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► **To cite this version:**

Dorian Parisis, Charlie Bernier, François Chasset, Laurent Arnaud. Impact of tobacco smoking upon disease risk, activity and therapeutic response in systemic lupus erythematosus: A systematic review and meta-analysis. *Autoimmunity Reviews*, 2019, 18, pp.1-25. <10.1016/j.autrev.2019.102393>. <hal-03489087>

HAL Id: hal-03489087

<https://hal.science/hal-03489087v1>

Submitted on 20 Jul 2022

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Impact of tobacco smoking upon disease risk, activity and therapeutic response in Systemic Lupus Erythematosus: a systematic review and meta-analysis

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest, no source of funding or sponsors or any relationship to organizations that could potentially influence the present work. The authors of the current study wish to state that tobacco companies were not provided with access to the drafts or to the final version of the manuscript.

FINANCIAL SUPPORT

None

ACKNOWLEDGMENTS

LA & DP conceived the study, were responsible for the study design and statistical analysis. DP, FC, and LA designed the search strategy, and DP and CB conducted the literature review. DP, CB and LA conducted the analysis. DP & LA drafted the initial manuscript, which was revised for critical content by all authors (DP, CB, FC, LA). All of the coauthors had access to data, reviewed the manuscript and provided critical input.

ABSTRACT (300 words)

Systemic lupus erythematosus (SLE) is a complex disease with variable presentations, course and prognosis. Published studies present conflicting data regarding the impact of cigarette smoking on SLE risk, disease activity, clinical manifestations and treatment response. We performed a comprehensive literature search using Medline, EMBASE and the Cochrane Collaboration database, and hand searches of relevant bibliographies. All original studies investigating the relationship between smoking and SLE were included in TABALUP. Two investigators systematically extracted data from the relevant studies. When possible, meta-analyses were performed. The meta-analysis of 9 case-controls studies show an increased risk of SLE in current-smokers compared to never-smokers (OR: 1.49 [95%CI: 1.06-2.08]), while former-smokers were not at increased risk of SLE. Data on passive smoking remains scarce and controversial. Pooled analysis studies did not find an over-risk of anti-dsDNA, anti-Sm or anti-SSA positivity according to smoking status. Tobacco smoking significantly reduced the therapeutic effectiveness of hydroxychloroquine in cutaneous lesions (pooled OR 0.53; 95%CI: 0.305-0.927) and belimumab in systemic manifestations (HR 0.10; 95% CI 0.02-0.43). In addition to its usual adverse effects, cigarette smoking is a risk factor of SLE and negatively influences the course of the disease and its treatment. We believe that smoking cessation should be one of the main target of physicians treating SLE patients.

KEY WORDS

Systemic Lupus Erythematosus, tobacco, cigarette smoking, risk, meta-analysis, systematic review

HIGHLIGHTS / KEY POINTS

- Current smoking (but not former-smoking) was associated with an increased risk of SLE
- Positivity for anti-dsDNA, anti-Sm, and anti-SSA was not influenced by the smoking status
- Tobacco smoking strongly reduced the therapeutic efficacy of hydroxychloroquine for cutaneous lupus and of belimumab for systemic manifestations of SLE.
- Smoking cessation should be a cornerstone of SLE treatment

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex disease with variable presentations, course and prognosis. As others systemic auto-immune diseases, pathogenesis of SLE remains unknown, but has been shown to result from complex multifactorial interactions between genetic, hormonal and environmental factors that result in the loss of self-tolerance.

Tobacco smoking is one the most prevalent habit and a well-known environmental factor associated with COPD, cancers and cardiovascular diseases. Its involvement in the induction and exacerbation of multiples systemic autoimmune diseases has been the subject of many publications in the past[1]. Despite the inherent limitations of studies design and heterogeneity, there is currently evidences for the role of tobacco smoking in diseases such as rheumatoid arthritis, Grave's disease, multiple sclerosis or Crohn's disease [1,2]. Moreover, in lupus patients, tobacco also increases comorbidities, such as atherosclerosis, with a similar risk as diabetes mellitus[3].

To date, published studies present conflicting data on the impact of cigarette smoking on SLE risk, auto-antibody profile, disease activity, damages and treatment response[1]. We performed a systematic review with meta-analysis (TABALUP) to investigate the relationship between smoking and lupus risk, antibodies profile and treatment efficacy in SLE patients.

2. MATERIALS & METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and the Meta-analysis of Observational studies in Epidemiology (MOOSE) guidelines. Given that the study did not involve primary data collection or analysis, the study was considered exempt from ethical committee review.

2.1. RESEARCH STRATEGY AND DATA SOURCES

We searched MEDLINE (via PubMed), EMBASE and the Cochrane Database of Systematic Reviews databases from inception to October 2017 for studies examining the association of lupus with tobacco smoking, without language restriction or additional filter. The search strategy used a combination of text words and thesaurus terms (supplementary document). The search was completed by the bibliography review of relevant paper to identify additional studies not indexed by the electronic databases. Attempts were made to contact authors to collect more information from potentially eligible abstracts but none of them sent additional data.

2.2. STUDY ELIGIBILITY

All original studies investigating the relationship between smoking and SLE were included in TABALUP. Studies were included in the analysis if: (i) they investigated the relationship between

smoking habits and lupus (case–control or cohort study); (ii) contained original data; and (iii) contained sufficient data to calculate odds ratios (ORs). We excluded the following: (i) studies containing duplicate or overlapping data; and (ii) case reports, case series, reviews, and letters to the editors.

2.3. STUDY SELECTION

We merged search results obtained from different databases using EndNote software, and removed duplicate references. Every titles and abstracts were independently screened by two investigators (DP and CB) to match the inclusion and exclusion criteria. If the information was insufficient, the decision was based on reading the full text of the article. First authors independently reviewed full-text of selected manuscripts to determine final study eligibility. In case of disagreement, the article was evaluated closely to reach a consensus. Remaining disagreements between the reviewers were resolved by a third party (LA).

2.4. STUDY QUALITY ASSESSMENT

The quality of each included paper was reviewed by the first two authors independently using the Newcastle-Ottawa Scale. In this meta-analysis, the studies with seven star-items or more were considered high-quality studies and those with six star-items or less were considered low quality studies.

2.5. DATA EXTRACTION

The following information was extracted from each paper by a reviewer (DP): author, year of publication, study population, demographics, sample size, smoking status, effect size data (OR or RR) and adjustment factors. When the data of interest could not be found in the articles, we contacted corresponding authors to request further information. When possible, smoking status was regarded as past, current or never smoked. If we could not obtain effect size data adjusted with other confounders, we estimated the crude OR from sample size data. For different studies of the same population (e.g., studies conducted on the same registry with overlapping years), we used the results of the most recent and detailed study. Extracted information was confirmed by a second reviewer (CB).

2.6. STATISTICAL ANALYSIS

Crude measures of effect or adjusted measures of effect were extracted from the individual studies. When possible, ORs and 95% confidence intervals (CI) were estimated for each study. Due to inherent biases in observational study designs, the random effect model was used to obtain the

combined OR and its standard error (SE). To assess heterogeneity among the studies included in meta-analysis, we used the I^2 statistics. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity. Publication bias was assessed by visual inspection of funnel plot. The leave-1-out sensitivity analysis was conducted to determine whether our assumptions or decisions had a major effect on the results of the review by omitting each study. All statistical analyses were completed using both JMP13 (SAS institute, Cary NC, USA) and MedCalc (MedCalc Softwares, Belgium) softwares. The criterion for statistical significance was considered to be two-sided p-value < 0.05.

3. RESULTS

3.1. FLOW CHART AND CHARACTERISTICS OF INCLUDED STUDIES

The flow diagram of study selection process is depicted in **Figure 1**. A total of 2493 potentially eligible references were identified using the described search strategy. After the exclusion of 604 duplicated articles, titles and abstracts of 1889 articles were reviewed. The remaining 229 papers were screened for eligibility. We excluded 78 references because they did not meet our inclusion criteria. Finally, 151 articles were included for further analysis.

3.2. TOBACCO SMOKING AND SLE RISK

Of the 151 studies identified by our literature search, 19 were selected for detailed review regarding this topic [4–25]. Two studies on the association of prenatal and early-life smoke exposure with SLE risk were set apart [6,11]. Another study on CYP1A1 and GSTM1 polymorphisms, smoking and SLE risk by Kiyohara *et al.* [16] was discussed separately. Two duplicate publications were excluded [24,25] and one study [12] was also ignored because it was conducted on the same registry than Barbhaiya *et al.* [7].

A total of 15 published articles (13 case-control studies and 2 cohort studies) examined the association of (active) smoking status with SLE risk [4,5,7–10,13–15,17–21,23]. Nine studies examined this association in former-smokers vs non-smokers [7–10,17–19,21,23]. Two case-control studies had been published as abstracts only [5,20]. General characteristics as geographic location, sample size, OR with 95% CI for risk of SLE, as well as adjusted factors to evaluate the risk of SLE in the selected articles are presented in **Table 1**.

Five out of 15 studies were conducted in Japan [8,10,15,20,23] and 5 in the US [4,7,9,18,21]. The remaining studies were done in Europe (Sweden [14], UK [19] and Finland [17]) and one in China [13].

Tobacco exposure was assessed by structured non-blinded interview [4,9,13,17–19] or self-administered questionnaires [7,8,10,14,15,21,23]. Smoker status was defined as smoking at least one cigarette per day for at least 3 months in 3 studies [9,18,19] and as smoking at least one cigarette per day for at least 12 months in 4 others studies [8,10,17,21]. Smoking definition was not clearly defined in 7 studies [5,7,13–15,20,23]. The evaluation of degree of exposure in each study varied significantly from study to study. In five studies, degree of exposure was not measured [4,5,13,15,20]. In all case-control studies, smoking status of cases was restricted to smoking exposures that preceded the date of diagnosis of SLE.

Lupus cases definition was based on the ACR 1997 classification criteria in all but one study [14].

Among those studies, 9 were appropriate for inclusion in our meta-analysis (table 2). All studies included in our analysis were case-control studies. We excluded 2 abstracts [5,20], 2 cohort studies [7,21] and 2 studies based on patients from the same study cohort (KYSS study) [10,20]. A total of 1738 cases and 3209 controls were included in the analysis. The forest plots of cumulative meta-analysis for the relationship between smoking status and SLE risk are shown in Figures 2A and 2B. For of the risk of SLE in current smokers versus never-smokers, the pooled OR was 1.49 (95%CI: 1.06-2.08) with significant heterogeneity ($I^2=78%$, $p=0.01$). For the risk of SLE in ever-smokers versus never-smokers, the pooled OR was 1.54 (95%CI: 1.06-2.23) with significant heterogeneity ($I^2=86%$, $p<0.0001$). For the risk of SLE in former-smokers versus never-smokers, the pooled OR was 0.97 (95%CI: 0.68-1.38) with significant heterogeneity ($I^2=63%$, $p=0.01$). The funnel plots demonstrated potential publication bias on this topic, as some small negatives studies were not identified in the published literature.

Ten out of 15 studies investigated the dose-effect of cigarette smoking. Only 4 of them, which included 3 original case-controls studies, showed such effect [8,10,19,23].

3.3. TOBACCO SMOKING AND AUTOANTIBODY PROFILES

Of the 151 studies identified by our literature search, 15 were selected for detailed review regarding this topic [26–40]. Characteristics of those studies are presented in table 3. Two of them were duplicate publications of previous results found in two others selected references, leading to additional information. Nine of them provided data suitable for the meta-analysis. Our meta-analysis did not demonstrate an increased risk of anti-dsDNA, anti-Sm or Anti-SSA positivity according to

smoking status (**Figure 3**). For the odds of SLE anti-dsDNA positivity in current-smokers versus ever-smokers, the pooled OR was 0.90 (95% CI: 0.42-1.93) with significant heterogeneity ($I^2=91%$, $p<0.0001$). In ever-smokers vs never-smokers, the pooled OR was 1.03 (95% CI: 0.85-1.25) without heterogeneity ($I^2=13%$, $p=0.33$). In former-smokers vs never-smokers, the pooled OR was 1.06 (95% CI: 0.62-1.82) with significant heterogeneity ($I^2=73%$, $p=0.01$).

For the odds of SLE anti-Sm positive in current-smokers versus never-smokers, the pooled OR was 0.58 (95%CI: 0.32-1.05) with significant heterogeneity ($I^2=85%$, $p=0.001$). Funnel Plot is suggestive of potential publication bias. The odds ratio of ever-smokers vs never-smokers and former-smokers vs never-smokers studies were not significant (data not shown).

For the odds of SLE anti-SSA positive in current-smokers versus non-smokers, the pooled OR was 0.79 (95%CI: 0.50-1.25) with significant heterogeneity ($I^2=69%$, $p=0.04$). Funnel Plot is not suggestive of potential publication bias. The odds ratio of ever-smokers vs never-smokers and former-smokers vs never-smokers studies were not significant (date not shown).

Four studies out of 13 were not included in this meta-analysis, either because data were missing or were provided as graphs, odd-ratios or ANA titers, not suitable to be pooled with others studies [28,37,39,40].

3.4. TOBACCO SMOKING AND TREATMENTS EFFICACY

Of the 151 studies identified by our literature search, 17 were selected [41–57] for detailed review regarding this topic.

Twelve studies investigated the effect of smoking on the efficacy of antimalarial drugs (primarily hydroxychloroquine) for treating cutaneous lesions in lupus patients. Characteristics of those studies are presented in **Table 4**. As dermatologic studies, Cutaneous Lupus Erythematosus (CLE) patients as well as SLE patients with dermatologic manifestations were included. Main endpoints and outcome evaluations varied among studies: five studies used qualitative clinical evaluation as their primary endpoint, 6 of them used the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)[58] and the last used study-specific criteria. In 4 studies, (near-)total healing of cutaneous lesions is also used as primary endpoint. Smoking status was mainly “current” vs “not-current” smokers (former- and never-smokers), except in two studies where smoking definition was ever vs never smokers. **Figure 4** shows the meta-analysis of the 11 observational studies investigating the effect of tobacco smoking on antimalarial cutaneous effect. This meta-analysis further updates a previous meta-analysis from our group [59]. The pooled OR based on a random-effect model for cutaneous favorable outcome in smokers vs non-smokers was 0.53 (95%CI: 0.305-0.927) with significant heterogeneity ($I^2=66%$, $p<0.002$). Visual inspection of the funnel plot did not reveal

obvious asymmetry for all publications. The 2 additional studies were unfortunately not meta-analyzable [52,54].

Five studies investigated the relationship between hydroxychloroquine blood concentration and cigarette smoking in patients treated for SLE or others connective tissue diseases [42–44,48,53]. The rationale behind this is that resistance of cutaneous lupus to hydroxychloroquine might be explained by modification of the metabolism of this drug, as cigarette smoking is a potent inducer of cytochrome P450. Those studies, including a total of 1497 patients, did not show any significant relationship between cigarette smoking and hydroxychloroquine concentrations.

Finally, one study [56] provides data on real-life effect of Belimumab in SLE with emphasis on predictors of treatment response. Fifty-eight patients were enrolled and followed longitudinally. Response to treatment was defined based on the SLE response index (SRI). After adjustment for baseline SLEDAI-2K scores and prednisone equivalent dosages, ever smokers had a decreased probability to attain SRI-4 response compared with never smokers (HR 0.46; 95% CI 0.22- 0.95), as well as current smokers compared with former smokers (HR 0.10; 95% CI 0.02-0.43).

4. DISCUSSION

Regarding the risk of SLE, we have shown in our meta-analysis of 9 case-control studies that current smokers have an increased risk of developing SLE, compared to non-smokers (OR 1.49 [95%CI: 1.06-2.08]). Similar results were observed when comparing ever versus never-smokers (OR 1.54 [95%CI: 1.06-2.23]). The increased risk of developing SLE appears to be associated with current tobacco use but not former-smoking.

To date, we are aware of 2 others reviews with meta-analysis addressing the same clinical question [60,61]. In Costenbader *et al.*, 9 studies (7 case-control and 2 cohort studies) were included. In Jiang *et al.*, 13 studies (11 case–control studies and 2 cohort studies) were included.

Despite the fact that we meta-analyzed contingency data (and not ORs) and more drastically selected the included studies, similar results similar were found.

The mechanisms involved in the link between smoking and SLE development remain speculative. According to current theories, tobacco smoking can promote the appearance of SLE by various mechanisms [62]. Combustion byproducts of tobacco contain thousands of toxic components, including tars, nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons among others. These toxins and induced oxidative stress can react with DNA molecules and increase cell apoptosis. This increase of the apoptotic material containing modified DNA in individuals predisposed to a defective elimination of apoptotic blebs could theoretically induce systemic auto-immunity. This transitory effect linked to smoking could explain the disappearance of the risk in the smokers who have been weaned for over a year (“former-smokers”).

Regarding ANA profiles, our meta-analysis of 9 case-control studies did not demonstrate an increased risk of anti-dsDNA, anti-Sm or Anti-SSA positivity according to smoking status. A link between smoking status and the presence of antinuclear antibodies (and especially anti-dsDNA) remains unclear in epidemiological studies. Results from Barbhaiya et al. [30], are often mentioned to highlight the increase in SLE dsDNA-positive in smokers. This study shows that this risk is linked to a consumption of more than 10 pack-years and disappears with smoking cessation. These results are used to support the hypothesis that active smoking, by modifying DNA and increasing its release via increased apoptosis, NETosis or necrosis, will induce a loss of tolerance and appearance of antibodies against double-stranded DNA in genetically susceptible individuals[1]. In addition, tobacco has been shown to be an environmental factor associated with survivin expression along with various autoimmune diseases. Survivin enhances antigen presentation, maintains persistence of autoreactive cells, and supports production of autoantibodies[63].

No study about the impact of tobacco smoking upon the efficacy of hydroxychloroquine for the systemic manifestations of SLE was found. Following our previous meta-analysis [59], 2 new studies were published [50, 52]. One of them had the design required to be included in the update of the previous meta-analysis [52]. Unfortunately, this study was only published as a congress abstract and did not provide enough information to be pooled. However, their conclusion goes in the same direction as the meta-analyzed data. Interestingly, cutaneous lupus differs from systemic lupus in the very high prevalence of smoking and the sex ratio. The conclusions of this meta-analysis may therefore not be generalizable to all lupus patients.

In the literature, 5 studies demonstrate that the pharmacokinetics of hydroxychloroquine is not influenced by cigarette smoking. Mechanisms by which tobacco smoking may interfere with hydroxychloroquine remain speculative. Others interactions such as modification of lysosomal accumulation of antimalarial drugs or increased disease activity must be investigated. Current data supports the hypothesis of a pharmacodynamic interaction between hydroxychloroquine and nicotine. Antimalarials accumulate in endosomes, bind nucleic acids and inhibit signaling via TLR-7 and TLR-9 [64]. On the other hand, nicotine increases the reactivity of TLR-9 to nucleic acids [65].

Finally, only one study [56] investigated the impact of tobacco smoking on response to belimumab and the same authors [66] showed that the negative effect of tobacco on the efficacy of belimumab is consistent for muco-cutaneous manifestations (SLEDAI2K items and CLASI) Smoking cessation should therefore be advised prior to introduction of such costly treatment to maximize efficiency.

Case-control studies, by their retrospective design, may suffer from several biases. Prospective cohort studies are usually underpowered to highlight significant differences. Finally, as demonstrated in this review, the definition itself of active smoking may differ from study to study. Tobacco smoking is itself a heterogeneous phenomenon in time and place. The composition and quality of tobacco may vary from one period or region to another. Finally, smoking is not limited to controlled smoke inhalation as in a laboratory study. As a social phenomenon, tobacco smoking is linked to many confounding factors such as socio-economic level, stress, consumption of other stimulating substances, bad health habits or lack of therapeutic adherence. All these elements combined the heterogeneity observed across the different studies.

5. CONCLUSION

In addition to its usual adverse effects, cigarette smoking appears to be an important risk factor for SLE and negatively influences the course of the disease as well as treatment efficacy. Based on these findings, it seems that smoking cessation remains a highly cost-effective piece of advice that could improve the management of SLE patients from any point of view and lead to many other benefits. Therefore, we believe that smoking cessation should be one of the primary concerns of physicians treating SLE patients and must be a cornerstone of treatment. More in-depth studies regarding the impact of smoking on SLE are needed and require harmonization of definitions of smoking status and standardization of publication of available data for meta-analysis.

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Table 1: Tobacco smoking as a risk factor of SLE - Literature Review results as shown in original articles

First author	Year	Geographic location	Number Cases/ Controls	Dose-response relationship	OR (95% IC) Current vs Never smokers	OR (95% IC) Ex-smokers vs Never smokers	OR (95% IC) Ever smokers vs Never smokers	Adjusted factors
Case-control studies								
Aggarwal <i>et al.</i>	2013	NA	821	821	Not assessed	-	-	1.27 (p=0.02) Age within five years, gender and ethnicity
Bengtsson <i>et al.</i>	2002	Sweden	85	205	No	-	-	1.8 (0.9-3.6) Age, gender, hypertension, drug allergy, familial history, skin type, blood transfusion, alcohol.
Cooper <i>et al.</i>	2001	USA	265	335	No	1.1 (0.7-1.7)	0.6 (0.4-1.0)	- Age, gender, race, state and education
Ekblom-Kullberg <i>et al.</i>	2013	Finland	205	862	No	1.14 (0.81-1.59)	1.35 (0.92-1.97)	1.65 (1.17-2.33) Age, gender, geographic vicinity
Ghaussy <i>et al.</i>	2001	USA	125	125	No	-	3.62 (1.22-0.70)	6.69 (2.59-7.28) Age, gender, race, past income, family history and education
Hardy <i>et al.</i>	1998	UK	150	300	Yes	1.95 (1.14-3.31)	1.23 (0.70-2.17)	- Age, gender and social class
Kiyohara <i>et al.</i>	2009	Japan	151	424	Yes	1.46 (0.54-3.90)	3.32 (2.00-5.53)	2.86 (1.78-4.60) Age, region, and alcohol intake.
Kiyohara <i>et al.</i>	2012	Japan	171	492	Yes	3.06 (1.86-5.03)	2.49 (0.97-6.44)	2.96 (1.85-4.76) Age, region, drinking status, and education background
Nagata <i>et al.</i>	1995	Japan	282	292	Yes	2.31 (1.34-3.97)	1.07 (0.37-3.10)	- Age, gender, geographic vicinity
Zou <i>et al.</i>	2014	China	260	260	Not assessed	-	-	NA Age, gender, term birth, eating habits, sun light exposure, residence, HBV vaccine,...
Nakano <i>et al.</i>	2017	Japan	59	244	Not assessed	-	-	2.14 (1.10-4.16) Age and gender
Reidenberg <i>et al.</i>	1993	USA	195	338	Not assessed	NA	NA	NA Age and gender
Washio <i>et al.</i>	2017	Japan	160	660	Not assessed	-	-	2.60 (1.76-3.85) Age, region and alcohol drinking
SUBTOTAL			2929	5358				
Cohort studies								
Barbhaiya <i>et al.</i>	2017	USA	286	230386	No	1.14 (0.81-1.61)	1.18 (0.89-1.55)	- Sex, gender, race, BMI, zip code-level median household, oral contraceptive use, age at menarche (≤10 vs >10 years), menopausal status and PMH use
Formica <i>et al.</i>	2003	USA	67	64433	No	1.6 (0.8-3.3)	1.6 (0.8-3.3)	- Age, gender, education, oral contraceptive use, alcohol consumption, and body mass index
SUBTOTAL			353	294819				

NA= not available; PMH = postmenopausal hormone

Table 2: Tobacco smoking as a risk factor of SLE - Characteristics of included studies

First author	Year	Localisation and case finding	Controls selection - matching	% female	Reponse rate Cases/controls	Duration between diagnosis and study	Newcastle-Ottawa Quality Assessment Scale		
							Selection	Comparability	Exposure
<i>Zou et al.</i>	2014	China (Anhui Province) Random computed sampling	Random from same counties Matched for gender and age	91.5	55.2% / NA	NA	★★★★	★★	★
<i>Ekblom-Kullberg et al.</i>	2013	Finland (Helsinki, Espoo and Vantaa) Helsinki University Central Hospital registry	Finnish health examination survey From same cities	100	NA / NA	13 (0-39) years	★★★★	★	★
<i>Kiyohara et al.</i>	2012	Japan (Kyushu) Kyushu Sapporo SLE (KISS) Study	- Nursing college students and care workers - Participants at a health clinic	100	NA / NA	11.9 ± 8.55 years	★★★★	★	★
<i>Bengtsson et al.</i>	2002	Sweden (Lund-Orup Healthcare District) Incidents cases – 1981-1999	Computerized population register Matched for date of birth	100	93% / 53%	9 (0-18) years	★★★★	★★	★
<i>Cooper et al.</i>	2001	USA (North Carolina and South Carolina) Carolina Lupus Study (incidents cases 95-99)	Driver's license records Matched for gender, age (+/-5y) and state	90	93% / NA	13 months	★★★★★	★★	★
<i>Ghaussy et al.</i>	2001	USA (New Mexico) University New Mexico SLE Database	GP outpatient clinics Matched for gender and age (+/-5y)	96.8	91% / 95%	8.69 years	★★	★★	★★
<i>Hardy et al.</i>	1998	UK (Nottingham) Geographically complete cohort	FHSA register (resident attached to a GP) Matched for gender and age	92	95% / 39%	NA	★★★★	★★	★
<i>Nagata et al.</i>	1995	Japan Intractable Diseases Registration - 1988-1990	Check-up list of same public health center Matched for gender and age (+/- 5y)	100	NA / NA	NA	★★	★★	★
<i>Reidenberg et al.</i>	1993	USA (Philadelphia) SLE cases - 1985-1987	- Friends matched for gender and age (+/- 5y) - Outpatients matched for gender and age (+/-5y)	89	NA / NA	< 3 years	★★★★	★★	★

NA= not available; SLE = Systemic Lupus Erythematosus; +/-5y = within 5 years. GP = General Practitioner

Table 3: Tobacco smoking and ANA profile - Literature Review

First author	Population	SLE (n)	Female (%)	Current (%)	Age (years)	Quality (NOQAS)	ANA of interest		
							dsDNA	Sm	SSa
Freemer <i>et al.</i> (2005)	USA – UCSF Lupus Genetics Project	410	91	–	33.0 ± 13.2	7★	Xb		
Rubin <i>et al.</i> (2005)	USA – New Mexico Lupus Cohort	119	100	26	NA	6★	Xa		
Smith <i>et al.</i> (2011)	USA - University of Chicago	214	NA	–	NA	<i>Abstract</i>	Xc	Xc	Xc
Jolly <i>et al.</i> (2013)	Multinational cohort	NA	NA	12.7	NA	<i>Abstract</i>	Xa		
Eklblom-Kulberg <i>et al.</i> (2014)	Finland – Helsinki Univ Central Hospital	223	92	–	NA	5★	Xc		
Gustafsson <i>et al.</i> (2014)	Sweden – Karolinska Univ Hospital	367	86	18.8	NA	7★	Xa		Xa
Young <i>et al.</i> (2014)	USA - Lupus Family Registry and Repository	1242	89	–	41.7 ± 13.2	7★	Xb	Xb	Xb
Arroro-Avila <i>et al.</i> (2015)	USA - PROFILE cohort	2322	91	15.4	34.4 ± 12.8	5★		Xa	
Xu <i>et al.</i> (2015)	China – CSTAR registry	730	90	8.9	NA	7★	Xa	Xa	Xa
Bourre-Tessier <i>et al.</i> (2015)	Canada – 1000 Canadian Faces cohort	1346	91	14	47.1 ± 14.3	5★	Xa	Xa	Xa
Montes <i>et al.</i> (2016)	Brazil – Antonio Pedro	105	96	61.9	40.7 ± 11.4	5★	Xa	Xa	
Sanchez-Guerrero <i>et al.</i> (2017)	NC – incidental cohort since 1970	487	87	32.1	36.1 ± 13.3	<i>Abstract</i>	Xa	Xa	Xa
Arbhaiya <i>et al.</i> (2017)	USA – NHS and NHSII	286	100	–	49.2 ± 10.3	6★	Xa		
TOTAL		7850+							

NA= not available; NOQAS = Newcastle-Ottawa Quality Assessment Scale; ANA = antinuclear antibodies; dsDNA = double-strand DNA; Sm = anti-Smith antibody; SSa = anti-SSa/Ro antibody; NHS = Nurse Health Study

Xa = raw data

Xb = data shown as graph or odds ratio only, no extractable data for meta-analysis

Xc = data shown as antibodies titers, no extractable data for meta-analysis

Table 4: Tobacco smoking as a risk factor of SLE - Literature review results as shown in original articles

Study	Study design and population							NO QAS	Improvement				(near)complete response			
	Type	N	Mean Age	Female %	SLE %	Endpoint (months)	Outcome criteria		Smokers		Non-smokers		Smokers		Non-smokers	
									Events	Total	Events	Total	Events	Total	Events	Total
Rahman and al. (1998)	retrospective	34	NA	NA	?	6	Clinical	NA	-	-	-	-	3	17	9	17
Jewell and al. (2000)	retrospective	61	NA	70.5	?	≥ 2	Clinical	6★	16	40	19	21	-	-	-	-
Lardet and al. (2004)	prospective	28	35.5 (19-68)	75	17	2	Study	6★	15	21	2	4	?	?	?	?
Kreuter and al. (2009)	retrospective	36	47.4 (24-70)	58	0	3	CLASI	7★	-	-	-	-	16	28	7	8
Wahie and al. (2011)	retrospective	200	40 (16-81)	80	?	6	Clinical	6★	77	125	43	75	-	-	-	-
Frances and al. (2012)	prospective	300	46.6 (12-85)	84.3	39	18	Clinical	6★	41	124	73	176	55	102	47	112
Piette and al. (2012)	prospective	88	NA	NA	?	6	CLASI	6★	21	48	16	40	-	-	-	-
Yokogawa and al. (2012)	retrospective	27	40.7 (18-58)	85	63	4	CLASI-RC	6★	6	7	17	20	?	7	?	20
Kuhn and al. (2014)	retrospective	838	50.2	77	?	NA	Clinical	6★	313	379	225	238	-	-	-	-
Kosi and al. (2015)	retrospective	65	NA	78.5	35	NA	CLASI	4★	18	48	9	17	-	-	-	-
Porta and al. (2016)	prospective	37	NA	NA	100	3-6-12	CLASI	NA	Adding quinacrine. Rate of CR higher in smokers (OR 5, p=0.024)							
Nanes and al. (2017)	retrospective	63	NA	NA	?	NA	CLASI	6★	-	-	-	-	-	-	-	-

NA= not available; NOQAS = Newcastle-Ottawa Quality Assessment Scale; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-RC = CLASI Response Criteria; CR = Clinical Response

FIGURE 1 Flowchart of the TABALUP study

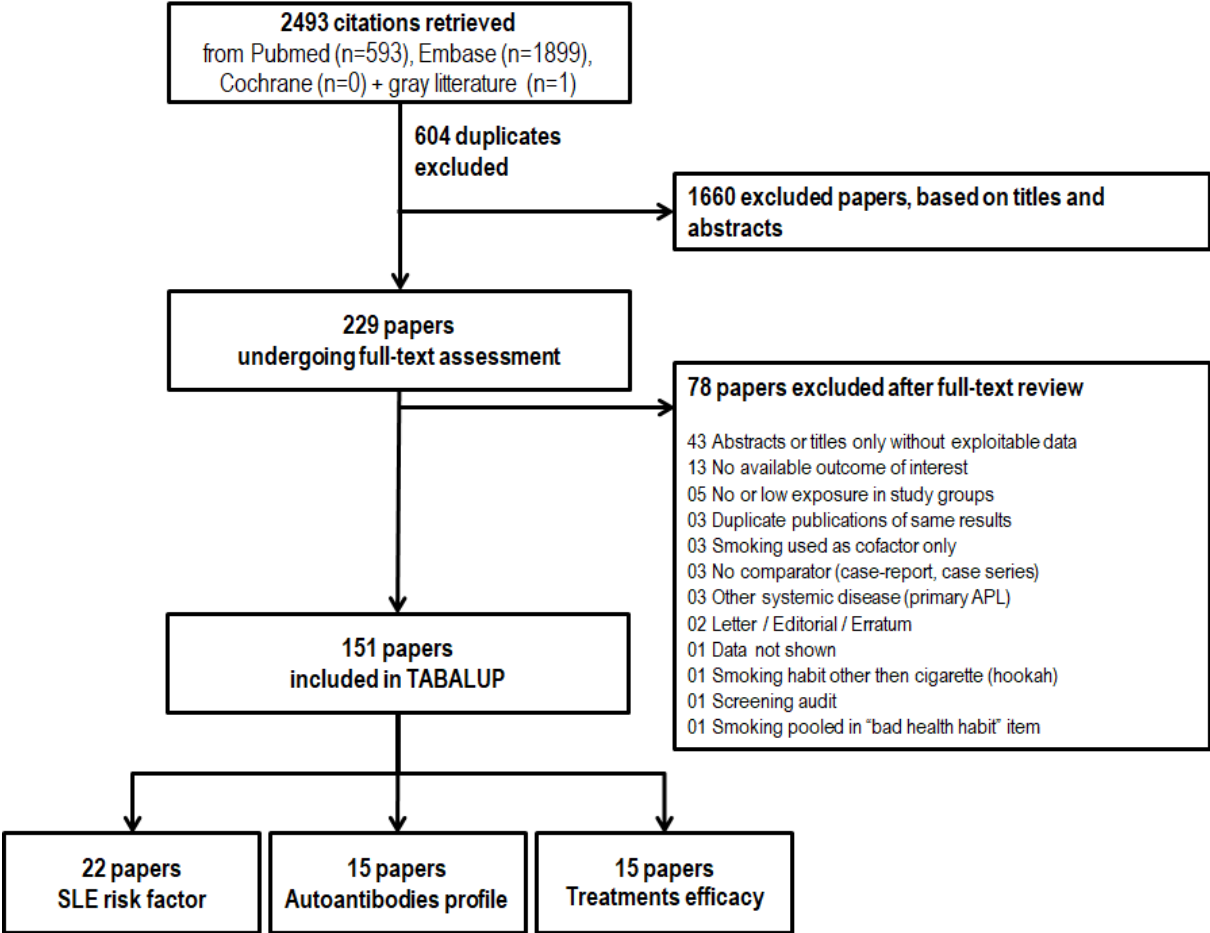


FIGURE 2A. Tobacco as SLE risk factor - EVER vs NEVER smokers

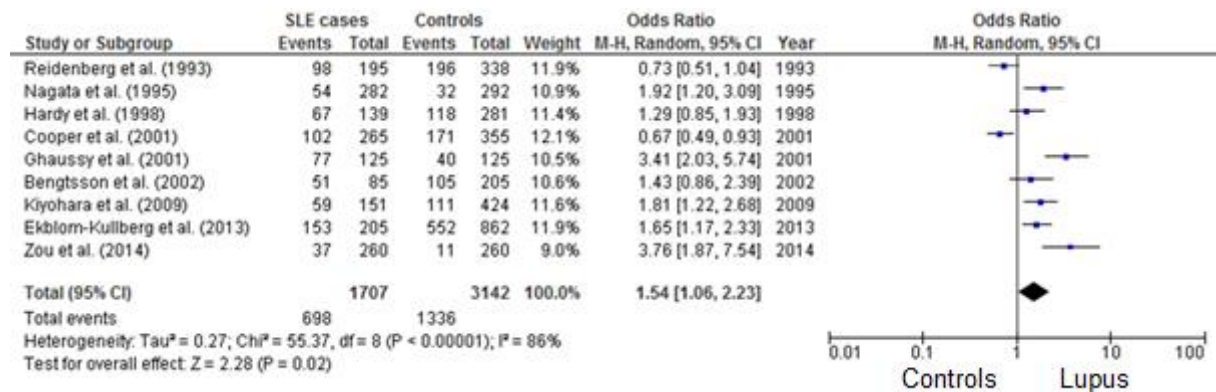


FIGURE 2B. Tobacco as SLE risk factor - CURRENT vs NEVER smokers

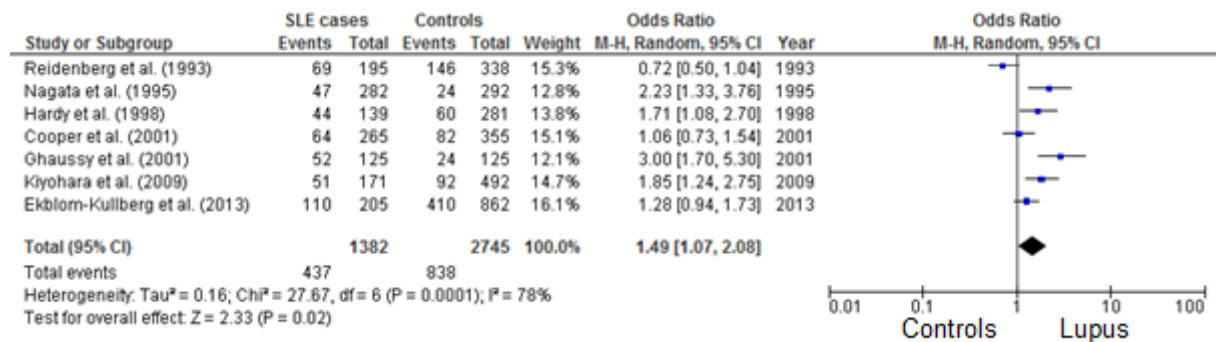


FIGURE 3A. Anti-dsDNA positivity - EVER vs NEVER smokers

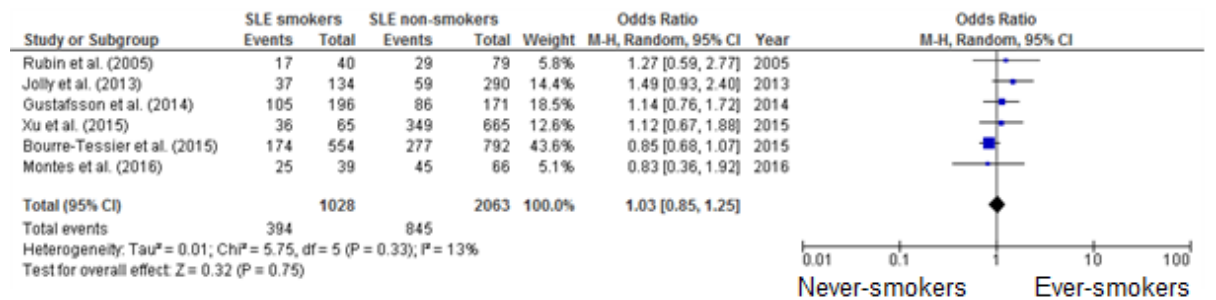


FIGURE 3B. Anti-Sm positivity - CURRENT vs NEVER smokers

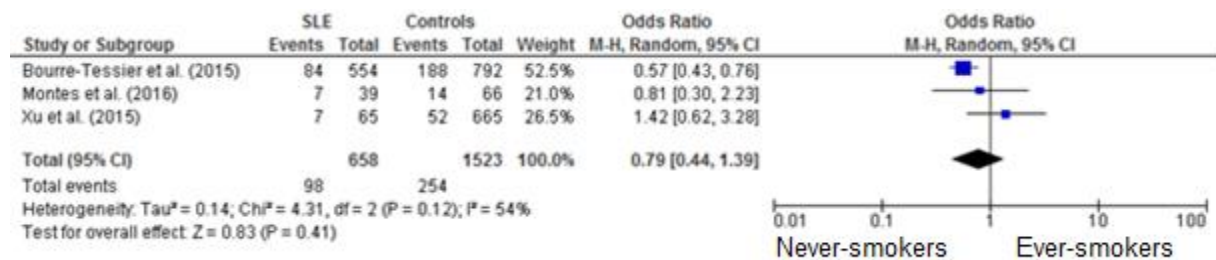
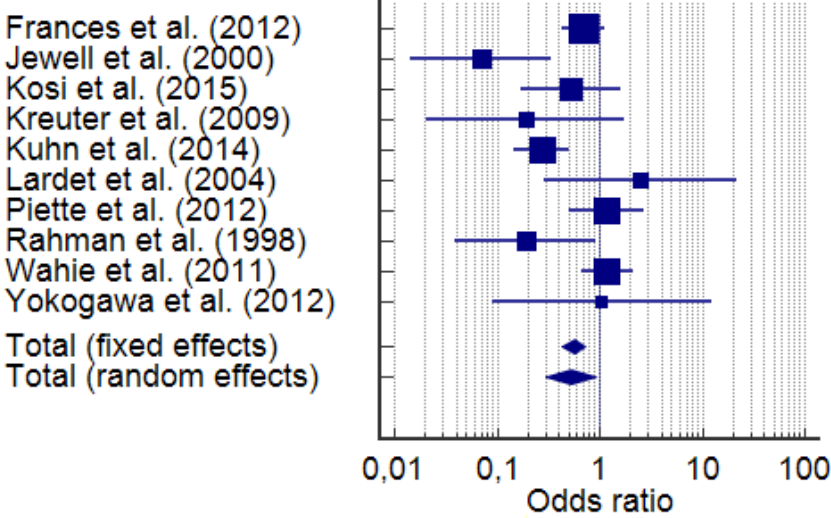


FIGURE 4. CLE response to Hydroxychloroquine - CURRENT vs NEVER



SUPPLEMENTARY DOCUMENT

SEARCH STRATEGY

PUBMED

((("Nicotine"[Mesh] OR "Tobacco Use Disorder"[Mesh] OR "Smoking"[Mesh] OR "Tobacco Smoke Pollution"[Mesh] OR "Tobacco"[tiab] OR "cigarette"[tiab] OR "smoking"[tiab]) AND ("Lupus Erythematosus, Systemic"[Mesh] OR "Lupus Erythematosus, Cutaneous"[Mesh] OR "Lupus Vasculitis, Central Nervous System"[Mesh] OR "Lupus Nephritis"[Mesh] OR "Lupus"[tiab] OR "Lupus-like"[tiab])).

EMBASE

((('nicotine'/exp OR 'nicotine':ab,ti OR 'tobacco dependence'/exp OR 'tobacco dependence':ab,ti OR 'tobacco use'/exp OR 'tobacco use':ab,ti OR 'smoking'/exp OR 'smoking':ab,ti OR 'passive smoking'/exp OR 'passive smoking':ab,ti OR 'tobacco'/exp OR 'tobacco':ab,ti OR 'cigarette'/exp OR 'cigarette':ab,ti) AND ('systemic lupus erythematosus'/exp OR 'systemic lupus erythematosus':ab,ti OR 'skin lupus erythematosus'/exp OR 'skin lupus erythematosus':ab,ti OR 'cutaneous lupus erythematosus':ab,ti OR 'discoïd lupus erythematosus'/exp OR 'discoïd lupus erythematosus':ab,ti OR 'lupus':ab,ti))