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Association Between Cigarette Smoking and Systemic Lupus Erythematosus: An Updated Multivariate Bayesian Metaanalysis

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ABSTRACT. ***Objective.*** The association between cigarette smoking and the risk of systemic lupus erythematosus (SLE) remains a matter for debate. Additionally, the effect of the change of smokers' demographics on the risk of development of SLE over time has not been formally addressed. We aimed to examine the association between cigarette smoking and the risk of SLE by performing an updated metaanalysis.

Methods. A literature search using 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 metaanalysis was conducted by computing the log-OR between current and never smokers, and between former and never smokers. The average log-OR (subsequently converted to OR) and their corresponding 95% credible intervals (CrI) were calculated. The effect of publication time, sex, and age of patients with SLE on the effect sizes was examined by multivariate metaregression.

Results. Data aggregation of 12 eligible studies comprising 3234 individuals who developed SLE and 288,336 control subjects revealed a significant association between SLE occurrence and current smoking status (OR 1.54, 95% CrI 1.06–2.25), while only a non-significant trend was demonstrated between SLE occurrence and former smoking status (OR 1.39, 95% CrI 0.95–2.08). Publication time, sex, and the mean age of patients with SLE did not explain the heterogeneity of the effect sizes.

Conclusion. Current smoking status is associated with risk of SLE. Sex and age of patients with SLE had no significant effect on the risk of SLE over time.

Key Indexing Terms: Bayesian, cigarette, risk, metaanalyses, smoking, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex and etiologically multifactorial autoimmune disease. While genetic susceptibility and environmental factors play a pathophysiologically important role in the development of SLE[1], studies addressing 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].

Among various environmental factors, cigarette smoking has been implicated to be associated with the development of autoimmune conditions such as Graves' disease, rheumatoid arthritis, and primary biliary cirrhosis[3,4,5,6,7]. In the National Institute of Environmental Health Sciences 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 proinflammatory 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 make it harder to discern 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, the proportion of adults in the United States 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 sex, most of the smokers were male and aged between 25 and 44

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years[13]. Compared to the United States, 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 2 decades. In a Swedish study, the point prevalence of cigarette smoking among women was reported to be as high as 23.5%, compared to 19.5% in men[14]. In addition, the prevalence of cigarette smoking was on the rise among younger women, for whom 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 a 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]. Because SLE predominantly affects women during their prime years, sex 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, because the absolute risk of the development of SLE is very small in the 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. Because the sample sizes of published observational studies that investigated the association between SLE and smoking are generally small, statistical aggregation of data with the use of metaanalysis is one of the reasonable methodological approaches to increase the statistical power for examining the relationship. In keeping with the findings of the first metaanalysis published in 2004 by Costenbader, *et al*[18], the second and latest metaanalysis to date in the literature, authored by Jiang, *et al* in 2015 (comprising 12 studies), demonstrated a significantly increased risk of SLE in current smokers compared to never smokers [OR 1.56, 95% credible interval (CrI) of 1.26–1.95], and only a trend of increased risk of SLE among former smokers[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 metaanalyses.

In addition to the 3 issues related to the limitations intrinsic to the previous metaanalyses, the confounding effect of the global increase in young female smokers on SLE over time and the potential implications from the prospective Nurses' Health Study (NHS) cohorts[20,21] warrant a scientific update that re-addresses the association between cigarette smoking and SLE. It is necessary to encapsulate a clearer perspective regarding the effect 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 metaanalysis with the Bayesian approach. This approach allows the generation of a reliable effect size resulting from aggregating a mixture of case-control and cohort studies. In addition, the multivariate metaregression approach adopted in the current study offers a platform to identify demographic factors that are potentially associated with the relationship between cigarette smoking and the risk of SLE.

MATERIALS AND METHODS

Literature search. The first and second authors (MHC and IAN) performed an extensive literature search using relevant key words such as "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 (AM) supervised the overall literature search and resolved conflicts as to whether articles with potential eligibility issues should be included or excluded, and ensured the accuracy of the data extracted for subsequent metaanalyses.

Selection of studies and data extraction. The metaanalysis was conducted according to the Meta-analysis Of Observational Studies in Epidemiology guidelines for the statistical synthesis of observational data[22]. Observational case-control and cohort studies were included that examined the relationship between the risk of the occurrence of SLE with reference to healthy subjects and the various cigarette smoking statuses. Metaanalyses, 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 among the first, second, and last authors 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 metaanalyst (MWC) and the last author with the use of the Bayesian multivariate approach[23,24,26]. The log-OR of the current smokers versus never smokers, and the former smokers versus never smokers were calculated as the effect sizes, with each study contributing 2 effect sizes. As the "never smokers" status was in both studies, the 2 effect sizes were not independent. Most metaanalytic 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 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 metaanalysis. 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 variable estimates is 0.01. Therefore, the findings were robust to the use of priors.

Because there were only 2 cohort studies included in this metaanalysis,

Table 1. Studies included in the metaanalysis.

First Author (Year)	Study Type	Location	Mean Age, Yrs, Case/control	Female (%)	Case/control, n	Log-OR, Current Smoker†	Log-OR, Ex-smoker†
Reidenberg (1993)[36]	Case-control	USA	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
Böckle (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	USA	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	USA	NA	90.5	265/355	0.8810	0.4820
Ghaussy (2001)[44]	Case-control	USA	44/44	96.8	125/125	3.8367	2.7668
Formica (2003)[45]	Cohort	USA, African American	NA	100	67/53,924	1.7686	2.0720
Barbhaiya (2018)[21]	Cohort	USA, nurses from NHS*	49.2*	100	286/230,672	0.8131	1.6088

† OR against non-smokers. * Mean age at the start of the study. NA: not available; NHS: Nurses' Health Study.

we assumed that the heterogeneity variances of the case-control and cohort studies were the same. The number of iterations and warmups were 100,000 iterations and 3000 iterations, respectively. The generated data in the warmup period were discarded from the analysis. During the warmup 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 > 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-OR and the heterogeneity in SD and their corresponding 95% CrI of the posterior distributions were reported. We transformed the OR into log-OR so that the effect size (log-OR) is about normally distributed in the metaanalysis. After the metaanalysis, we converted log-OR back to OR for ease of interpretations. In contrast to OR, which range from 0 to positive infinity with 1 as the point of equal chance, log-OR range from negative infinity to positive infinity with 0 as the point of equal chance.

Because there have been demographic changes of smoking behavior, particularly with regard to sex and age over time as described, other variables were used as moderators in the multivariate models: 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. Publication bias was assessed by funnel plot. All statistical analyses in this metaanalysis 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 3636 articles through database searches. Among these studies, 3597 studies were excluded during our first-stage assessment because they (1) did not appear to address the occurrence of SLE as an outcome (n = 2959); (2) did not study smoking as a risk factor of SLE (n = 447); (3) did not have a comparator (n = 11); (4) were animal or *in vitro* studies (n = 55); and (5) were review articles (n = 89), and case reports and/or metaanalyses (n = 36). Thirty-nine papers were then subjected to the second-stage evaluation, of which 27 were excluded because they were (1) review articles (n = 12); (2) studies with data duplication (n = 3); (3) studies without stating clearly on smoking status (n = 3); (4) studies that only examined the pathogenesis of cigarette smoking in SLE (n = 3), and (5) studies that 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 that did not follow the American College of Rheumatology (ACR) criteria for diagnosis of SLE, and a study that mainly analyzed the effect 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 metaanalysis. These 12 studies comprise 10 retrospective case-control and 2 cohort studies. Of these 12 studies, 5 studied SLE in women only, while 5 studies combined the data for both men and women, and only 1 study had separate data for the 2 sexes 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-OR of the current smokers versus never smokers were first computed, and the difference between these 2 OR was subsequently calculated. The difference between the case-control and cohort studies in log-OR was 0.42, 95% CrI –0.60 to 1.43 (OR 1.52, 95% CrI 0.55–4.18). Similarly, the log-OR of former smokers versus never smokers in the case-control and cohort studies were calculated, and the difference between them was –0.31, 95% CrI –1.31 to 0.71 (OR 0.73, 95% CrI 0.27–2.03). Because there were only 2 cohort studies included in this metaanalysis, the calculated 95% CrI were quite wide (refer to Supplementary Figure 1, available from the authors on request, 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-OR of the current and former smokers against never smokers were 0.43, 95% CrI 0.08–0.80 (OR 1.54, 95% CI 1.06–2.25) and 0.33, 95% CrI –0.04 to 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 SD

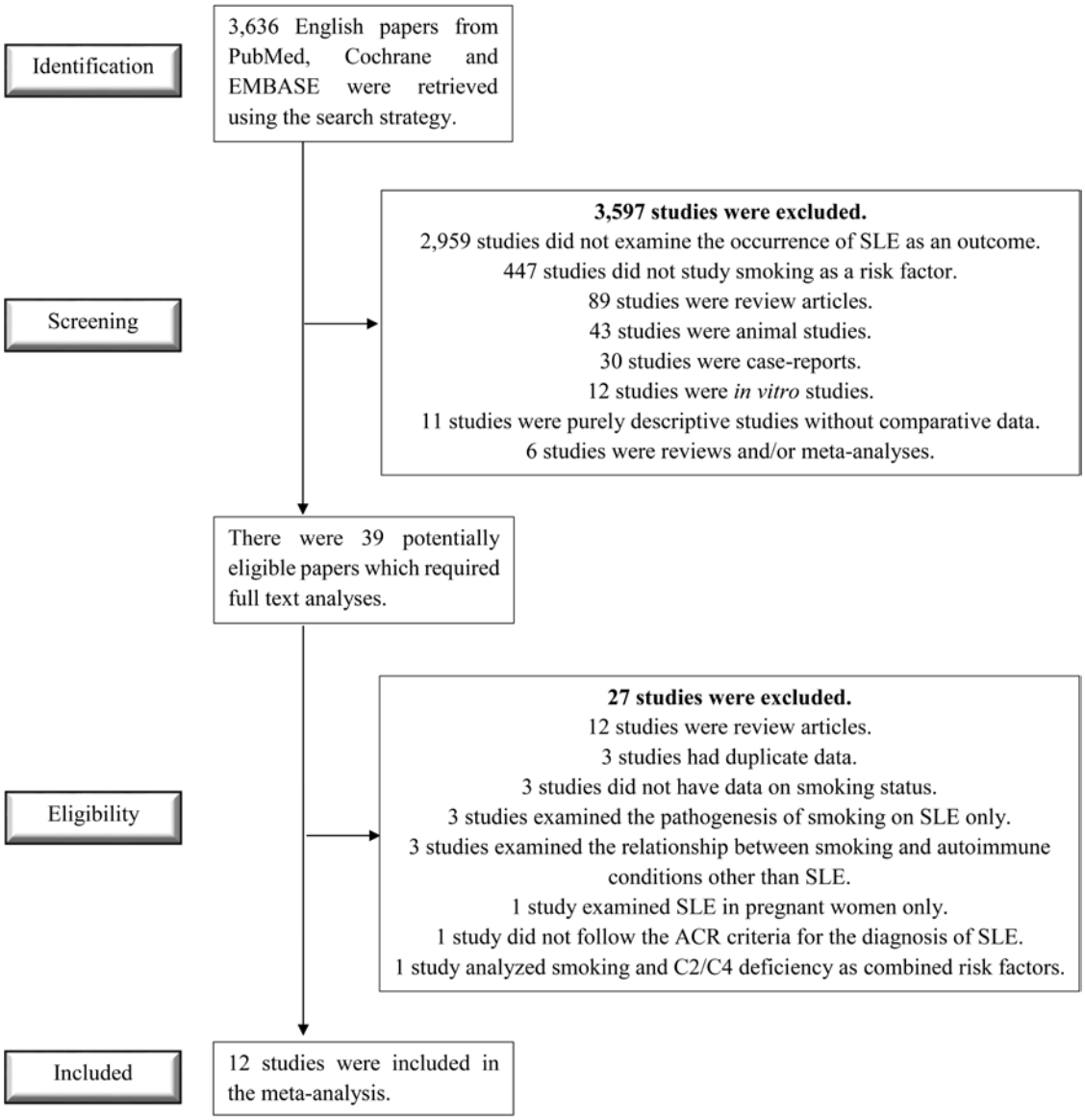

Figure 1. Results of literature search. SLE: systemic lupus erythematosus; ACR: American College of Rheumatology.

(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-OR of the current smokers and the former smokers was 0.55. Supplementary Figure 2 (available from the authors on request) shows the posterior distributions of the variables.

Figure 2 displays the forest plots of the studies and the average effects. The estimated difference between log-OR of the current versus never smokers and the former smokers versus never smokers was 0.10, 95% CrI –0.27 to 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.

Metaregression and publication bias. In the multivariate model, the estimated coefficients of year of publications in the log-OR of the current smokers and the former smokers were –0.00 (95% CrI –0.05, 0.04) and 0.02 (95% CrI –0.02, 0.07), respectively. When the mean age was used as the moderator, the estimated coefficients in the log-OR of the current smokers and the former smokers were –0.03, 95% CrI (–0.12, 0.07) and 0.01, 95% CrI (–0.08, 0.08), respectively. Regarding the proportion of the females followed in the studies, the estimated coefficients in the log-OR of the current smokers and the former smokers were 1.90 (95% CrI –3.48, 7.38) and 3.07, (95% CrI –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. Because only 12 studies were involved in this metaanalysis, more studies may

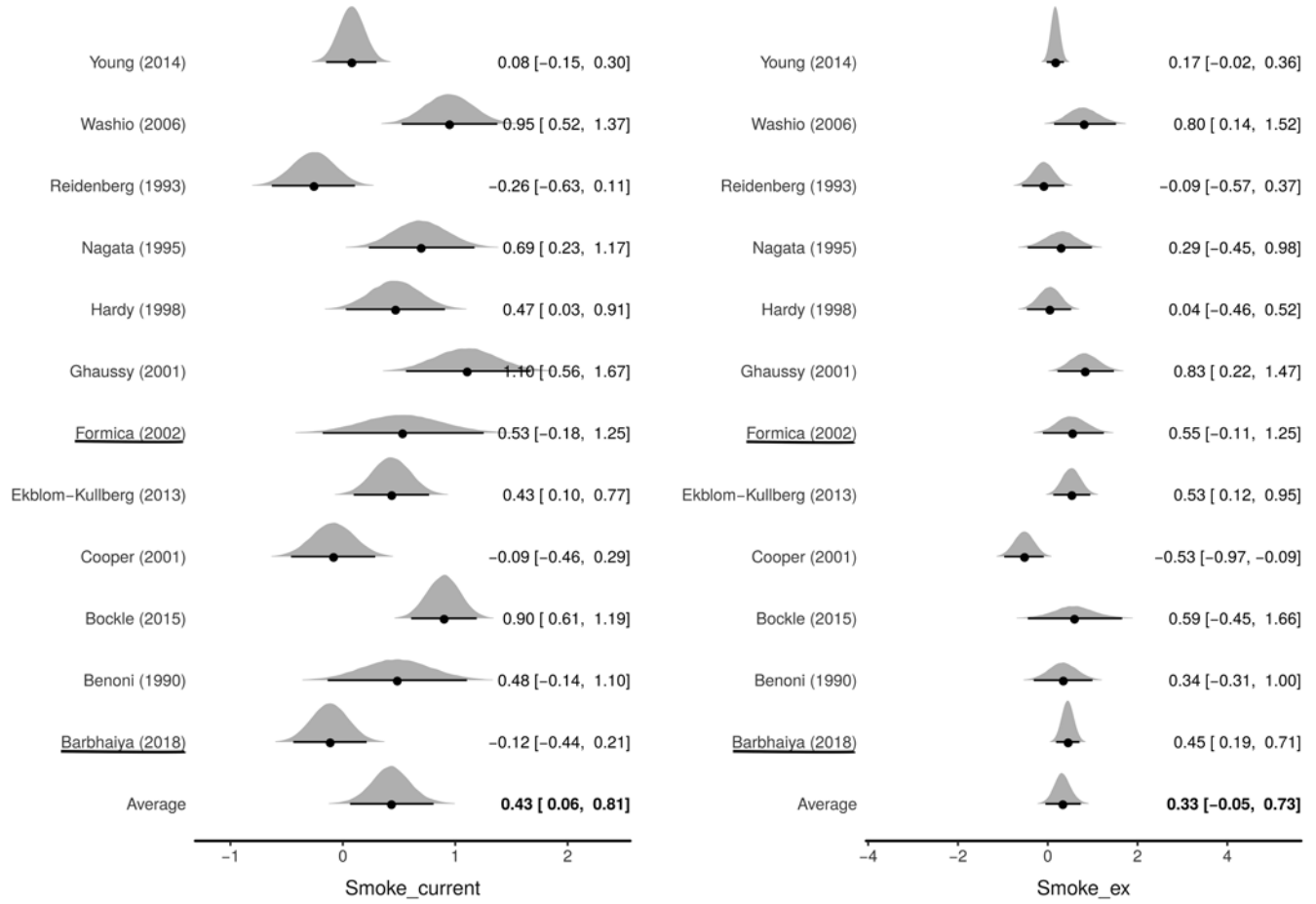

Figure 2. Forest plots for the posterior distributions of effect sizes of the metaanalyses. Left panel: Current smokers vs non-smokers. Right panel: Former smokers vs non-smokers. Cohort studies are underlined. [OR were transformed into log-OR so that the effect size (log-OR) is about normally distributed in the meta-analysis. Log-OR range from negative infinity to positive infinity with zero as the point of equal chance.]

be required to verify the patterns. However, there were limitations met in obtaining more than 2 cohort studies.

DISCUSSION

Our current Bayesian metaanalyses showed that current smokers were more likely to develop SLE as compared with patients with SLE 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 metaanalyses[18,19], we hereby confirmed that current exposure to cigarette smoke has a stronger effect than previous cigarette smoke exposure on the risk of SLE. In addition, unique to this metaanalysis, to our knowledge, our metaregression analysis revealed that publication time, age, and sex 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 2 decades. Results, however, are inconsistent. Two large prospective studies conducted in the USA did not reveal a statistically significant higher risk of development of SLE among smokers[45,46] and those who were exposed to cigarette smoke during early childhood[47]. Conversely, Asian studies appear to suggest otherwise and propose the basis of genetic polymorphisms that mediate the risk of SLE among 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 among current smokers against non-smokers[49]. Studied by the same group of investigators, the presence of at least 1 G allele of TNFRSF18rs1061622 was shown to confer an excess risk of 49% for SLE in smokers[50]. Because there were only 2 studies from Asia, we did not conduct a moderator test on it. When there are more Asian studies in the future, researchers may empirically test this hypothesis. Further, 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 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

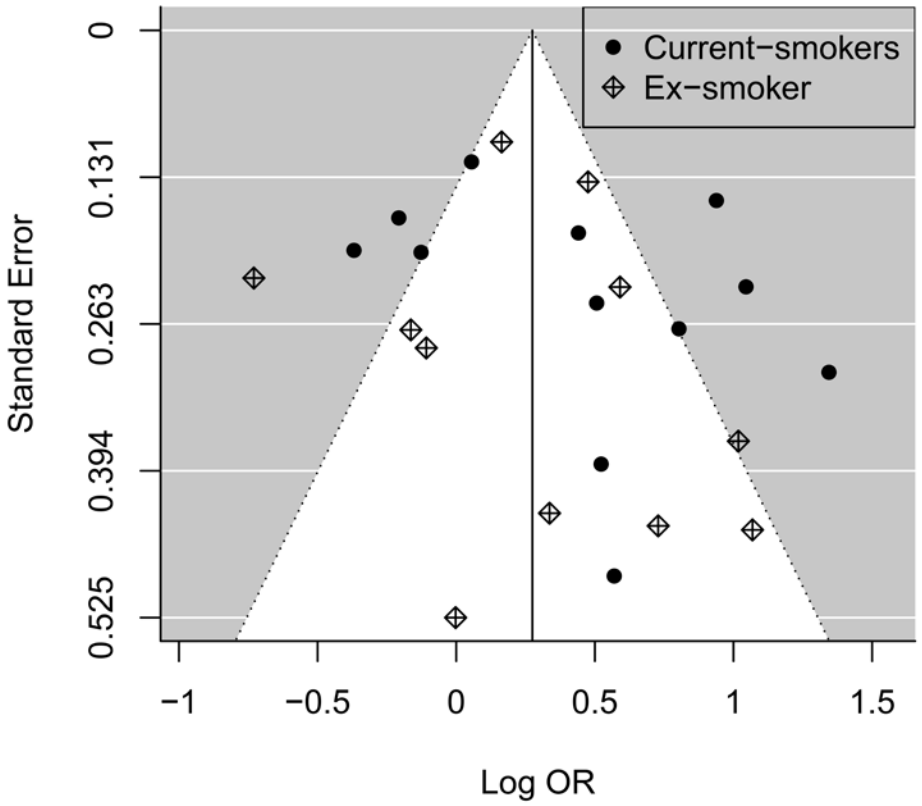

Figure 3. Funnel plot for the effect sizes. Filled circles and crossed diamonds represent the effect sizes of current smokers and former smokers, respectively.

trigger, interacts with susceptible genes and immune systems with proinflammatory propensity before exerting its influence to trigger SLE and perpetuate SLE-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 antimalarials, leading to increase in SLE disease activity overall, as well as acute, subacute, and chronic cutaneous SLE[63]. More recently, it has been observed that patients with SLE who smoked had reduced efficacy toward belimumab, a monoclonal antibody against B-cell activating factor that was approved by the US Food and Drug Administration as a treatment option of SLE[64].

Based on the results of the present study and the 2 published metaanalyses, as well as the harm of cigarette smoking as aforementioned, patients with SLE should be advised to stop smoking and against smoking initiation. Regarding 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]. Inflammatory changes reverse more rapidly upon cessation of low doses and short-term exposures to cigarette smoke than after heavy and longterm exposures[67].

There are several limitations to our study. First, this metaanalysis is a statistical aggregation of observational studies. 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 at 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. Therefore 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 metaanalysis. In addition, heterogeneity intrinsically exists in the metaanalysis. Thus caution should be taken when interpreting the findings. Last, while we were able to discern the effect 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 our study.

Results from our updated Bayesian metaanalysis confirmed that smoking is associated with the occurrence of SLE, with a statistically significant higher risk of SLE development among current smokers compared to people who never smoked. While there have been concerns over whether the changes of the demographics

of smokers over time might affect the occurrence of SLE, meta-regression did not suggest that age and sex have exerted an influence on the risk of SLE over time. While our study can trigger further investigation as to the potential mechanism mediating the effect 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.

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