**Smoking, alcohol consumption and disease-specific outcomes in rheumatic and musculoskeletal diseases (RMDs): systematic reviews informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs**

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Key messages

What is already known about this subject?

• Smoking and alcohol consumption are well-established risk factors for many adverse health outcomes in the general population.

What does this study add?

• Our study summarized current literature on the association between smoking and alcohol consumption with disease-specific outcomes in 7 RMDs and suggests that smoking and alcohol consumption are detrimental to symptoms, function, disease activity, disease progression and occurrence of comorbidities.

How might this impact on clinical practice or future developments?

• Health professionals should encourage and support people with RMDs to stop smoking and should inform them about the detrimental effects of smoking and alcohol consumption.

• More studies assessing the effectiveness of interventions on smoking cessation and alcohol consumption reduction on disease-specific outcomes in people with RMDs are required.

**Abstract** (word count: 250)

**Background:** A EULAR taskforce was convened to develop recommendations for lifestyle behaviours in rheumatic and musculoskeletal diseases (RMDs). The aim of this paper was to review the literature on the relationship between smoking and alcohol consumption with regard to RMD-specific outcomes.

**Methods:** Two systematic reviews were conducted to identify systematic reviews and meta-analyses, published between 2013 and 2018, related to smoking and alcohol consumption in seven RMDs: osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), systemic sclerosis (SSc) and gout. Two additional systematic reviews were performed to identify original longitudinal studies on smoking and alcohol consumption and disease-specific outcomes.

**Results:** Nine reviews and 65 original studies on smoking as well as two reviews and 14 original studies on alcohol consumption met the inclusion criteria. While most studies were moderate/poor quality, smoking was significantly associated with poorer outcomes: cardiovascular co-morbidity; poorer response to RA treatment; higher disease activity and severity in early RA; axSpA radiographic progression. Results were heterogeneous for OA while there was limited evidence for PsA, SSc and gout. Available studies on alcohol mainly focused on RA, reporting a positive association between alcohol intake and radiographic progression. Five studies assessed alcohol consumption in gout, reporting a significant association between the number and type of alcoholic beverages and the occurrence of flares.

**Conclusion:** Current literature supports that smoking has a negative impact on several RMD-specific outcomes and that moderate or high alcohol consumption is associated with increased risk of flares in RA and gout.

Key words: tobacco, alcohol, disease-specific outcomes, RMDs, systematic reviews

Manuscript word count: 5195

**Background**

Rheumatic and musculoskeletal diseases (RMDs) are among the most prevalent and burdensome non-communicable diseases in Europe; including more than 200 degenerative, inflammatory and autoimmune conditions predominantly affecting the musculoskeletal system [1]. RMDs negatively impact health-related quality of life through chronic pain and social exclusion [2] and constitute a major cause of disability [3]. In addition to pharmacological strategies, modifications in lifestyle behaviours may play an important role in the prevention of progression of RMDs and in the reduction of important associated comorbidities.

Therefore, in 2018, a EULAR taskforce was convened to synthesize current literature to formulate evidence-based recommendations for lifestyle improvements in individuals with prevalent RMDs. The taskforce decided to focus on six lifestyle factors, including smoking and alcohol consumption which are the focus of the present manuscript and seven diseases referred to collectively as RMDs: rheumatoid arthritis (RA), osteoarthritis (OA), systemic lupus erythematosus (SLE), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), systemic sclerosis (SSc) and gout.

For the general population, recommendations from the World Health Organisation (WHO) regarding smoking and alcohol consumption are clear. Given tobacco-related morbidity and mortality, the WHO European Strategy for Smoking Cessation was implemented to provide guidelines and support to the Member States in building their capacity to promote smoking cessation [4, 5]. Similarly, the WHO made the reduction of the harmful use of alcohol a public health imperative [6]. However, smoking and alcohol consumption have not yet been taken into account in coherent public health strategies to preserve musculoskeletal health. Additionally, various European stakeholders (e.g. patients, health professionals) expressed the need to better understand the effect of lifestyle factors on the progression of musculoskeletal diseases.

 This manuscript presents the results of the systematic reviews of existing systematic reviews and meta-analyses as well as the findings of systematic reviews of individual studies on the relationship between smoking and alcohol consumption and disease-specific outcomes in the RMDs of interest.

**Methods**

These reviews were conducted following EULAR’s standard operating procedure for EULAR- endorsed recommendations [7] and are reported according to PRISMA guidelines [8].

*Search strategy*

In a first step, we conducted a search on MEDLINE, EMBASE and Cochrane Library databases to identify existing systematic reviews and meta-analyses on the five included lifestyle behaviours of interest – including smoking - and RMD-specific outcomes that were published from 1/1/13 to 18/9/18 (Supplementary table 1).

After a teleconference with all taskforce members in January 2019, we decided to include alcohol as an additional exposure of interest and performed a separate systematic review of systematic reviews and meta-analyses in March 2019 (Supplementary table 2). Records from both searches were screened independently and in duplicate by two reviewers (MW and JG) on the basis of the title and abstract. Full texts were selected, independently and in duplicate, by four reviewers (MW, JG, JRC, GC). In a second step, we performed two systematic reviews of original studies on smoking and alcohol in RMDs, respectively. Original studies focusing on smoking in individuals with axSpA, published before 2017, were not searched because of the recent systematic review performed by Villaverde-Garcia et al.[9] in 2017.

Search strategies (Supplementary tables 3 and 4) were implemented in the MEDLINE, EMBASE and CENTRAL databases (dates when strategies were implemented: smoking: 22/05/2019; alcohol: 21/03/2019). Titles and abstracts, followed by full texts, were screened independently by two reviewers (smoking: MW, MR; alcohol: MW, JG).

*Inclusion and exclusion criteria*

Systematic reviews were eligible if (a) the study population involved people with a RMD (OA, RA, SLE, axSpA, PsA, SSc, gout), (b) the aim was to assess the relationship between lifestyle exposures (diet, exercise, weight, smoking, alcohol, work) and (c) data on outcomes of interest was reported (Supplementary table 5 for list of included outcomes).

Individual studies were eligible if (a) the exposure studies was smoking or alcohol consumption, (b) the study population involved people with a RMD (OA, RA, SLE, PsA, SSc, gout [and axSpA for the alcohol review]), (c) the study design was longitudinal (randomised controlled trials, non-randomised trials, single-arm intervention studies, longitudinal observational studies), and (d) the aim was to investigate the relationship between smoking or alcohol and outcomes of interest (Supplementary table 5 for list of included outcomes).

We excluded original studies if they were cross-sectional, were conducted on children or animals, protocols, letters or conference abstracts.

*Assessment of risk of bias and methodological quality*

The risk of bias of included systematic reviews and meta-analyses was assessed using the AMSTAR-2 tool [10]. Each included review or meta-analysis was rated as critically low, low, moderate or high quality. The QUIPS tool was used to assess the quality of observational studies considering six potential biases: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and adjustment, and analysis [11]. Studies with low or moderate risk of bias in all six domains were classified as high quality while studies with high risk for at least one domain of bias were classified as low quality.

*Data extraction and analysis*

The data was independently extracted by two pairs of reviewers (smoking: MW, MR and alcohol: MW, JMG) using a structured form. The information extracted included first author, disease of interest, study design, exposure definition, outcome definition and measurement method, inclusion criteria, adjustment variables, number of participants, length of follow-up, demographics of the study population, and main findings. Studies were grouped by disease and by type of exposure (e.g. cigarette smoking vs smokeless tobacco - snuff). The effect size, the statistical significance of the results, the methodological quality of the reviews or individual studies and their respective evidence level (EL, defined based on the Oxford Centre for Evidence-based Medicine Levels of Evidence – Supplementary table 6) were taken into account in the qualitative data analysis.

**Results**

*Search strategy and study characteristics*

The search strategy to identify existing systematic reviews and meta-analyses identified 1507 abstracts, of which 16 duplicates were removed. From remaining studies, 125 full manuscripts were screened, of which 103 were included (Figure S1). Nine of these focused on smoking. The search strategy for studies on alcohol exposure identified 63 systematic reviews or meta-analyses. Once each duplicate was removed, 62 titles and abstracts were screened, followed by screening of seven full manuscripts. In total, two studies were included (Figure S2).

The search strategy to identify individual studies on smoking resulted in a total of 2528 papers. After removal of 187 duplicates and studies already included in existing systematic literature reviews, 2341 titles and abstracts were screened. Finally, 65 articles were included in the review after screening the full-text of 110 manuscripts (Figure S3). For alcohol, the literature search resulted in a total of 961 articles. After duplicates were removed, 905 titles and abstracts were screened. The full texts for the remaining 18 articles were assessed for eligibility, which resulted in 14 papers included in the systematic review (Figure S4).

***Smoking***

Our search strategies did not identify any systematic reviews or meta-analyses on smoking and disease-specific outcomes in individuals with PsA, SSc or gout. Overall, the individual studies included in the present review used self-reported smoking habits as exposures with most of them using three categories: current smokers, previous smokers and never smokers. Five studies collected information on the number of pack-years smoked [12-16].

Osteoarthritis

A summary of current evidence is provided in Table 1. Three reviews assessed the association between smoking and outcomes among patients with OA (Supplementary table 7). Two reviews concluded that there was no association between smoking and OA joint damage [17, 18]. One review reported that evidence regarding the association between smoking and pain was inconsistent but that evidence for no association between smoking and poorer function was strong among individuals with knee OA [19].

Three prospective cohort studies investigated the relationship between cigarette smoking and knee/hand OA (Supplementary tables 8 and 9). Among them, two controlled for potential confounders; mainly age and body mass index [20, 21]. One study including exclusively men showed that current smokers with knee OA were at increased risk for cartilage loss at the medial compartment of the tibio-femoral joint (Odds Ratio [OR]=2.3, 95% Confidence Interval [CI] 1.0 to 5.4) and of the patellofemoral joint (OR=2.5, 95% CI 1.1 to 5.7) but not the lateral compartment (OR=1.2, 95% CI 0.3 to 4.2) [20]. The adjusted change in knee‐specific VAS pain scores was not different between subjects who were and were not current smokers [20]. Conversely, in a study including both sexes with knee OA, Nishimura et al. found that cigarette smoking was not associated with radiographic progression (OR=0.7, 95% CI 0.1 to 6.2) [22]. In another study, cigarette smoking was not associated with progression rate of hand OA [21].

Rheumatoid arthritis

There were two reviews of smoking and outcomes among people with RA (Supplementary table 10), with one concluding an increased risk of cardiovascular (CV) events (meta-relative risk: 1.50, 95% CI 1.15 to 1.84) [23] and the other concluding a lower response to a first-line disease-modifying anti-rheumatic drug (DMARD)  with a positive predictive value ranging from 38% to 71% [24], for smokers compared to non-smokers.

The current evidence on early RA and cigarette smoking is summarized in Table 2. Twelve prospective cohort studies investigated the relationship between smoking status and disease activity and severity. In these studies, early RA was specifically defined by a disease duration of less than one year or less than two years. Most of the studies controlled for age, sex, disease duration and treatment use such as DMARDs or glucocorticosteroids.

Levitsky et al. found that current smokers had a 2.6-fold increased odds of EULAR non-remission, compared to non-current smokers (95% CI 1.1 to 6.3) [25]. There was no association between smoking status and: the rate or the occurrence of remission [26, 27]; the EULAR response [26, 28]; or functional status [28, 29]. Conflicting results were observed for disease activity, with two studies reporting a significant association between smoking and higher disease activity [15, 30] (vs two studies reporting no association [28, 31]). Similarly, results were inconsistent across studies regarding C-reactive protein (CRP) levels [28, 30], pain [28, 30, 32], radiographic progression [26, 30, 31, 33, 34], and extra-articular manifestations [15, 35].

When smokers were classified according to number of pack-years, disease activity parameters and radiographic progression did not differ with increasing number of pack-years smoked [15]. Further details are provided in Supplementary tables 11 and 12.

Early RA and snuff – One study showed that snuff users had lower disease activity scores than never smokers and previous smokers (disease activity scores at three months of follow-up: 2.0 vs. 3.7, p= 0.001 and at six months: 2.1 vs. 3.2, p = 0.003) [36]. There was a significant difference in physical function scores with worse function and greater disability among snuff users, compared with never smokers at two years of follow-up (Health Assessment Questionnaire scores: 0.4 vs. 0.3, p = 0.03). No significant difference in EULAR response was observed between snuff users and never, previous and current smokers (Supplementary tables 11 and 12). All estimates were adjusted on socio-economic status, disease duration and treatment.

The current evidence on RA and cigarette smoking is summarized in Table 3.

Fifteen prospective cohort studies investigated the association between smoking and RA outcomes. Main confounders included were age, sex, body mass index, treatment use, disease duration and characteristics. Two studies reported significant associations between smoking and progression of radiographic erosions [12], and higher odds of interstitial lung disease prior to or after DMARDs exposure (OR= 2.2, 95% CI 1.2 to 4.0 and OR=1.9, 95% CI 1.1 to 3.3) [37]. Conversely, in other studies, smoking was not associated with radiographic progression (measured with the Ratingen score) [16] and lower odds of remission [38]. Two studies reported no significant difference in CRP levels between smokers and non-smokers [16, 39]. Five additional studies reported that smoking was a negative prognostic factor for EULAR response (OR=0.69, 95% CI 0.51 to 0.95 and OR=0.69, 95% CI 0.50-0.93, respectively) [39, 40], was associated with a higher risk of CV events (Hazard ratio[HR]= 1.98, 95% CI 1.52 to 2.58) [41], higher odds of infections (HR = 1.42, 95% CI 1.10 to 1.84) [42] and higher odds of belonging to persistent pain trajectories [43]. However, there was no association between cigarette smoking and higher odds of infections requiring hospitalization [42]. One study reported a significant association between smoking and higher risk of obstructive lung disease (HR = 4.38, 95% CI 2.14 to 8.99)[44]. Results regarding radiographic progression (measured with the Sharp-van der Hejde score [45]) [46, 47], functional disability [12, 13, 39, 40, 47] and disease activity [13, 16, 39, 40] were conflicting across studies.

When considering the number of pack-years, two studies found no evidence for more rapid progression of radiographic joint damage among smokers compared to non-smokers [12, 16]. However, radiographic erosions evolved significantly more slowly in heavy smokers (smoking more than one pack/day) than in non-smokers (average progression of 1.21%, 95% CI 0.23–2.25 vs 2.86%, 95% CI 2.65–3.07, p< 0.001). One study reported a significant association between heavy smoking (more than 10 pack-years) and functional disability [13].

Four retrospective cohort studies assessed cigarette smoking in RA patients. Gonzalez et al. [48] found that smoking was not associated with an increased risk of developing selected CV events (myocardial infarction, heart failure and CV death). Conversely, Kremers et al. reported an increased absolute risk for CV events (coronary revascularization procedures, silent or non-fatal myocardial infarctions, heart failure and CV deaths) in RA participants who were smokers compared with non-RA participants who were smokers (absolute risk in the 40-49 age group: 5.1% vs 2.9%) [49]. In two studies, smoking status was also found to be associated with development of peptic ulcers in RA patients on long-term nonsteroidal anti-inflammatory drugs treatment (OR = 2.71, 95% CI 1.13 to 6.53), [50] and with an increased risk of hospitalisations for CV events or for respiratory tract infection (HR = 2.23, 95% CI 1.46 to 3.40) [51]. However, , cigarette smoking was not associated with the odds of acute coronary events [52] (Supplementary tables 13 and 14).

RA and passive smoking – One prospective cohort study showed that passive smoking might be responsible for higher disease activity in female RA patients and that never smoking might be associated with good clinical response in RA [53] (Supplementary tables 13 and 14).

Inflammatory polyarthritis and smoking – In one prospective cohort study, current smoking at baseline was a predictor of obstructive lung disease, compared with never smoking (OR = 15.25, 95% CI 3.14-73.99), independently of age and sex [54]. At 15 years of follow-up, smoking was significantly associated with greater odds of obstructive lung disease in both current and former smokers (OR = 15.91, 95% CI 3.00 to 84.3and OR=5.90, 95% CI 1.32 to 26.40, respectively), compared to never smokers. There was no significant association between smoking status and restrictive lung disease [54] (Supplementary tables 13 and 14).

Systemic lupus erythematosus

A summary of current evidence is provided in Table 4. Three reviews included studies of smoking and outcomes in SLE and reported that smoking was associated with increased odds of developing CV risk factors [55], and having increased risk of rash and worse SF-36 scores [56]. One review reported that smoking was associated with higher disease activity [56], whereas another review concluded that there was not enough data to make a definitive conclusion [57] (Supplementary table 15).

Fourteen prospective cohort studies assessed smoking in SLE. The most frequent confounders included in the analyses were age, sex and race. In one study, past or current smoking (vs never) was significantly associated with increased risk of organ damage (HR=1.7, 95% CI 1.1 to 2.6) [58]. In other studies, smoking was associated with increased: risk of lung cancer [59]; odds of thrombotic events [60, 61]; frequency, odds and risk of CV and cerebrovascular events [62-64]; odds of fracture [65]; odds of cutaneous damage; and odds of early myocardial infarction [66]. Three studies did not find any association between smoking and the risk of myocardial infarction and/or stroke [67], depression [68] and cutaneous features of active lupus [69], respectively. Results regarding coronary artery disease were contradictory [70, 71].

Two retrospective cohort studies found that current smokers with SLE-related interstitial pneumonia had significantly worse prognosis (vs ex and never smokers) (HR = 6.69, non-available CI, p=0.02) [72] and higher risk of severe infections in individuals with any history of tobacco smoking (HR = 1.33, 95% CI 1.12 to 1.58) [73]. Bernatsky et al. [74] found that the risk of all cancer or haematological cancer was not statistically different between ever and never smokers (Supplementary tables 16 and 17).

Axial spondyloarthritis

Results are summarized in Table 5. One review reported that patients with axSpA who smoked had more pain, worse physical function, worse disease activity, radiological progression and poorer health-related quality of life compared with non-smokers [9] (Supplementary table 18). There was no difference regarding morning stiffness. Five prospective cohort studies assessed smoking in axSpA. Three studies reported a significantly increased: rate of progression of functional disability among current smokers (vs non-smokers) [75]; odds of spinal radiographic progression among male ever-smokers (vs never smokers) (OR = 3.53, 95% CI 1.42 to 8.77) [76]; risk of having radiographic vertebral fractures among patients with a smoking duration of ≥ 20 years (vs non-smokers and individuals with shorter smoking duration) (approximatively 30% vs 10–15%) [77]. In two studies, smoking was associated with higher odds of spinal radiographic progression (vs non-smoking) (OR = 2.75, 95% CI 1.25 to 6.05) [78] and lower odds of remission at two years [79]. One retrospective cohort study reported that work disability did not differ between current or former smokers, compared with never smokers [80] (Supplementary tables 19 and 20).

Psoriatic arthritis

One prospective cohort study showed that current or ever smokers were more likely to have poorer physical function, compared with never smokers [81] (Supplementary tables 21 and 22).

Systemic sclerosis

Three prospective cohort study assessed smoking in SSc patients. Past or present smoking was not associated with digital ulcers in univariate analysis [82] while current smoking was associated with worse hand function in unadjusted analysis [83]. Smoking 10–20 pack-years, or more than 30 pack-years, was anindependent risk factor for lung cancer in individuals with SSc compared with never smoking (HR = 5.04, 95% CI 1.11 to 22.85) [14] (Supplementary tables 23 and 24).

Gout

In one retrospective cohort study [84], tobacco use was not identified as a risk factor for renal function deterioration. In another study, the proportion of smokers was not significantly different between gout patients with and without disability and between gout patients with and without renal failure (in univariate analysis) [85] (Supplementary tables 25 and 26).

***Alcohol consumption***

Our search strategies did not identify any meta-analyses, systematic reviews or individual studies on alcohol consumption and disease-specific outcomes in individuals with axPsA, PsA and SSc. Overall, the definitions of alcohol consumption were heterogeneous, making their synthesis difficult. A summary of cut-offs used for alcohol exposure is provided in Supplementary table 27.

Osteoarthritis

One review included two studies investigating alcohol consumption as a predictor of post-operative function in OA patients undergoing total hip replacement, both reporting no association with postoperative function [86] (Supplementary table 28).

Rheumatoid arthritis

*Alcoholism -* One prospective cohort study reported a significantly higher risk of infections in individuals with RA who suffered from alcoholism (multivariate HR=1.67 , 95% CI 1.16 to 2.41)[42] (Supplementary tables 29 and 30).

*Alcohol intake –* A summary of current evidence is provided in Table 6.Six prospective cohort studies assessed alcohol intake in RA patients with inconsistent results. Papers presenting multivariate analyses mainly controlled for age, sex, disease duration and treatments. Sageloli et al. found a significant association between moderate consumption and higher odds of radiographic progression at 60 months, only among women (OR = 1.73, 95% CI 1.01 to 2.96) [87]. Similarly, significantly greater radiographic progression was found in heavy drinkers (consumption of alcoholic beverages on several occasions per day), compared with occasional and daily drinkers [88] and among individuals consuming more than 15 drinks per month [89]. However, Nissen et al. reported less radiographic progression in occasional and daily drinkers, compared with non-drinkers [88]. No effect modification by the quantity of alcohol consumption was found but moderate alcohol consumption (5.1–10.0 grams/day) was associated with better functional status only in HLA-SE positive patients [13]. In two studies, alcohol intake was not associated with disease activity [13] while a daily, moderate and heavy alcohol consumption (vs never) was associated with improved odds of remission (OR=3.51, 95% CI 1.68 to 7.34) [27]. In a large study, each increased unit of alcohol consumed was associated with increased risk of transaminitis (HR =1.01, 95% CI 1.00 to 1.02), especially among patients consuming more than 21 units per week, compared with non-drinkers (HR =1.85, 95% CI 1.17 to 2.93) [90].In one retrospective cohort study, individuals who consumed more than one drink per week had decreased odds of occurrence of overall extra-articular manifestations, compared with individuals who consumed less than one drink per week (OR= 0.22, 95% CI 0.09 to 0.54) [91]. Further details are provided in Supplementary tables 29 and 30.

Systemic lupus erythematosus

One prospective cohort study found that an alcohol intake greater than 15g/month was inversely correlated with the development of cerebrovascular, CV and peripheral arterial organ damage [92]. There was no association between alcohol intake and susceptibility to infections (Supplementary tables 31 and 32).

Gout

A summary of current evidence is provided in Table 7. One review of guidelines for the management of gout was identified in the literature. In total, 12/15 guidelines recommended reducing alcohol consumption for gout patients, but the evidence was rated as either moderate/low or very low for all guidelines (Supplementary table 28) [93].

Two prospective cohort studies focused on alcoholism in gout. One of these studies did not find any significant difference in functional status or occurrence of renal failure between individuals with and without history of alcoholism [85]. However, chronic and reformed alcoholic individuals were found to have significantly lower levels of serum urate during acute gout flares [94]. When considering alcohol intake, one small retrospective case review reported that alcohol consumption was identified as a key risk factor for a suboptimal outcome [95]. Alcohol consumers were less likely to achieve ACR recommended uric acid concentration within 6 months [95]. In another study, there was no association between alcohol consumption and deterioration of renal function [84]. In a prospective study, consuming more than 1-2 drinks in a 24-hour period (vs no alcohol intake) was associated with increased odds of gout attacks (OR=1.36, 95% CI 1.00 to 1.88) [96]. Every type of alcoholic beverage intake (wine, beer, hard liquor vs no intake) was associated with increased odds of recurrent gout attacks, after controlling for diuretic use, purine intake, gout-related medication use and water intake (Supplementary tables 33 and 34).

**Discussion**

This paper synthesizes current scientific evidence regarding the relationship between smoking and alcohol consumption, and presentation, progression or comorbidities among people with seven RMDs.

Our search strategies did not identify any systematic reviews or meta-analyses on smoking and disease-specific outcomes in individuals with PsA, SSc or gout. Similarly, there was insufficient evidence from individual studies to enable conclusions about the relationship between smoking and physical function in axSpA; risk of lung cancer, digital ulcers and hand function in SSc; disability and renal function deterioration in gout.

Among individuals with OA, smoking was not consistently associated with poor outcomes in small systematic reviews and individual observational studies. Our search strategy identified only three additional prospective cohort studies focusing on different OA sites and outcomes, making quantitative synthesis impossible. In two systematic reviews, smoking in RA was related to higher CV morbidity [23] and lower odds of response to first line DMARDs [24].

In the two highest-quality individual studies focusing on early RA, current smokers had more active disease and significantly higher CRP levels [15] but similar physical function [29], compared with ex-smokers, and never smokers. Of note, these studies, unlike others, considered rheumatoid factor positivity as a confounder, but not anti-cyclic citrullinated peptide antibodies positivity. It is well established that smoking increases the risk of seropositive RA by inducing mechanisms that accelerate the citrullination of autoantigens in the lungs, especially among individuals carrying the HLA–DRB1 shared epitope [97]. Since individuals with anti-citrullinated protein antibodies have specific genetic risk factors and differ from autoantibody-negative counterparts in their clinical course and prognosis, studies should account for these biomarkers in their analyses [98]. The lack of adjustment for these factors in some studies could thus partly explain the inconsistency of results regarding smoking and RA-specific outcomes.

The lack of consistency in the results in this population may also be attributed to the existence of a collider stratification bias [99]. Indeed, in a moderate-quality study, heavy smoking was paradoxically found to be associated with a significantly lower progression of radiographic erosions. While this finding might be partially explained by the anti-inflammatory properties of nicotine [100], this risk factor paradox may be due to this type of selection bias that can particularly affect the findings of studies investigating the risk of a disease progression when several risk factors for progression are also risk factors for the development of this disease.

Furthermore, several authors distinguished early RA from established RA, leading our choice to present results for both study population separately. While individuals with early RA may be more likely to achieve low disease state or remission than patients with established RA [101, 102], the association between smoking and disease-specific outcomes by disease stage remains to be investigated among individuals with RA.

Among SLE patients, smokers also tended to have worse outcomes, for example, worse scores on SF-36 mental and physical domains, more rashes, worse disease activity [56] and more CV morbidity [55]. Smoking in axSpA was also associated with worse outcomes across all the evaluated studies (other than morning stiffness). Three high-quality additional studies reported poorer outcomes among smokers regarding radiographic progression, functional disability and vertebral fractures [75-77].

Taken together, current evidence suggests that people with these RMDs should be encouraged and supported to quit smoking and be informed that smoking has a negative impact on several outcomes such as symptoms, physical function, disease activity, disease progression and occurrence of comorbidities. Additionally, people with RA and health professionals should be particularly aware that smoking may affect DMARD treatment response. Therefore, supporting and advising people with RMDs to stop smoking should be considered an essential part of the rheumatology outpatient consultation. While our literature searches did not identify trials testing interventions to reduce and stop smoking among these individuals, more recent publications have suggested that smoking cessation is achievable among rheumatology patients and that simple and brief interventions can be successful [103, 104]. Nevertheless, in their Cochrane review published in 2019, Roelsgaard et al. concluded that high-quality, adequately powered studies are needed given the number of included participants, the imprecision of effects, and the risk of bias of existing trials [105].

Our systematic literature reviews did not include any meta-analyses, systematic reviews or individual studies on alcohol consumption and disease-specific outcomes in individuals with axPsA, PsA and SSc. Also, scientific evidence was too weak to draw conclusions on the association between alcohol intake and cerebrovascular, cardiovascular and peripheral arterial organ damage and susceptibility to infections in people with SLE.

Only two reviews focused on alcohol and outcomes in RMDs. The first was a review of post-operative function of OA patients after hip replacement which found no significant association with alcohol consumption [86]. The second study was a review of guidelines for gout patients, with the majority of guidelines advising reductions in alcohol consumption for gout patients [93]. Most of the individual studies we identified focused on alcohol intake in individuals with RA. One high-quality study reported increased odds of radiographic progression in people with RA drinking alcohol, especially among women [87]. A few studies assessed alcohol consumption in gout, reporting a significant association between the number and type of alcoholic beverages and the occurrence of flares [96]. Given the lack and the insufficiency of evidence for several RMDs, larger and better-quality studies are thus needed to further investigate the relationship between alcohol intake and health outcomes. Further, studies should give more importance to ethnicity and geographical residence to account for cultural differences in alcohol consumption [106]. Despite this, results from existing studies suggest that the alcohol consumption of people with RMDs should be discussed with health professionals, especially when starting new treatments. Notably, health professionals and people with RA should be aware that moderate alcohol consumption is associated with increased risk of flare and comorbidities. Additionally, health professionals and people with gout should be aware that moderate alcohol consumption is associated with increased risk of flare. Considering current scientific evidence, individuals with RMDs may be reassured that marginal alcohol consumption is unlikely to negatively impact RMD outcomes specifically, although caution is advisable for other health domains or in certain situations (e.g. among individuals with RMDs and liver disease or when using certain treatments such as methotrexate or leflunomide).

While the definition used to characterize alcohol intake varied across studies, heterogeneity was also found in the definitions chosen for smoking status (ever, past, or current) and several outcomes such as radiographic progression in RA, making comparison of results difficult between studies. Thus, future studies with more consistency in terms of outcome and exposure definition and measurement are needed for comparison and data pooling. Other limitations need consideration in interpreting these reviews. Given the observational design of the studies focusing on smoking and alcohol exposure, the level of evidence from these studies is not optimal (2B) but is the highest that could be achieved for ethical considerations. For the same reason, caution should be exercised when interpreting the results since causality cannot be inferred from these studies. Additionally, shortcomings in the included studies may have influenced the results. Indeed, most of the studies regarding smoking or alcohol consumption were rated as low or moderate methodological quality. Overall, we found high and moderate risks of bias particularly in study attrition and study confounding. Improving the reporting of reasons for dropout or loss to follow‐up will prevent bias and allow for stronger conclusions. Besides, smoking and alcohol‐related behaviours are known to be positively associated [107] and may confound each other. Future works should explore the synergism between smoking and alcohol consumption with regard to RMD-specific outcomes, taking into account important potential confounders such as socio-economic variables (e.g. blue-collar occupation, education level). At last, some reviews, especially in OA, included a small number of published studies that addressed the association of smoking with the progression of OA (16, 3 and 2, respectively) and this limitation might have particularly affected the power of their meta-regression [17].

In conclusion, results from these literature reviews about smoking and alcohol informed the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. Current scientific evidence suggests that individuals with RMDs should be encouraged to quit smoking and be informed that smoking has a negative impact on several disease-specific outcomes and may affect their response to treatment. Additionally, alcohol consumption of people with RMDs should be discussed together with health professionals and they all should be aware that moderate or high alcohol consumption is associated with increased risk of flares in RA and gout.

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**CONTRIBUTORS**

Study concept and design: SMMV; MW, JMG, FG, Acquisition of data: SMMV, MW. Analysis and interpretation of data: JMG, MW, JRC, ABa, HBF, ABo, GC, SdS, AdT, TED, RHM, PP, LSF, TS, KWB, JW, MZS, FG, SV; Review of manuscript: JMG, MW, JRC, ABa, HBF, ABo, GC, SdS, AdT, TED, RHM, PP, LSF, TS, KWB, JW, MZS, FG, SV

**CONFLICT OF INTERESTS**

The authors declare no conflicts of interest.

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Table 1. Osteoarthritis and smoking: summary of evidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Site of osteoarthritis** | **Outcomes** | **Smoking associated with outcome** | **Evidence** **level** | **Study** **quality** |
| All sites | Radiographic progression  | 🗶 | 2A | Moderate |
| Knee | Pain  | 🗶 | 2A2B | ModerateModerate |
| Physical function  | 🗶 | 2A | Moderate |
| Radiographic progression  | 🗶🗶 | 2A2B | ModerateLow |
| Cartilage loss  | Adverse association ✓ | 2B | Moderate |
| Hand | Radiographic progression  | 🗶 | 2B | Low |

Evidence level: 2A. Evidence from a systematic review of cohort studies; 2B. Evidence from individual cohort studies

🗶: No evidence for an association between smoking and outcome; ✓: Evidence for an association between smoking and outcome

Table 2. Early RA and smoking: summary of evidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Exposure** | **Outcome** | **Smoking associated with outcome** | **Evidence level** | **Study** **quality** |
| Smoking status | Pain | 🗶Adverse association ✓🗶 | 2B2B2B | ModerateLowLow |
| CRP levels | Adverse association ✓Adverse association ✓🗶 | 2B2B2B | HighModerateLow |
| Disease activity | Adverse association ✓ 🗶Adverse association ✓ 🗶 | 2B2B2B2B | HighModerateLowLow |
| EULAR non-remission | Adverse association ✓ | 2B | Moderate |
| Rate of remission | 🗶 | 2B | Low |
| Remission | DAS 28-ESR 🗶 | 2B | Low |
| Functional status | 🗶🗶 | 2B2B | HighModerate |
| Radiographic progression | SHS score: Adverse association ✓SHS score 🗶SHS score: Favourable association ✓SHS score: 🗶EJC: Adverse association ✓Larsen score: Adverse association ✓ | 2B2B2B2B2B2B | ModerateModerateLowLowModerateModerate |
| EULAR response | 🗶🗶 | 2B2B | ModerateLow |
| Extra-articular manifestations | 🗶Adverse association ✓ | 2B2B | HighModerate |
| Number of pack years | Disease activity | 🗶🗶 | 2B2B | HighLow |
| Radiographic progression | Larsen score 🗶SHS score 🗶 | 2B2B | HighLow |

Evidence level: 2B. Evidence from individual cohort studies

EULAR: European League Against Rheumatism; DAS-28 ESR: Disease Activity Score-28 for Rheumatoid Arthritis with erythrocyte sedimentation rate; EJC: erosion joint count; SHS: Sharp/van der Heijde score; 🗶: No evidence for an association between smoking and outcome; ✓: Evidence for an association between smoking and outcome

Table 3. RA and smoking: summary of evidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Exposure** | **Outcome** | **Smoking associated with outcome** | **Evidence level** | **Study quality** |
| Smoking status | Pain | Adverse association ✓ | 2B | Low |
| CRP levels | 🗶🗶 | 2B2B | ModerateLow |
| Disease activity  | RF +: 🗶 RF -: Adverse association ✓DAS28-CRP3 🗶ESR, CRP and DAS28: Adverse association ✓DAS28 🗶 | 2B2B2B2B | ModerateModerateLowLow |
| Remission (DAS-28) | 🗶 | 2B | Moderate |
| Functional status | HAQ 🗶HAQ 🗶 Modified HAQ: Adverse association ✓HAQ: Favourable association ✓ | 2B2B2B2B | ModerateLowModerateLow |
| Radiographic progression  | Ratingen score 🗶Erosions: Adverse association ✓SHS score: Adverse association ✓SHS score 🗶SHS score 🗶 | 2B2B2B2B2B | ModerateModerateModerateModerateLow |
| Treatment response  | Adverse association ✓ | 2A | Low |
| EULAR response | Adverse association ✓ | 2B | Low |
| Obstructive lung disease | Adverse association ✓ | 2B | Low |
| Interstitial lung disease | Adverse association ✓ | 2B | Moderate |
| Hospitalizations for respiratory infection | Adverse association ✓ | 2B | Moderate |
| Infections | Adverse association ✓ | 2B | Low |
| Hospitalizations for infections | 🗶 | 2B | Low |
| Peptic ulcers | Adverse association ✓ | 2B | Moderate |
| CV outcomes | Adverse association ✓ | 2B | Moderate |
| CV morbidity | Adverse association ✓ | 2A | Moderate |
| CV events | Adverse association ✓🗶Adverse association ✓ | 2B2B2B | ModerateModerateLow |
| Acute coronary events | 🗶 | 3B | High |
| Hospitalizations for CV events | Adverse association ✓ | 2B | Moderate |
| Number of pack years | Functional status  | HAQ: Adverse association ✓ | 2B | Moderate |
| Radiographic progression | Ratingen score 🗶Erosions: Favourable association ✓ | 2B | Moderate |

Evidence level: 2A. Evidence from a systematic review of cohort studies; 2B. Evidence from individual cohort studies; 3B. Evidence from individual case-control studies

CV: Cardiovascular; SHS: Sharp/van der Heijde score; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; DAS-28: Disease Activity Score-28; HAQ: Health Assessment Questionnaire

🗶: No evidence for an association between smoking and outcome; ✓: Evidence for an association between smoking and outcome

Table 4. Systemic lupus erythematosus and smoking: summary of evidence

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Smoking associated with outcome** | **Evidence** **level** | **Study quality**  |
| Disease activity (SLEDAI) | Adverse association ✓🗶 | 2A2A | ModerateModerate |
| Organ damage (SDI) | Adverse association ✓ | 2B | Moderate |
| Cutaneous damage | SLICC / ACR-DI: Adverse association ✓SLEDAI-2K 🗶 | 2B2B | LowLow |
| Rash | Adverse association ✓ | 2A | Moderate |
| Quality of life (SF-36) | Adverse association ✓ | 2A | Moderate |
| Interstitial pneumonia | Adverse association ✓ | 2B | Moderate |
| Severe infections | Adverse association ✓ | 2B | Moderate |
| Fractures | Adverse association ✓ | 2B | Low |
| Depression | 🗶 | 2B | Low |
| Cardiovascular risk factors  | Adverse association ✓ | 2A | Moderate |
| Cardiovascular events | 🗶 | 2B | Moderate |
| Thrombotic events | Adverse association ✓ | 2B | Low |
| Cardiovascular and cerebrovascular events  | Adverse association ✓ | 2B | Low |
| Coronary artery disease | Adverse association ✓🗶 | 2B2B | LowLow |
| Myocardial infarction | Adverse association ✓ | 2B | Low |
| Risk of lung cancer | Adverse association ✓ | 2B | Low |
| Risk of cancer | 🗶 | 3B | Moderate |

Evidence level: 2A. Evidence from a systematic review of cohort studies; 2B. Evidence from individual cohort studies; 3B. Evidence from individual case-control studies

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Slicc damage index score; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; 🗶: No evidence for an association between smoking and outcome; ✓: Evidence for an association between smoking and outcome

Table 5. Axial spondyloarthritis and smoking: summary of evidence

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Smoking associated with outcome** | **Level** **of evidence** | **Study quality** |
| Pain | Adverse association ✓ | 2A | Moderate |
| Disease activity | BASDAI: Adverse association ✓ | 2A | Moderate |
| Remission | ASDAS-CRP: Adverse association ✓BASDAI: Adverse association ✓ | 2B2B | LowLow |
| Quality of life  | Adverse association ✓ | 2A | Moderate |
| Physical function | Adverse association ✓Adverse association ✓ | 2A2B | ModerateHigh |
| Morning stiffness | 🗶 | 2A | Moderate |
| Work disability | 🗶 | 2B | Low |
| Radiological progression | Adverse association ✓Men: Adverse association ✓ Women 🗶Adverse association ✓ | 2A2B2B | ModerateHighLow |
| Prevalent vertebral fractures | Adverse association ✓ | 2B | High |
| Incident vertebral fractures | 🗶 | 2B | High |

Evidence level: 2A. Evidence from a systematic review of cohort studies; 2B. Evidence from individual cohort studies

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein

🗶: No evidence for an association between smoking and outcome; ✓: Evidence for an association between smoking and outcome

Table 6. RA and alcohol consumption: summary of evidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Exposure** | **Outcomes** | **Smoking associated with outcome** | **Evidence level** | **Study quality** |
| Alcoholism | Infections  | Adverse association ✓ | 2B | Low |
| ≥ 1 drink / week | Extraarticular manifestations  | Favourable association ✓  | 2B | Low |
| Heavy drinkers (several occasions/day) | Progression of radiographic joint damage  | Adverse association ✓ | 2B | Low |
| ≥ 15 drinks/month | Progression of radiographic joint damage  | Adverse association ✓ | 2B | Low |
| Moderate intake (≤ 20 g/day for women, ≤ 30 g/day for men) | Progression of radiographic joint damage  | At 36 months: 🗶At 60 months: Men 🗶Women: Adverse association ✓  | 2B | High |
| Alcohol intake | Progression of functional disability  | 🗶 | 2B | Low |
| 5.1-10.0 g/day | Progression of functional disability  | HLA-SE+: Favourable association ✓ | 2B | Low |
| Alcohol intake | Disease activity  | 🗶 | 2B | Low |
| Daily, moderate (30-40 g) & heavy (>40 g) intake | DAS28-ESR remission  | Favourable association ✓ | 2B | Low |
| > 21 units/week | Episode of transaminitis  | Adverse association ✓ | 2B | Moderate |

Evidence level: 2A. Evidence from a systematic review of cohort studies; 2B. Evidence from individual cohort studies

DAS-28 ESR: Disease Activity Score-28 for Rheumatoid Arthritis with erythrocyte sedimentation rate

🗶: No evidence for an association between alcohol consumption and outcome; ✓: Evidence for an association between alcohol consumption and outcome

Table 7. Gout and alcohol consumption: summary of evidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Exposure** | **Outcomes** | **Smoking associated with outcome** | **Evidence level** | **Study quality** |
| History of alcoholism Chronic or reformed alcoholism | Physical disability Renal failure Levels of serum urate during acute flares  | 🗶🗶Favourable association ✓ | 2B2B | LowLowLow |
| Alcohol intake  | ACR recommended acid uric concentration Renal function deterioration  | Adverse association ✓🗶 | 2B2B  | LowLow |
| Up to 1 drink in a 24h-period> 1-2 drinks in a 24h-periodModerate consumption (> 2 drinks/day for men and 1 drink/day for women)**Type of alcoholic beverage**0–1 serving of wine>1–2 servings of wine>2 servings of wine* 1. servings of

beer >2-4 servings of beer>4-6 servings of beer > 6 servings of beer0–2 serving of hard liquor> 2-4 servings of hard liquor> 4-6 servings of hard liquor> 6 servings of hard liquor | Gout attacks Gout attacks Gout attacks Gout attacks Gout attacksGout attacks Gout attacks Gout attacks Gout attacks Gout attacks Gout attacks Gout attacks Gout attacks Gout attacks  | 🗶Adverse association ✓ Men: Adverse association Women: 🗶🗶Adverse association ✓🗶🗶Adverse association ✓Adverse association ✓Adverse association ✓🗶Adverse association ✓🗶Adverse association ✓ | 2B | Low |

Evidence level: 2B. Evidence from individual cohort studies

ACR: American College of Rheumatology

🗶: No evidence for an association between alcohol consumption and outcome; ✓: Evidence for an association between alcohol consumption and outcome