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Inhalant and Additional Mucosal-Related Environmental Risks for Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with the classic clinical manifestations being symmetric inflammatory arthritis of the small joints. Extra-articular manifestations such as subcutaneous nodules, osteoporosis, cardiovascular disease, and lung disease, among others, are also common and illustrate the systematic nature of RA. The heritability of RA is estimated to be between 25 and 50%, with *HLA-DRB1* alleles accounting for the strongest genetic risk.^{1,2} Many studies have been conducted to identify environmental risk factors for RA as well as their potential gene-environment interactions.³ A growing body of evidence suggests that exposures or diseases causing inflammation of the lung, oral, or gastrointestinal mucosa may affect RA risk by affecting early tolerance loss, with the early initiation and propagation of RA-related autoimmunity occurring at these mucosal sites. This review highlights some of the recent advances in the understanding of inhalant- and other mucosal-related risk factors for RA.

Inhalants and the Lung Mucosa

Cigarette smoking

The association between cigarette smoking and the risk of RA is well established, serving perhaps as a prototypical link between lung mucosal and inhalant exposures with the development of RA (Table 1). A 2010 meta-analysis of 16 studies estimated that cigarette

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smoking was associated with a two-fold higher risk of RA.⁴ This effect was strongest in men and for seropositive RA.⁴ A dose-response relationship between cigarette smoking and RA exists, though cigarette smoke exposure beyond 20-pack-years has little additional impact on RA risk.⁵ Additionally, a gene-environment interaction occurs in which cigarette smoking among individuals with *HLA-DRB1* shared epitope alleles markedly increases the risk of seropositive RA.⁶ It has been estimated that smoking is responsible for 35% of cases of anti-citrullinated protein antibody (ACPA)-positive RA, increasing to 55% among subjects that are dual positive for shared epitope alleles.⁷ Therefore, the elimination of cigarette smoking as an environmental exposure would substantially reduce the incidence of RA, preventing up to 1 in 2 cases among those with the greatest genetic predisposition. Importantly, the elevated risk associated with cigarette smoking appears to decrease following smoking cessation, although some residual risk is still evident even 30 years after smoking cessation.⁸ In contrast, studies evaluating passive (or 'second-hand') cigarette smoke exposure have not consistently demonstrated clear associations between second-hand smoke exposure and disease risk,⁹⁻¹¹ though passive smoke exposure at certain timepoints in life, such as in childhood, may predispose to the development of RA in later life.¹² Beyond its impact on developing RA, cigarette smoking may increase the risk of other disease consequences including higher disease activity, poorer treatment response, and the development of RA-related lung disease, cardiovascular disease, and lung cancer.¹³⁻¹⁵

Occupational exposures

In addition to cigarette smoking, other environmental and occupational exposures (Table 2) are thought to increase RA risk by stimulating immune responses within the respiratory mucosa. Occupational inhalation exposure to silica during work-related activities such as sand-blasting or concrete/brick sawing or drilling has consistently been implicated as a risk factor for RA. Meta-analyses of epidemiologic studies have estimated a 2-fold higher odds of developing RA among those exposed to silica, an effect that, similar to cigarette smoking, appears to be stronger for seropositive RA and among those who have ever smoked.^{16,17} Bricklayers, concrete workers, material handling operators, and electrical and electronics workers were found to have an increased odds of developing RA independent of cigarette smoking and other risk factors in a Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study,¹⁸ an effect that was hypothesized to relate to noxious airborne occupational exposures other than silica. Among a population of older males residing in the Appalachian region of the U.S., previous work in coal mining, an occupation associated with inhalational exposures to coal, silica, and other mineral dusts, was estimated to contribute to 33% of the risk for RA after adjusting for smoking and other risk factors.¹⁹ This was higher than the population attributable fraction estimated for silica (10%), and no interaction between coal mining and silica was observed.¹⁹ In a study of September 11th World Trade Center rescue and recovery workers compared to controls, there were increased odds of developing autoimmune disease (of which RA was the most common diagnosis) among exposed workers, and these odds increased with longer periods of exposure.²⁰

Several studies of inhalant exposures have been conducted among those who served in the military. Among a U.S. cohort of veterans with RA, reported exposure to military burn pits was associated with 1.7-fold higher odds of anti-cyclic citrullinated peptide (CCP)

antibody positivity, which was increased to 5.7-fold higher odds among those who were positive for shared epitope alleles.²¹ This is in contrast to an earlier study that did not find a significant association between close proximity to burn pits and the development of RA in the Millennium Cohort Study, although this study was limited by a low number of RA cases and short duration of follow-up.²² Finally, among a sample of U.S. veterans serving during Iraq and Afghanistan wars, military inorganic dust exposure determined by occupational codes was associated with a small (10%), but significantly higher, rate of RA development.²³

Occupational tasks including the application of chemical fertilizers, painting, and the use of solvents have also been associated with an increased odds of developing RA (hazard ratios ranging from 1.26 to 1.50) among pesticide applicators and their spouses.²⁴ Additionally, the frequent direct or indirect use of pesticides at childhood residence, as well as reported exposure to pesticide use on a childhood farm, have been associated with increased odds of developing RA later in adulthood.²⁵ Although epidemiologic links between the aforementioned occupational exposures and the risk of developing RA are still being elucidated, it is poorly understood whether these occupational inhalant exposures are associated with disease severity or other relevant disease-related outcomes.²¹

Pollution and particulates

Airborne pollution and particulate matter (including carbon dioxide, ozone precursors, black carbon, sulfate, nitrogen oxides, volatile organic compounds, and particulate organic material) generated from human influences such as burning fossil fuels (e.g., power plants and vehicles) and biomass, as well as naturally-occurring events (e.g., forest fires, dust storms), have been implicated in numerous health conditions.²⁶ Limited studies investigating these exposures as risk factors for RA have yielded mixed results (Table 2). Higher levels of ozone (O₃) exposure as well as closer proximity to roadways, a proxy for air pollution, were associated with RA in a meta-analysis of epidemiologic studies.²⁷ In contrast, there was no association between nitrogen dioxide (NO₂), carbon monoxide (CO), and sulfur dioxide (SO₂) exposures with RA, and there appeared to be an inverse association between exposure to fine particulate matter (<2.5 μm) and incident RA.²⁷ The conclusions that can be drawn from this meta-analysis are limited by the small number of eligible studies (range of 2 to 5 studies evaluating each individual exposure), substantial heterogeneity among the included studies, and likely bias related to confounding (e.g., socioeconomic status) given the geographic variables used in some studies. Further investigations evaluating the potential roles of airborne pollutants and particulate matter with regards to RA risk are warranted.

These same exposures have been studied in at-risk and established RA populations. Among first-degree relatives of RA patients, greater exposure to particulate matter by residential zip codes and ambient air pollution monitoring data was not associated with the presence of RA-related autoantibodies or tender/swollen joint counts.²⁸ In contrast, particulate matter exposure (defined using the same data sources) was associated with ACPA concentration in US veterans with established RA.²⁹

Biologic mechanisms underpinning the link between airborne pollutants (as well as other inhalant exposures) and RA are not well understood. In recent efforts, investigators have

leveraged novel animal modeling approaches to help elucidate the mechanisms linking different inhalant exposures to RA pathogenesis and RA clinical manifestations.³⁰⁻³³ These models have utilized the collagen induced arthritis (CIA) model in DBA/1J mice in addition to intranasal treatment with organic dust extract (ODE), an agriculture-related extract that induces airway inflammation, or lipopolysaccharide (LPS), a ubiquitous inflammatory agent found in many different environmental exposures that triggers airway inflammation. Initial findings from these models of particular importance include sex differences in disease expression following these exposures, susceptibility to lung disease, and transitions of inflammatory lung manifestations to fibrotic disease.³⁰⁻³³

Lung and articular disease in RA, a bi-directional relationship

The aforementioned data linking several inhalant exposures with disease risk builds upon the clinical recognition that lung diseases are over-represented in RA. Pulmonary manifestations have long been recognized as a complication of RA and can include interstitial lung disease (ILD) targeting the lung parenchyma, nodules, airway inflammatory diseases, and pleural disease.³⁴ While understood that RA can be responsible for the development of lung disease, there is now mounting evidence that lung disease may be a risk factor for developing RA. These findings suggest the possibility of a bi-directional relationship between the articular disease that is most characteristic of RA and the less frequent manifestation of lung disease. As an illustration of this potential bi-directionality, up to 14% of patients with RA-ILD from a population-based Danish cohort were diagnosed with ILD 1-5 years prior to being diagnosed with RA.³⁵

Recent studies examining lower and upper respiratory tract disorders have suggested these conditions may also be associated with an increased risk of developing RA. In a meta-analysis, preexisting asthma was associated with a 1.4-fold higher risk of developing RA using pooled data from six cohort studies. While a similar association was present among fourteen case-control studies, it did not reach statistical significance.³⁶ There was also a high degree of heterogeneity among both the cohort and case-control studies in this meta-analysis which may be related to differences in the classification of asthma and RA (e.g., diagnostic codes vs. self-report), variable confounder adjustment, and concern for publication bias of positive findings.³⁶ In addition to asthma, the presence of COPD was associated with a near 2-fold higher risk of developing RA in the Nurses' Health Study.³⁷ Similarly, a case-control study utilizing the Swedish EIRA cohort found acute and chronic lower respiratory diseases to be associated with RA, particularly seropositive RA.³⁸ This same study observed a weaker association between chronic, but not acute, upper respiratory disease and RA, findings that were more pronounced among non-smokers.³⁸ Findings are conflicting on whether allergic rhinitis is associated with RA risk.³⁹ Respiratory infections have also been suggested as risk factors for the development of RA. Using an ecological study design, incident RA was found to be more likely to develop during the weeks following peaks of respiratory viral infections including parainfluenza virus, coronavirus, and metapneumovirus.⁴⁰ Cases of new onset RA have been reported after infection with SARS-CoV-2, the etiologic agent of COVID-19,⁴¹ but larger epidemiologic studies are needed to determine whether a true association exists.

Lung microbiome

While initially thought to be a sterile mucosal site, differences in the composition of the lung microbiome in patients with various lung diseases versus healthy individuals have established that the lung microbiome exists and that lung microbial diversity may accompany or contribute to disease risk.⁴² Little is known about the role of the lung microbiome in RA compared to the more commonly studied mucosal sites such as the gastrointestinal tract or oral cavity in RA. In a small cross-sectional study, patients with early DMARD-naïve RA were found to have a lower microbial diversity in fluid samples obtained via bronchoalveolar lavage (BAL) and evaluated by 16S rRNA sequencing compared to healthy controls.⁴³ Namely, *Actinomyces* and *Burkholderia* as well as some periodontopathic taxa (e.g., *Prevotella*) were decreased in RA, findings that were similarly observed in patients with pulmonary sarcoidosis.⁴³ In contrast to controls and sarcoidosis patients, BAL fluid of RA patients showed increased levels of *Pseudonocardia*,⁴³ although little is understood about the role of this genus in RA pathogenesis. Further characterization of the lung microbiome in RA, RA-associated lung diseases, and at-risk populations is needed to better understand its potential role in the development and perpetuation of RA, which may later facilitate its use as an indicator of risk and as a potential therapeutic or preventive target.

The lungs and RA-related autoimmunity

Several of the previously described epidemiologic studies linking inhalant exposures with RA have observed stronger associations with seropositive RA, suggesting that the lungs may be an early site of autoimmunity. Supporting these epidemiologic data, ACPAs have been detected in the sputum of established RA patients⁴⁴ as well as first-degree relatives of RA patients (i.e., at-risk for RA), including some who lacked ACPAs in the serum.^{44,45} Smoking, an established risk factor for RA, has been shown to increase citrullination and levels of peptidylarginine deiminase 2 (PAD-2) on BAL cells of healthy smokers relative to non-smokers.⁴⁶ Antibodies to PAD-4, which can increase PAD-4 activity *in vitro*, have also been found in the sputum of RA patients,⁴⁷ suggesting that these antibodies may play a role in driving RA-related autoimmunity in the lungs. Further supporting shared immune responses in the lungs and the joints, biopsy specimens from the lungs and synovium of RA patients revealed shared citrullinated peptides, including citrullinated vimentin, at both sites.⁴⁸

Immunoglobulin A (IgA) is the second most prevalent immunoglobulin in the serum but represents the primary immunoglobulin present at mucosal surfaces. At mucosal surfaces, IgA is present in a secretory form consisting of a dimer of two IgA molecules linked by a J chain and complexed with a secretory component.⁴⁹ During the development of disease-specific autoimmunity that typically precedes RA onset, rheumatoid factor (RF) IgA has been shown to be present several years before other RF isotypes in pre-clinical banked serum of RA patients.⁵⁰ In contrast, IgA ACPA does not appear to predate other ACPA isotypes during the evolution of pre-clinical autoimmunity.⁵⁰ Circulating IgA, as well as IgG, anti-malondialdehyde-acetaldehyde (MAA) antibodies also pre-date clinically apparent RA, but appear after RF and ACPAs.⁵¹ Secretory IgA ACPA has been detected in the serum of a subset of early RA patients and was more likely to be present among ever smokers

compared to non-smokers.⁵² Furthermore, levels of free secretory component (not bound to IgA) in the blood have been shown to be elevated in early RA patients compared to controls and associate with both ACPA and smoking,⁵³ These elevations in IgA antibodies and related secretory component of pre- and early RA patients suggest the possibility that mucosal irritants, such as smoking or other inhalant exposures, may lead to citrullination and other post-translational protein modifications in the lungs with the potential to drive an early autoimmune response that could ultimately lead to clinically apparent RA.

The presence of RA-related autoimmunity may not only indicate a risk of developing articular features of RA, but also lung abnormalities. First degree relatives of RA patients who were without inflammatory arthritis but positive for either ACPA and/or 2 RF isotypes were more likely to have high-resolution computed tomography (HRCT) abnormalities including bronchial wall thickening, air trapping, and airways disease compared to autoantibody-negative controls. These HRCT findings were similar to early RA patients within the same cohort suggesting that, like the measurement of autoantibodies, detectable airway disease may precede disease onset.⁵⁴ Similarly, in a cohort of patients with recently diagnosed RA, a higher number of ACPA fine specificities was associated with parenchymal abnormalities on HRCT.⁵⁵ The presence of serum ACPA secretory component in early RA patients has also been associated with parenchymal abnormalities on HRCT.⁵⁶

Findings from patients with RA-associated lung disease may provide insights into RA-related autoimmunity in the lungs. Organized lymphoid aggregates were discovered on lung biopsy specimens from patients with RA-associated ILD (RA-ILD), termed inducible bronchus-associated lymphoid tissue (iBALT), but much less frequently or not at all in other lung disorders such as idiopathic pulmonary fibrosis.⁵⁷ Moreover, these iBALT aggregates had elevated levels of PAD-2, which facilitate citrullination of peptides, as well RF- and ACPA-producing plasma cells.⁵⁷ Bronchiectasis, another RA-associated lung disease,⁵⁸ has additionally been proposed as a model for the loss of immune tolerance and development of autoimmunity. In a cross-sectional study, patients with bronchiectasis and without RA were shown to have increased frequencies of ACPA when compared to healthy controls, which correlated with the presence of antibodies to related arginine-containing peptides.⁵⁹ However, among patients with bronchiectasis and RA, the autoantibody response was specific for ACPA and did not correlate with antibodies to arginine-containing peptides. It was hypothesized that chronic exposure to citrullinated peptides in the inflamed lung with bronchiectasis may facilitate epitope spreading and a citrulline-specific autoimmune response.⁵⁹ These thought-provoking findings require further validation.

Additional Mucosal Sites

In addition to the lungs, evidence has accumulated supporting a role for other mucosal sites, such as the oral and gut mucosa, in RA pathogenesis. At these sites the microbiome has been of particular interest, with dysbiosis of the oral and gut microbiota of RA patients being identified through sequencing of fecal, oral, and dental samples.⁶⁰ Given the female predominance of RA, the urogenital tract has also been speculated as a possible site of RA risk, although data on this site remains limited.⁶¹

Periodontal disease and the oral microbiota

Oral health has been linked to systemic diseases and RA since ancient times. A meta-analysis of 17 studies comparing RA patients to healthy controls showed a modestly (~13%) increased risk of periodontitis among RA patients, although there was a large degree of heterogeneity among the included studies.⁶² In this same study, subanalyses were completed on four studies comparing RA and osteoarthritis (OA) patients, finding no significant difference in the prevalence of periodontitis. Again, there was substantial heterogeneity and negative findings were driven largely by a single, relatively small study.⁶² Given the largely cross sectional nature of these studies, it is difficult to determine whether the link between periodontal disease and RA is one of causality or instead related to shared risk factors (e.g. cigarette smoking) or a consequence of systemic disease. Suggesting the possibility that periodontal disease predates the clinically apparent RA, ACPA-positive patients without clinical arthritis were found to have a higher prevalence of periodontal disease and increased abundance of the periodontal related pathogen *Porphyromonas gingivalis* compared to controls.⁶³ In addition to being more common among RA patients, periodontitis may also be associated with a more severe RA disease course.⁶⁴

Porphyromonas gingivalis has been the subject of much of the research regarding the role of the oral microbiota in the pathogenesis of RA. This is predominantly related to *P. gingivalis* possessing its own unique active PAD enzymes (PPAD) which may contribute to the citrullination of human proteins.⁶⁵ However, interest has extended beyond *P. gingivalis*, more broadly characterizing the oral microbiota in patients with RA. In a study of new-onset, DMARD-naïve, seropositive RA patients, subgingival biofilm samples evaluated with 16S rRNA sequencing showed no significant differences in microbial richness or diversity when compared to established RA or non-RA controls.⁶⁶ Rather, differences in microbial composition at various taxonomic levels were explained by the presence or absence of periodontal disease.⁶⁶ Similarly, the prevalence and abundance of *P. gingivalis* did not correlate with the presence of RA, but rather with moderate- to severe periodontal disease in this study.⁶⁶ A subsequent case-control study of RA and OA patients again showed no compelling differences in the subgingival microbiome related to RA status, but distinctive microbial patterns based on the presence vs. absence of periodontal disease.⁶⁷ In contrast, a microbiome analysis of salivary samples was performed among RA and OA patients that was able to discriminate between diseases with high accuracy with eight bacterial biomarkers.⁶⁸ *Aggregatibacter actinomycetemcomitans* is another pathogen in the oral cavity hypothesized to have implications in RA pathogenesis. Incubation of neutrophils with *A. actinomycetemcomitans*, but not other microbial species, has been shown to induce hypercitrullination *in vitro*.⁶⁹ This is relevant to RA pathogenesis since the pattern of hypercitrullination in the periodontal microenvironment is similar to that in RA synovium.⁶⁹

With several studies identifying periodontal disease as a risk factor for RA and a more severe disease course, it is possible that the treatment of periodontal disease may prevent RA onset, or if already present, lead to improved RA control. No trials have evaluated RA prevention through periodontal treatment and only a few small trials have evaluated periodontal treatment for RA control. In a meta-analysis of nine smaller clinical trials (n = 60), patients randomized to non-surgical periodontal treatment had a moderately

(approximately half the minimum important difference) greater improvement in clinical disease activity (disease activity score in 28 joints [DAS28]) compared to controls.⁷⁰ The impact of periodontal treatment on individual components of composite clinical measures and other inflammatory cytokines were less consistent. Tender and swollen joint counts as well as C-reactive protein (CRP) tended to improve among those receiving periodontal treatment, but no significant difference was seen for erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), or tumor necrosis factor alpha (TNF- α).⁷⁰

Gut microbiota

Marked advances have occurred in the understanding of how the gut microbiome contributes to health and disease. Specific to RA, studies over the last decade have demonstrated differences in the microbiome of patients with RA when compared to healthy controls and other inflammatory disease states, including an over-representation of *Prevotella copri*. Through the use of 16S rRNA sequencing of stool samples, Scher et al.⁷¹ demonstrated that treatment naive, new-onset RA patients had a markedly higher rate of carriage of *P. copri* in their intestinal microbiota (77%) compared to healthy controls (21%). Similarly, in a cohort of first-degree relatives of RA patients, those with RA-related autoimmunity and/or signs/symptoms of possible RA had increased levels of *P. copri* in stool samples when compared to controls lacking these characteristics.⁷² Further supporting a possible pathogenic role of *P. copri* in RA, a subset of patients with new-onset RA have been shown to have Th1 responses to *P. copri* peptides.⁷³ Moreover, serum antibody responses to *P. copri* have been detected in a subset of both new-onset and chronic RA patients, a finding encountered only rarely among individuals with other rheumatic diseases and healthy controls.⁷³ A mendelian randomization study did not find a causal link between the gut microbiome and RA risk,⁷⁴ but there were questions regarding the degree to which genetics influence the gut microbiome and their suitability as instrumental variables.⁷⁵

While alterations in the microbiome may contribute to RA onset, treatment of RA with DMARDs appears to partially restore a healthy oral and gut microbiome in a subset of patients, particularly among those with a good clinical response to therapy.⁶⁰ Treatment specifically with methotrexate, the anchor drug for RA, has been demonstrated to lead to shifts in the gut microbiome.⁷⁶ Moreover, machine learning derived models from pre-treatment metagenomic gut microbiome data have shown an ability to predict methotrexate response in a small cohort of new-onset RA patients.⁷⁷ Data from healthy adults has suggested that even a single course of minocycline or other antibiotics can lead to long-lasting shifts in the composition of the intestinal microbiome, whereas the salivary microbiome was shown to be more resistant to these changes.⁷⁸ It is conceivable that the observed beneficial effects of minocycline in the treatment of RA⁷⁹ may partially be related to its impact on the microbiome of the gut or other sites (e.g., oral microbiome).

Discussion

Mounting evidence supports the notion that the risk of developing RA is multifactorial and impacted by many genetic and environmental factors (Figure 1). Particularly among individuals who carry *HLA-DRB1* risk alleles, environmental exposures and diseases

affecting the respiratory tract act as major risk factors for the development of RA, with a leading theory being that the lung mucosa may be an initial site of autoimmunity in RA. Exposures and diseases at other mucosal sites including the oral cavity and gastrointestinal tract similarly seem capable of stimulating immune responses characteristic of RA. However, the totality of the epidemiologic and translational evidence for these mucosal sites is less than for the lungs. While this review has focused on mucosal related triggers of RA, it is important to understand that environmental risk factors very likely influence RA risk through mechanisms beyond the mucosa. A key question moving forward is how mucosal and non-mucosal factors interact to affect RA risk as well as disease phenotype across various populations, such as in men and women or those defined by autoantibody status.

As our understanding of these risk factors has improved, a future step will be harnessing and applying this information to prevent RA. Given the many different environmental risk factors for RA, a detailed personalized risk assessment will ultimately prove valuable for identifying relevant risks at an individual level. Disclosure of these risks has the potential to motivate healthy behaviors.⁸⁰ Cigarette smoking cessation, use of an appropriate mask when exposed to noxious inhalants, good dental hygiene, and adhering to a healthy diet may eventually be recommended by clinicians as part of a personalized approach not only for minimizing RA risk and burden but also for general health benefits yielded from these indicated (and relatively low cost) interventions. Ultimately, the development and implementation of effective RA prevention strategies that target the reviewed environmental risk factors could dramatically reduce the morbidity, mortality, and exorbitant costs that accompany RA.

Summary

Inhalant exposures including cigarette smoking and a variety of other occupational and environmental biohazard exposures are associated with a higher risk of developing RA. Similarly, respiratory diseases such as asthma, COPD, and infections have been linked to RA risk, though the relative contributions of these diseases vs. the environmental exposures that led to these diseases largely remains to be determined. Beyond the respiratory tract, periodontal disease and alterations of the oral and gastrointestinal microbiome are more common in patients with RA and likely influence disease risk. RA-related autoimmunity occurring with or prior to the development of clinically apparent RA may be originating at these mucosal surfaces as a result of genetic predisposition and relevant environmental exposures.

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Key Points:

- Several inhalant exposures including cigarette smoke, silica, and other occupational exposures have been associated with an increased odds of developing rheumatoid arthritis (RA) in epidemiologic studies.
- Articular and lung manifestations in RA demonstrate a bi-directional temporal relationship with airway and lung parenchymal involvement most frequently developing after arthritis, although lung disease may be the initial presenting finding.
- Mucosal surfaces, particularly those within the airways and lungs, may be early sites of RA-related autoimmunity.
- Dysbiosis of the microbiome of the gut, oral, and lung mucosa has been identified in RA patients and may have a pathogenic role in RA.

Synopsis:

Rheumatoid arthritis (RA) occurs as the result of a complex interplay of environmental factors in a genetically susceptible individual. There is considerable evidence that the lungs may serve as an initial site of tolerance loss in the generation of RA-related autoimmunity, and several environmental inhalant exposures and lung diseases have been associated with RA risk. There is additionally evidence that immune and microbial dysregulation of other mucosal sites, including the oral and gastrointestinal mucosa, may contribute to the development of RA. Epidemiological evidence linking mucosal exposures to various environmental insults as risk determinants in RA will be reviewed.

Clinics Care Points

- Many exposures at the respiratory, oral, and gastrointestinal mucosa have been associated with the development of RA, and mitigation of these risk factors may help to decrease the individual and societal burden of RA.
- Environmental inhalant exposures may incite autoantibody responses within the lungs that predate the onset of clinically apparent RA as well as contribute to the development of RA-associated lung diseases.
- Dysregulation of the oral, gastrointestinal, and respiratory microbiome has been identified in RA patients, and elucidating the role of the microbiome in disease pathogenesis and its effects on treatment response may help guide RA management in the future.

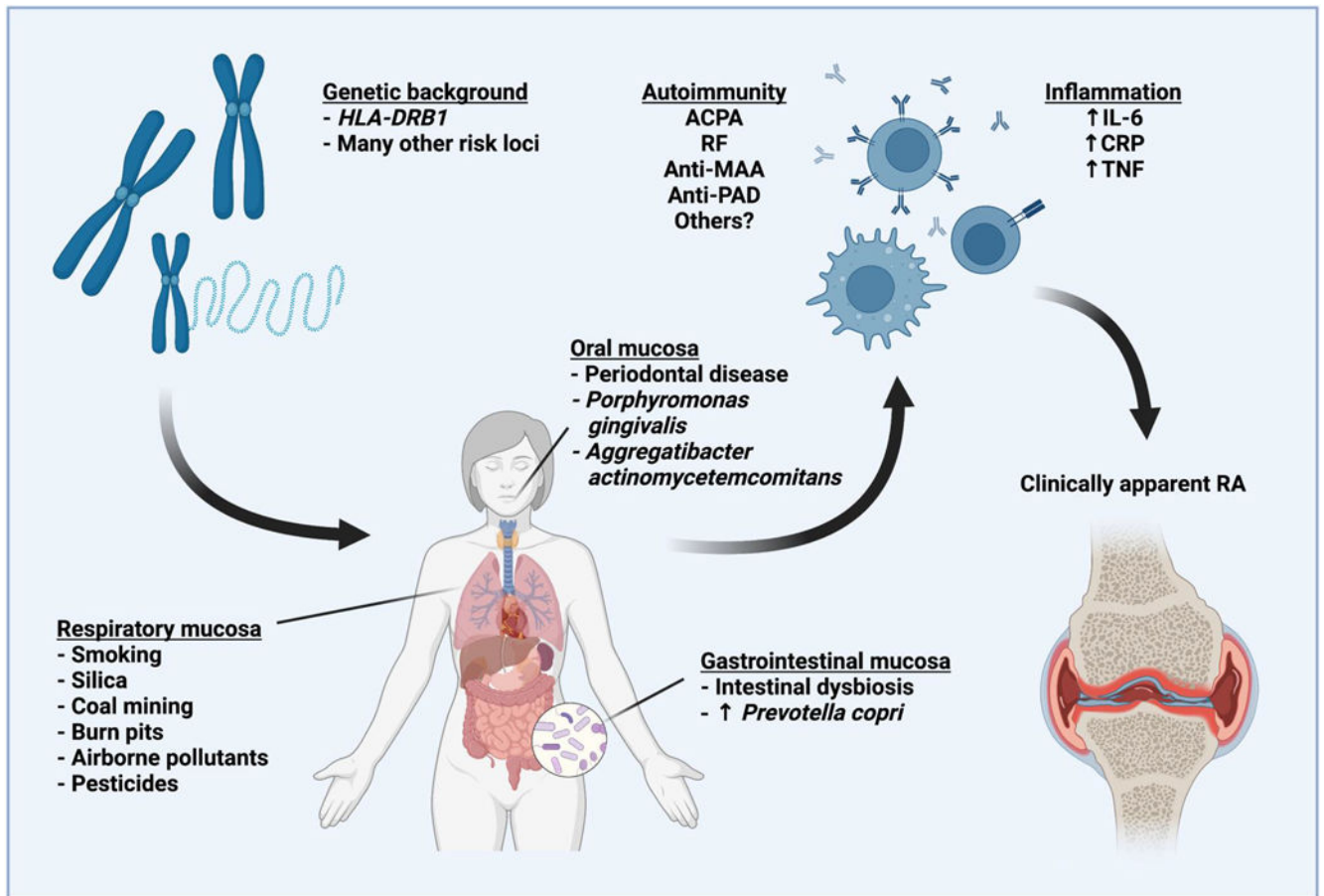


Figure 1. Contribution of environmental exposures at mucosal surfaces to the development of clinically apparent RA.

Genetic variants predispose to RA, with the most established genetic risk variant being *HLA-DRB1* shared epitope alleles. Many environmental exposures have been associated with the development of RA, with relevant exposures at respiratory, oral, and gastrointestinal mucosal sites being shown. Following environmental exposures in a genetically susceptible individual, RA-related autoimmunity and inflammation develop, frequently preceding clinically apparent RA by several years. *Created with BioRender.com.*

Abbreviations: RA = rheumatoid arthritis, ACPA = anti-citrullinated protein antibodies, RF = rheumatoid factor, MAA = malondialdehyde acetaldehyde, PAD = peptidylarginine deiminase, IL = interleukin, CRP = C-reactive protein, TNF = tumor necrosis factor.

Table 1.

Association of cigarette smoking exposures with rheumatoid arthritis.

Exposure type	Evidence of association with RA
Ever smoking	
Overall	<p>In a meta-analysis of epidemiologic studies, ever smoking was associated with an increased risk of RA (OR 1.40) compared to never smoking. Similarly, the OR for current smoking was increased at 1.35, while past smoking was associated with a lower but significant OR of 1.25.⁴</p>
Sex	<p>Smoking appears to have a greater impact on RA risk among men compared to women. In a meta-analysis, ever smoking showed a greater association with RA among men (OR 1.89) than among women (OR 1.27).⁴</p>
Seropositivity	<p>The risk incurred by cigarette smoking is greatest for the development of seropositive RA. In a meta-analysis, ever smoking was more strongly associated with RF-positive RA (OR 1.66) than with all RA (OR 1.40). This increased risk was especially prominent among men (OR 3.2 for RF-positive RA vs. 1.89 for all RA).⁴</p>
Duration/intensity of smoking exposure	<p>A meta-analysis of 3 prospective cohort and 7 case-control studies showed an increase in the risk of RA as pack-years of smoking increased, with a plateau around a 20 pack-year smoking history⁵</p> <p>RR for 1-10 pack-years = 1.26 (1.14, 1.39)</p> <p>RR for 11-20 pack-years = 1.70 (1.44, 2.01)</p> <p>RR for 21-30 pack-years = 1.94 (1.65, 2.27)</p> <p>RR for 31-40 pack years = 2.02 (1.44, 2.82)</p> <p>RR for > 40 pack-years = 2.07 (1.15, 3.73)</p>
Passive smoke exposure	<p>In case-control studies, there was no significant association between passive smoke exposure and RA.^{10,11} In a French cohort, passive smoke exposure during childhood showed a borderline, but not statistically significant, increased risk of RA in adulthood both among never-smokers and ever-smokers.⁹ In the NHS prospective cohort, parental smoking during childhood was associated with seropositive RA in adulthood (HR 1.41).¹²</p>
Smoking cessation	<p>In the NHS prospective cohort, sustained smoking cessation was associated with a lower risk of developing RA compared to current smoking or recent cessation, and was more pronounced as the duration of smoking cessation increased.⁸</p> <p>HR never smoker = 1 (referent)</p> <p>HR quit smoking 0-5 years ago = 1.57 (1.26, 1.95)</p> <p>HR quit smoking 5-10 years ago = 1.63 (1.30, 2.04)</p> <p>HR quit smoking 10-20 years ago = 1.37 (1.15, 1.64)</p> <p>HR quit smoking 20-30 years ago = 1.19 (0.99, 1.45)</p> <p>HR quit smoking >30 years ago = 1.25 (1.02, 1.53)</p>
Gene-environment interaction	<p>A significant gene-environment interaction exists between smoking and shared epitope alleles for seropositive RA, as illustrated by the following results from a Swedish case-control study:⁸¹</p> <p>RR for non-smokers with 0 SE alleles = 1 (referent)</p> <p>RR for non-smokers with 1 SE allele = 3.3 (1.8, 5.9)</p> <p>RR for non-smokers with 2 SE alleles = 5.4 (2.7, 10.8)</p>

Exposure type	Evidence of association with RA
	RR for smokers with 0 SE alleles = 1.5 (0.8, 2.6) RR for smokers with 1 SE allele = 6.5 (3.8, 11.4) RR for smokers with 2 SE alleles = 21.0 (11.0, 40.2)

Abbreviations: RA = rheumatoid arthritis, OR = odds ratio, RF = rheumatoid factor, RR = relative risk, NHS = Nurses' Health Study, HR = hazard ratio, SE = shared epitope

Table 2.

Inhalant exposures associated with rheumatoid arthritis.

Inhalant exposure	Evidence	Association with seropositive vs. seronegative disease	Gene-environment or environment-environment interactions
Silica	Meta-analysis of 12 epidemiologic studies found silica exposure to be associated with a nearly two-fold increased odds of RA ¹⁷	Silica exposure most closely associated with seropositive disease (OR 1.7) although associations also observed for seronegative RA (OR 1.2) in meta-analysis of 7 studies ¹⁷	Unknown
Coal mining	Coal mining associated with RA (OR 3.6) in random telephone survey of 973 Appalachian men aged 50 years ¹⁹	Unknown	While exposure to silica may co-occur with exposure to coal dust, coal mining appears to be independently associated with RA risk ¹⁹
Military exposure	Reported exposure to burn pits was associated with seropositivity among a population of known RA patients, ²¹ but deployment within a 3-mile radius of burn pits was not associated with a self-reported diagnosis of RA. ²² Among a sample of 438,086 veterans, inorganic dust exposure during military service estimated via military occupation codes was associated with RA (OR 1.10) defined by ICD codes. ²³	Anti-CCP antibodies were more common among U.S. veterans with RA reporting exposure to military burn pits (OR 1.7). ²¹ Inorganic dust exposure was associated with seronegative (OR 1.25) but not seropositive RA. ²³	Association of burn pits with anti-CCP antibodies stronger (OR increased from 1.7 to 5.7) among those positive for shared epitope alleles ²¹
Pesticides	Among a large cohort of women, a significant trend was observed with more frequent and more direct/personal application of pesticides in childhood (OR 1.8 for direct and frequent use). ²⁵ Among women with childhood-only farm residence, RA was associated with a history of personal exposure to pesticide use on crops (OR 1.8) and livestock (OR 2.0). ²⁵	Unknown	Unknown
Airborne pollutants and particulate matter	Mixed findings: meta-analysis found positive associations with RA and ozone exposure (RR 1.16) and close proximity to roadway (RR 1.34), with two eligible studies for each respective exposure. In contrast, no association was observed between RA and particulate matter, NO ₂ , CO, or SO ₂ (range of 2-5 studies per exposure). ²⁷	Fine particulate matter associated with anti-CCP antibody concentration, but not RF, in 557 veterans with established RA. ²⁹	Unknown

Abbreviations: RA = rheumatoid arthritis, OR = odds ratio, CCP = cyclic citrullinated peptide, ICD = International Classification of Diseases, RF = rheumatoid factor, NO₂ = nitrogen dioxide, CO = carbon monoxide, SO₂ = sulfur dioxide.