking status and the development of SLE. In keeping with the findings of the previous 2 meta-analyses [18, 19], we hereby confirmed that current exposure to cigarette smoke has a stronger impact than previous cigarette smoke exposure on the risk of SLE. In addition, unique to this meta-analysis, our meta-regression analysis revealed that publication time, age and gender did not exert a significant effect on the risk of SLE.

A number of observational studies have been performed to address whether cigarette smoking would increase the risk of SLE in the past two decades. Results; however, are inconsistent. Two large prospective studies conducted in the United States did not reveal a statistically significant higher risk of development of SLE amongst smokers [45, 46] and those who were exposed to cigarette smoke during early childhood [47]. Conversely, Asian studies appear to suggest the otherwise and propose the basis of genetic polymorphisms that mediate the risk of SLE amongst smokers [48]. For example, a case-control study of 171 female patients with SLE and 492 healthy women in Japan demonstrated an OR of 3.06 (95% CI: 1.86-5.03) of SLE occurrence amongst current smokers against non-smokers [49]. Studied by the same group of investigators, the presence of at least one G allele of TNFRSF18*rs1061622* was shown to confer an excess risk of 49% for SLE in smokers [50]. Since there were only 2 studies from Asia, we did not conduct a moderator test on it. When there are more Asian studies in future, researchers may empirically test this hypothesis. Furthermore, a dose-response relationship between smoking and the risk of SLE was demonstrated [51]. Until very recently, the data from the NHS which involved over 230,000 women recruited between 1976 and 1989 demonstrated a strong and specific risk associations between current smokers with positive anti-dsDNA and the risk of SLE, after an observation of over 30 years [21]. All this evidence implies that cigarette smoke, as an environmental trigger, interacts with susceptible genes and immune system with pro-inflammatory propensity before exerting its influence to trigger SLE and perpetuate lupus-related inflammation in certain subsets of individuals [52-62]. Undoubtedly, larger studies with longer observation and more laboratory work that aims to unravel the mechanism of immune alteration by cigarette smoke are required to address this complex phenomenon.

Beyond the effect of cigarette smoking in the immune system, cigarette smoke has been proven to affect the treatment of SLE by blunting the pharmacological responses to certain medications. For example, cigarette smoke was shown to reduce the efficacy of anti-malarials, leading to increase in SLE disease activity overall, as well as acute, subacute and chronic cutaneous lupus [63]. More recently, it has been observed that lupus patients who smoked had reduced efficacy towards belimumab, a monoclonal antibody against B-cell activating factor which was approved by the FDA as a treatment option of SLE [64].

Based on the results of the present study and the two published meta-analyses as well as the negative impact of cigarette smoking as aforementioned, patients with SLE should be advised for smoking cessation and against smoking initiation. Alluded to the evidence that smoking cessation partially reverses airway inflammation [65], cessation of smoking stops the exposure to inflammation-inducing agents, leading to reduction of SLE risk and disease flares theoretically. While the exact mechanism of the reversal of oxidations and inflammation after smoking cessation is not fully understood, the intensity of smoking; that is, the amount and duration of smoking, are paramount [66]. At low dose of and short-term exposures to cigarette smoke, inflammatory changes reverse more rapidly upon cessation than those among heavy and long-term smokers [67].

There are several limitations to this study. First, this meta-analysis in a statistical aggregation of observational studies. Obviously, it does not reveal the biological pathway of the effect of smoking on SLE risk. The lack of sufficient information such as frequency, duration and age of cessation of cigarette smoking in the selected studies did not allow statistical inference as to the causative effect of cigarette smoking in the occurrence of SLE. As such, these observational studies can safely suggest an association, but not causation between the risk of SLE and

cigarette smoking. Second, while we had 10 suitable case-control studies, only 2 cohort studies were found to be suitable with sufficient data for an up-to-date meta-analysis. In addition, heterogeneity intrinsically exists in the meta-analyses. As such, cautions should be taken when interpreting the findings. Lastly, while we were able to discern the impact of smoking status on the occurrence of SLE, the dose-response relationship between cigarette smoking and the risk of SLE could not be addressed in this study. In conclusion, results from our updated Bayesian meta-analysis confirmed that smoking is associated with the occurrence of SLE, with a statistically significant higher risk of SLE development amongst current smokers as compared to people who never smoked. While there have been concerns as to whether the changes of the demographics of smokers over time might impact the occurrence of SLE, meta-regression did not suggest that age and gender have exerted an influence on the risk of SLE over time. While this study can trigger further investigation as to the potential mechanism mediating the impact of current smoking on the pathogenesis of SLE, it also highlights the importance of the detrimental effects of smoking in SLE and the potential benefit of smoking cessation in patients with SLE, regardless of the demographics of the patients.

Acknowledgement

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Figure legends

Figure 1. Results of literature search

Figure 2. Forest plots for the posterior distributions of effect sizes of the meta-analyses. Left panel: Current smokers versus non-smokers. Right panel: Former smokers versus non-smokers.

Cohort studies are underlined.

(ORs were transformed into Log-ORs so that the effect size [log-ORs] is approximately normally distributed in the meta-analysis. Log-ORs range from negative infinity to positive infinity with zero as the point of equal chance.)

Figure 3. Funnel plot for the effect sizes. Filled circles and crossed diamonds represent the effect sizes of current-smokers and former smokers, respectively

Supplementary Figure 1. Posterior distributions in comparing the effect sizes between the case-control vs. cohort studies. Top panel: Comparing the log-OR (current-smokers vs. non-smokers) case-control studies with log-OR (current-smokers vs. non-smokers) cohort studies. Bottom panel: Comparing the log-OR (former smokers vs. non-smokers) case-control studies with log-OR (former smokers vs. non-smokers) cohort studies.

Supplementary Figure 2. Posterior distributions of the parameter estimates for the studies. The panels from top to bottom are referred to the log OR ((current smokers vs. non-smokers)), log-OR (former smokers vs. non-smokers), SD of log-OR ((current-smokers vs. non-smokers)), SD of log-OR (former smokers vs. non-smokers), and the correlation between the two log-ORs.

Table legends

Table 1. Studies included in the meta-analyses

Table 1: Studies included in the meta-analysis

First author (Year) (Ref.)	Study type	Location	Mean age case/ control	Female (%)	Case (n)/control (n)	Log-OR current smoker	Log-OR ex-smoker
Reidenberg (1993) (36)	Case-control	US	38/37	88.5	195/143	0.6918	0.8491
Nagata (1995) (37)	Case-control	Japan	33/37	100	282/292	2.2331	0.9978
Hardy (1998) (38)	Case-control	UK	47/47	92.0	150/300	1.6601	0.8977
Bockle (2015) (39)	Case-control	Austria	43.3/NA	84.7	186/101	2.5564	NA
Washio (2006) (51)	Case-control	Japan	31.7/33.6	100	175/517	2.8448	2.9110
Ekblom-Kullberg (2013) (40)	Case-control	Finland	47.1/47.8	100	205/862	1.5541	1.8053
Young (2014) (41)	Case-control	US	41.7/41.7	79.3	1242/946	1.0570	1.1779
Benoni (1990) (42)	Case-control	Sweden	NA	85.8	56/99	1.6867	1.4000
Cooper (2001) (43)	Case-control	US	NA	90.5	265/355	0.8810	0.4820
Ghaussy (2001) (44)	Case-control	US	44/44	96.8	125/125	3.8367	2.7668
Formica (2003) (45)	Cohort	US, African American	N/A	100	67/53,924	1.7686	2.0720
Barbhaiya (2018) (21)	Cohort	US, nurses from NHS*	49.2*	100	286/230,672	0.8131	1.6088

Abbreviations: Ref; references; OR, odds ratio; US, United States; UK, United Kingdom; NA, not available; NHS, Nurses' Health Study
† OR against non-smokers
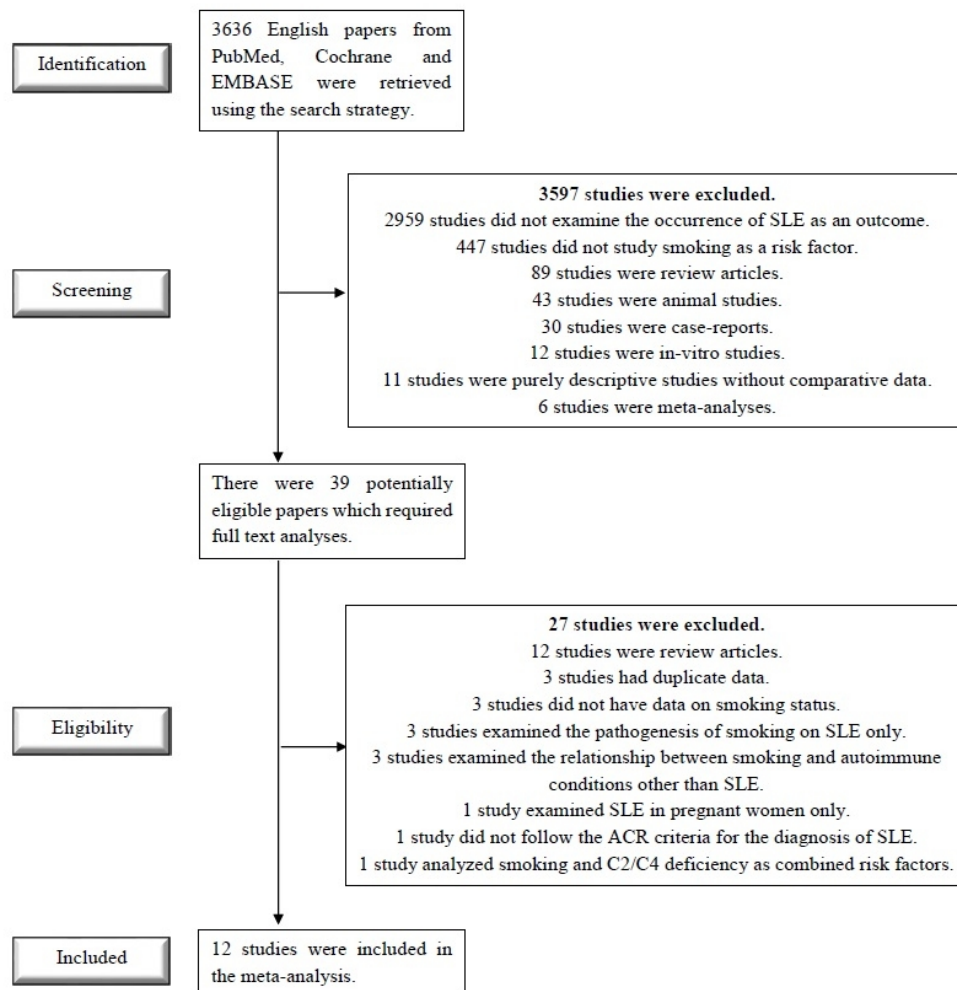* mean age at the start of the study

Figure 1. Results of literature search

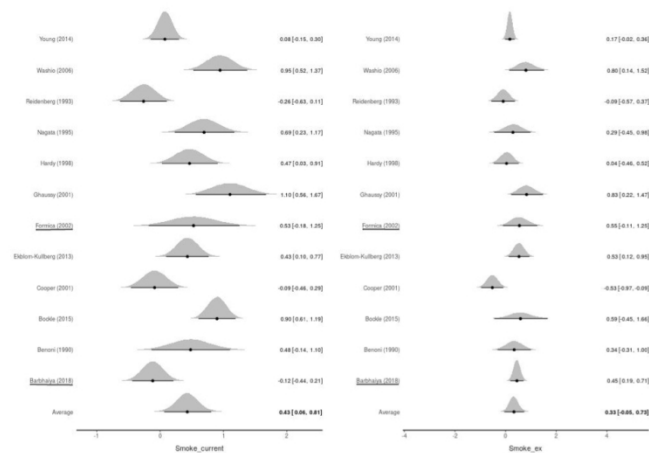Figure 1. Result of literature search

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Figure 2. Forest plots for the posterior distributions of effect sizes of the meta-analyses. Left panel: Current smokers versus non-smokers. Right panel: Former-smokers versus non-smokers. Cohort studies are underlined.

(ORs were transformed into Log-ORs so that the effect size [log-ORs] is approximately normally distributed in the meta-analysis. Log-ORs range from negative infinity to positive infinity with zero as the point of equal chance.)

Forest plots for the posterior distributions of effect sizes of the meta-analyses. Left panel: Current smokers versus non-smokers. Right panel: Former smokers versus non-smokers.
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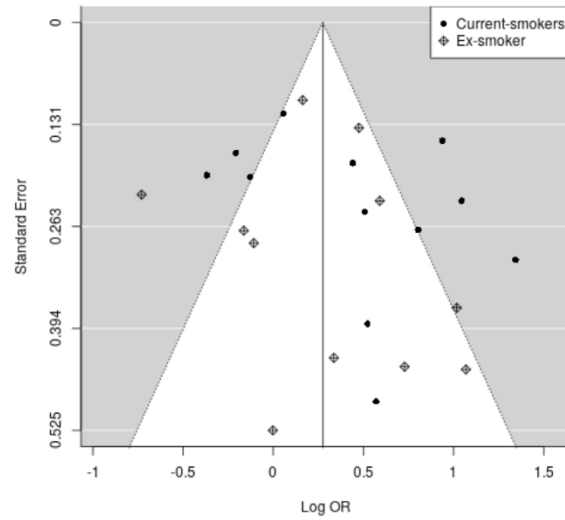
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Figure 3. Funnel plot for the effect sizes. Filled circles and crossed diamonds represent the effect sizes of current-smokers and former smokers, respectively.

Funnel plot for the effect sizes. Filled circles and crossed diamonds represent the effect sizes of current-smokers and former smokers, respectively.

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