Review

Environment and arthritis

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ABSTRACT

The present narrative review explores the multifactorial aetiology of rheumatoid arthritis (RA) and other immune-mediated inflammatory disorders (IMIDs), emphasising the significant role of various environmental factors in disease development and exacerbation. Key modifiable environmental factors such as cigarette smoking and air pollution are identified as major contributors to RA. We will also focus on the influence of weather, seasonality, and particularly vitamin D levels, on RA activity, suggesting potential for seasonal management and supplementation to mitigate disease severity. The emerging role of diet and the gut microbiome in RA pathogenesis and progression is discussed as well, with dietary interventions and specific nutrients like omega-3 fatty acids offering protective benefits against inflammation. Despite the mounting evidence around these factors, further research is needed, to better understand the clinical impacts on RA, including well-designed randomised clinical trials.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease. The prevalence of RA varies globally, with generally a higher prevalence in industrialised countries (1). While this observation might be due to a greater diagnostic competence, epidemiological studies show that the incidence and the prevalence of immune mediated inflammatory disorders (IMIDs) are increasing steadily in the last decade. The etiopathogenesis of RA and most IMIDs is still unknown but it certainly involves genetic, epigenetic and environmental factors. Unrevealing the factors associated with the development and exacerbation of IMIDs is crucial in order to discovery new and effective targets for therapies and, possibly, to set up appropriate public health prevention strategies (2). In the present narrative review, we will summarise the effect of common and widely studied environmental (and partially modifiable) factors associated with the development of RA and other IMIDs of interest (Fig. 1).

Cigarette smoke

The most common modifiable risk factor for RA is cigarette smoking. Cigarettes have been associated with both severity and exacerbation of RA (3, 4). Several case-control studies, retrospective studies and meta-analyses showed that in heavy smokers, the risk of developing RA is around 2-fold higher compared to never smokers, with evidence of a dose-response based on pack-year exposure. The risk with smoking appears to be much stronger for the development of seropositive RA, rather than seronegative including both rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) positive RA (5, 6). Interestingly, patients with cigarettes related lung disease had been shown to develop more commonly RF positive RA, as opposed to ACPAs (7), but the underlining mechanisms is largely unknown. The risk of the development of RA in smokers appeared to be higher in long-lasting smokers than in short-period one with a significant dose-response trend as shown in a prospective study of Karlson *et al*. (8). Intensity and duration of smoking contribute independently to the relative risk of RA (8). Cigarette smoking generates a proinflammatory process, with multiple effects on key immune cells both systemically and at the mucosal surface. Combustion smoke contains thousands of chemicals including immunomodulators such as nicotine, carbon monoxide, acrolein and oxygen free radicals (9). Cigarette smoke contains several toxic molecules such as tar, carbon monoxide, nicotine,

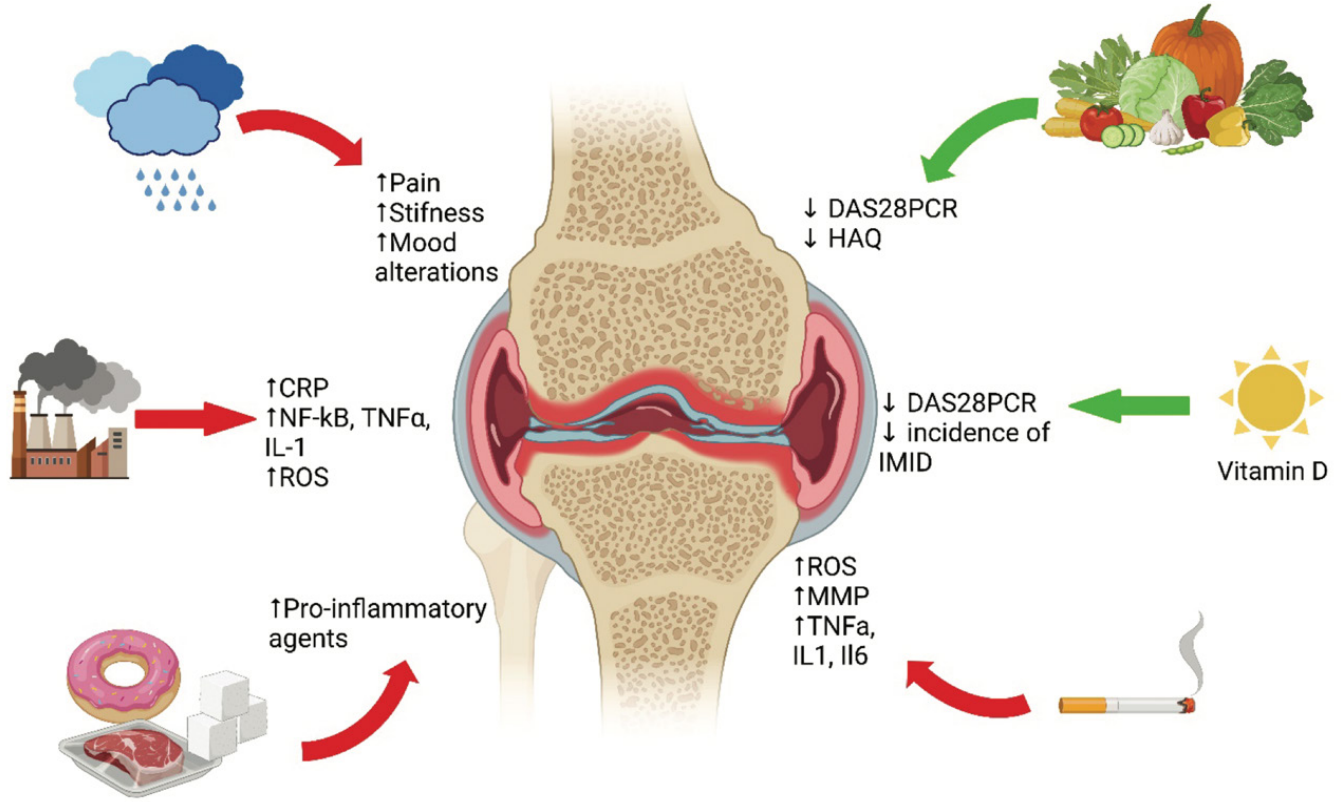

Fig. 1. Environmental exposures and arthritis, a complex interplay.

acetaldehyde, methane, hydrogen cyanide (HCN) and others (10). Although it is still unknown which molecules determine the increase of the risk of development of RA or the production of ACPA, some studies found that the ratio of TNF-α/sTNFRII (TNF receptor II) released from stimulated T lymphocytes was significantly higher in both current and past smokers than in those who had never smoked (11).

At the mucosal surfaces, cigarette smoke activates local epithelial cells to produce pro-inflammatory cytokines, which enhances immune cell recruitment to illicit an inflammatory response (12). At a systemic level, cigarette smoking skews the immune system towards a proinflammatory response. Multiple studies suggested that smoke influences helper T-cell polarisation skewing differentiation towards Th1 and Th17 CD4 T-cells (6).

Cigarette smoke was also studied as a risk factor for more severe type of RA regarding radiologic progression of the disease: in a randomised-trial of Van Vollenhoven *et al*. current smoking habits was found as a strong independent predictor of radiographic progression (13). Smoke is not only a risk factor for the development of RA and RA-associated autoantibodies but may also contribute to a weaker response to csDMARD Methotrexate and anti-TNF therapy (14, 15). In an observational study of Van Laar *et al*. smoking status was found as a rather moderate, but robust predictor for discontinuation of TNF-i therapy (16).

Regarding the remission and response to therapy lower rates of sustained remission had been demonstrated in current smokers compared with ex-or never smokers (17).

Smoke can be considered a risk factor for the development of RA, a higher radiologic progression-rate and a lower response to therapies but smoking reduction and cessation are associated with a lower risk of development of RA and mortality (18) therefore we should encourage patients to stop smoking.

Environmental air pollution

In the last years the exposure to air pollution has been implicated in the occurrence and development of several autoimmune diseases such as inflammatory bowel disease (19), multiple sclerosis (20), and systemic rheumatic disease. Combustion derived environmental air pollution shares numerous toxic components with cigarette smoking and, therefore, is it not surprising of such association. Air pollution is a complex mixture of particulate matter (PM) and gases (*e.g*. carbon monoxide [CO], nitrogen dioxide [NO2], ozone [O3] and sulfur dioxide [SO2]) (21). Similarly to cigarette smoking, airborne air pollution can negatively alter the immune response. It has been prove that many components of diesel combustion can bind to the aryl hydrocarbon receptor (AHR) to regulate Th17 and Treg cells (22). Oxidative stress and inducible bronchus associated lymphoid tissue (iBALT) caused by the pollutants can influence T and B cells, resulting in the production of proinflammatory cytokines. These cytokines further stimulate the immune response, contributing to autoimmunity development. New evidence suggests that mucosal sites such as the periodontium, gastrointestinal tract and/or lung, could be potential sites of early autoantibody production

in RA patients prior to diagnosis. It has been postulated that reactive oxygen species released by gaseous pollutants could enter the respiratory tract and activate production of pro-inflammatory cytokines; the resulting inflammation might preferentially target synovial joints and lead to peptide citrullination and ACPA production, ultimately leading to RA development (23).

Moreover, air pollutants may induce epigenetic changes to contribute to IMIDs risk (21). PM exposure has been associated with an increased production of interleukin IL-1, IL-6 and tumor necrosis factor (24). The fine particulate matter PM2.5 (2.5 micrometers) are derived from combustion processes, including vehicle emissions, wildfires, wood and coal burning and industrial processes appears to be the most harmful as it includes multiple particles (sulfates, nitrates, acids, and metals) adsorbed onto their surfaces (25). PM2.5 inhalation has been shown to stimulate alveolar macrophages, leading to increased CRP, platelet, and leukocyte activation and increased pro-inflammatory mediators (26). Kerr *et al*. conducted a study on air pollution and autoantibodies status in RA finding out that fine particulate matter (PM2.5) exposure independently predicted higher ACPA concentration (27).

The assessment of the impact of air pollution on health involves analysing both long-term and short-term exposure, each requiring distinct methodologies. For long-term effects, air pollution needs to be measured over extended periods. However, these methods face challenges in estimating lifetime exposure, particularly since systematic measurements began only in the late 20th century. Consequently, long-term exposure is often approximated from specific time windows, potentially leading to misclassification due to factors like patient relocation. In contrast, acute exposures are examined through different study design. Case-crossover studies are commonly utilised to this aim (28, 29). Case-crossover studies are particularly effective for studying the impact of short-term pollution exposure on the onset of acute diseases. Unlike traditional case-control studies, case-crossover designs compare different time periods within the same patient group, allowing for improved control of confounders. Conditional logistic regression is commonly employed in these studies to address time-varying confounders, offering a more precise analysis of the transient effects of air pollution on health. Nonetheless, other designs like interrupted time series design have been used to assess the impact of time-varying pollutants on health outcomes. Interestingly, in the field of IMIDs, several studies showed a difference between chronic and acute exposure to air pollution.

A recent case-crossover study found that short-time exposure to high levels of air pollution can exacerbate RA. Interestingly, a dose-response association between airborne pollutants concentrations and CRP levels has been demonstrated (30). In addition, concentrations of pollutants were higher before treatment failures in chronic arthritides, including RA, suggesting a possible inference of air pollution on retention rate of such medications (31). The acute exposure and the effect on disease activity was also studied in Systemic Lupus Erythematosus by Rezayat *et al*. who published a comprehensive meta-analysis including six studies delineating a positive correlation between an incremental to PM2.5 and the SLE disease activity index (SLEDAI) (32).

On the other hand, there is ample evidence supporting the association between chronic exposure to air pollution and the risk of developing RA (33–36). Studies on influence of air pollution on IMIDs are several, not only for RA but also for other common rheumatic disease. One recent study of Brito-Zerón *et al*. showed that patients with Sjogren Disease living in more polluted areas had higher typical symptoms such as mouth and eyes dryness and higher disease activity index (ESSDAI) at the diagnosis. They also found a significant association between worse expositions to air pollutants and severe systemic disease (37). Regarding systemic sclerosis, a recent French retrospective study of patients with SSc-associated ILD evaluated the contribution of the principal air pollutants (PM_{10}, $PM_{2.5}$, NO_2, and O_3) to the natural course of SSc-associated ILD finding out that O_3 (ozone) exposure was significantly associated with the presence of extensive ILD and with progression at 24 months (38). Air pollution could also be related to the occurrence and development of systemic vasculitides, such as antineutrophil cytoplasmic antibody (ANCA) or Kawasaki disease, as evaluated in several studies (39, 40).

Considering the strong evidence linking air pollution exposure to the aggravation of autoimmune diseases, including its emerging role in the development, severity, and recurrence of RA, it becomes imperative for policymakers worldwide to take action. Yet, further studies are essential to identify the specific pollutants most implicated in the pathogenesis and activity of RA. By understanding which pollutants are most harmful, governments can target these modifiable environmental factors with interventions aimed at reducing exposure and, consequently, the burden of autoimmune diseases such as RA. This knowledge is crucial for developing strategies to mitigate the impact of air pollution on public health, especially for those living with IMIDs.

Weather and seasonality

The assumption that climatic environment influences the signs and symptoms of RA is widely believed. Several seasonality factors may contribute to the disease activity and pain such as humidity, atmospheric pressure, temperature, UV exposure (41).

In the clinical practice we routinely notice that many patients with RA complained of fluctuation in joint symptoms according to climatic factors such as air temperature, humidity, and atmospheric pressure; however, there is a paucity of scientific evidence supporting this generally held assumption. It is also commonly reported that climate and the environment are associated RA pathogenic factors (42).

Humidity is among the most frequently studied climate factor. An animal experimental study showed that a state of high humidity (80± 5%) could aggravate arthritis by increasing arthritis score, serum autoantibodies (*i.e*. AC-

PAs), and proinflammatory cytokines (IL-6, IL-17A, and G-CSF). This came with upregulation of Xylitol and L-pyroglutamic acid in the microbiome, underling the association between gut, environment and immune system (43). In addition, a recent, but arguably small, population study highlighted the possibility that climatic environment, such as air temperature and pressure, might have an effect on the proportion of T and B cell subpopulations, possibly triggering autoimmunity in RA (44).

The potential link between seasonality and the activity of RA is a subject of increasing interest within the medical community, particularly concerning the role of vitamin D (45). Vitamin D, known for its fluctuating levels across different seasons, emerges as a significant variable directly associated with RA disease activity. Research, including a recent comprehensive review, has highlighted an inverse relationship between the levels of activated vitamin D in the plasma and the severity of RA symptoms (46). This relationship was meticulously quantified using the Disease Activity Score in 28 joints (DAS-28). The findings suggest that lower plasma levels of vitamin D, which are common during the less sunny months, could exacerbate RA symptoms. This seasonality effect underscores the importance of vitamin D as not only a marker of disease activity but also potentially a modifiable risk factor in the management and treatment of rheumatoid arthritis, hinting at the therapeutic potential of vitamin D supplementation in mitigating disease severity according to seasonal variations. (46, 47). Vitamin D can act in the pathogenetic RA process at multiple levels. Vitamin D can directly downregulate the expression of macrophage aromatases, reducing the production of auto-reactive B lymphocytes and modulate cytokines expression (45, 48, 49). In spring, a worsening of inflammatory articular symptoms had been reported (50). In contrast, RA appeared to be less symptomatic in autumn (50). Levels of vitamin D reaches a nadir during late winter and early spring, and this could explain the exacerbation of disease during early spring when levels of vitamin D are still at their lowest (51). Moreover, RA onset during winter or spring (low UV and low vitamin D) rather than summer or autumn seemed to be associated with a rapidly progressive erosive disease (52)**.** Fascinatingly, the VITAL trial revealed that regular intake of vitamin D was linked to a reduced occurrence of autoimmune diseases (53). This correlation became evident after two years of daily vitamin D consumption and diminished once supplementation ceased (54).

However, the specific clinical benefits of vitamin D supplementation in managing RA still require clarification through well-conducted randomised clinical trials that are sufficiently powered and employ appropriate dosages and durations of supplementation.

Other rheumatic diseases convey the seasonality, for instance systemic lupus erythematosus. Exposure to sunlight and ultraviolet radiation (especially UVA and UVB) induce photosensitivity, skin rashes, and recurrence in patients with pre-existing SLE (55). SLE has been shown to have seasonal variation, with higher incidence in the summer, during which UVR is the strongest (56) The influence of seasonality was also found on disease activity of SLE, some studies have demonstrated that there are more cases of new onset and recurrence of SLE in winter and spring than in summer and autumn (56, 57). In Sjögren's syndrome a correlation between vitamin D levels and extraglandular involvement, especially peripheric nervous system involvement, was studied considering the neuroprotective and neuroactive properties of vitamin D (58). It could increase nerve growth factor in Schwann cells, glial cells that generate myelin sheath and provide trophic support to the neurons (59). Taken together, all the data suggest a possible role for vitamin D in the peripheral neuropathy of SD and incite further exploration (60).

Diet and microbiome

In recent years, an increasing number of studies suggested that diet has a central role in RA risk and progression. In this context, nutrition has both direct roles in disease development through the provision of (anti)-inflammatory food components, and indirect roles through effects on the body mass index (BMI), visceral fat accumulation and by contributing to the development of diabetes and CVD (61). Several nutrients, such as polyunsaturated fatty acids, present anti-inflammatory and antioxidant properties, featuring a protective role for RA development, while others such as red meat and salt might have a harmful effect (62). Specifically, the effect of fasting, the Mediterranean diet, vegetarian diet and specific food substances on disease activity in RA has been investigated in various studies all over the world (63, 64).

Gut microbiota alteration and body composition modifications are indirect mechanisms of how diet influences RA onset and progression. Even if the relationship between RA and diet is not as strong as other risk factors (smoke primarily), dietary influence has been widely studied, also considering the complex nature of nutrient provision. Moreover, diet represents a major factor influencing microbiota composition, which has been involved in the disease's development (65).

One hypothesis for the pathogenesis of RA is that disease begins at mucosal sites because of interactions between the mucosal immune system and an aberrant local microbiota, and then transitions to involve the synovial joints. Alterations in the composition of the microbial flora in the lungs, mouth and gut in individuals with preclinical and established RA suggest a role for mucosal dysbiosis in the development and perpetuation of RA, although establishing whether these alterations are the specific consequence of intestinal involvement in the setting of a systemic inflammatory process, or whether they represent a specific localisation of disease, is an ongoing challenge (4, 66). Dietary habits could represent both disease risk and protective factor, based on the properties of specific foods. Specific dietary choices can indeed show pro-inflammatory effects (for example red meat, salt, excessive caloric intake) or on the contrary reduce inflammation (oil, fatty fish, fruit and others) (67).

Although most studies focused on pathogenesis, there is evidence that the microbiome and diet could impact on

disease expression, course and outcome (68). Several studies have recently suggested that the use of omega-3 and moderate alcohol consumption may have a protective effect on RA evolution, particularly among smokers or individuals at high risk (69). Fasting resulted in significant but transient subjective improvements and the Mediterranean diet demonstrated improvements in some RA disease activity measures. Other dietary regimens such as vegetarian, elimination, peptide, or elemental diets showed very individualised responses.

Among food nutrients associated with inflammation and risk of auto-immune diseases one of the most studied is omega-3 fatty acid. The risk reduction of RA associated to a higher intake of omega-3 fatty acids is related to their anti-inflammatory properties, inhibiting leucocyte chemotaxis, adhesion molecule expression and production of pro-inflammatory leukotrienes and prostaglandins from omega-6 fatty acids (70, 71). A recent systematic review and meta-analysis on effects of PUFAs concluded significant positive effects on several outcomes in RA, although not in DAS28 (72). The Sweden group of Vadell *et al*. conducted a randomised, controlled crossover trial on patients with active RA comparing the effects on disease activity of an anti-inflammatory diet (rich in unsaturated fat, fish, vegetables, wholegrain cereals) compared to a control diet consisting of, among other things, meat, refined grains daily, white bread. The study found no significant difference in effects on DAS28 and its components between the intervention and the control diet. But a significant improvement in disease activity was obtained during the intervention period and significantly lower DAS28 after intervention than after control diet (73).

The gut microbiota, including all the commensal and potentially pathogenic bacteria residing in the human gastrointestinal system, plays a major role in the physiologic and immunologic homeostasis of the organism and its alteration could be related to the pathogenesis of several inflammatory diseases, including RA (74). Several authors reported an abundance of *Prevotella coprii* in early RA patients with a significant effect on the inflammatory response: an increase of related Th17 cytokines (*i.e*. IL-6, IL-23), an increased gut permeability with a major penetration of external antigens and bacteria, and a mutual decrease of protective species (75). Interestingly, *Prevotella spp* is a diet-responsive bacteria: in particular its increase is related to high-fibre diet *(76)*. Some authors postulate that the microbiota and the intestinal barrier may be a missing link between the various nutritional factors and the development of RA. The modification of microbiota using dietary interventions and focusing on the improvement of the intestinal barrier function may become an important component for "preventive" nutritional strategies (77).

Not only in RA but also in primary Sjögren's syndrome researchers gave attention to bacteria and microbiome in pathogenesis and severity of the disease: it is possible that distorted immune response to a normal microbiota, rather than specific infections, may be a first step in the pathogenesis of pSS. Autoimmune epithelitis and dryness of mucosal surface, as well as autoimmune processes, may sensitise to certain bacterial infections (78). Three pathways might help to clarify the potential contribution of microbiota to pSS pathogenesis: molecular mimicry, metabolite changes and epithelial tolerance breakdown (79). Similar type of research was made also in patients with systemic lupus erythematosus: researchers found out that several pathobionts and pathways are related to local or systemic inflammation processes and immune system dysregulation in animal lupus models, but remains to be determined how consistent they are among different patient populations and which microbial antigens drive immune intolerance to produce several lupus-related autoantibodies (80)

In aggregate, some dietary approaches may improve RA symptoms and thus it is recommended that nutrition should be routinely addressed (81).

Conclusion

In conclusion, in the present review we underscored the multifaceted nature of RA, highlighting the significant interplay between genetic, epigenetic, and environmental factors in the etiopathogenesis. Notably, modifiable risk factors such as cigarette smoking and air pollution have been identified as key contributors to the development and exacerbation of RA, with smoking cessation and pollution reduction emerging as critical strategies for disease prevention. Furthermore, the complex relationship between weather, seasonality, and RA activity – particularly the role of vitamin D – underlines the potential for seasonal management strategies and supplementation to mitigate disease severity. The emerging evidence linking diet and the gut microbiome to RA pathogenesis and progression points to the importance of dietary interventions in managing RA, with specific nutrients such as omega-3 fatty acids offering protective benefits against inflammation. We also recognised the necessity for further research, particularly well-designed randomised clinical trials, to better understand the clinical impacts of these environmental and lifestyle factors on RA. Such insights are crucial for developing more effective therapies and public health prevention strategies, ultimately aiming to alleviate the burden of these diseases and improve the quality of life for affected individuals. The collective findings from various studies emphasise the importance of a holistic approach in the management and treatment of RA, incorporating both pharmacological interventions and lifestyle modifications to address the complex interplay of factors contributing to the disease.

References

1. FINCKH A, GILBERT B, HODKINSON B *et al*.: Global epidemiology of rheumatoid arthritis. *Nat Rev Rheumatol* 2022; 18(10): 591-602. https://doi.org/10.1038/s41584-022-00827-y
2. NANDAKUMAR KS, FANG Q, WINGBRO ÅGREN I, BEJMO ZF: Aberrant activation of immune and non-immune cells contributes to joint inflammation and bone degradation in rheumatoid arthritis. *Int J Mol Sci* 2023; 24(21): 15883. https://doi.org/10.3390/ijms242115883
3. HAHN J, MALSPEIS S, CHOI MY *et al*.: Association of healthy lifestyle behaviors and the risk of developing rheumatoid arthritis among women. *Arthritis Care Res* 2023; 75(2): 272-76. https://doi.org/10.1002/acr.24862
4. ZAISS MM, WU H-J J, MAURO D, SCHETT G, CICCIA F: The gut-joint axis in rheumatoid ar-

thritis. *Nat Rev Rheumatol* 2021; 17(4): 224-37. https://doi.org/10.1038/s41584-021-00585-3
5. ELOFF E, MARTINSSON K, ZIEGELASCH M *et al*.: Autoantibodies are major predictors of arthritis development in patients with anti-citrullinated protein antibodies and musculoskeletal pain. *Scand J Rheumatol* 2021; 50(3): 189-97. https://doi.org/10.1080/03009742.2020.1818820
6. MAISHA JA, EL-GABALAWY HS, O'NEIL LJ: Modifiable risk factors linked to the development of rheumatoid arthritis: evidence, immunological mechanisms and prevention. *Front Immunol* 2023; 14: 1221125. https://doi.org/10.3389/fimmu.2023.1221125
7. WOUTERS F, MAURITS MP, VAN BOHEEMEN L *et al*.: Determining in which pre-arthritis stage HLA-shared epitope alleles and smoking exert their effect on the development of rheumatoid arthritis. *Ann Rheum Dis* 2022; 81(1): 48-55. https://doi.org/:10.1136/annrheumdis-2021-220546
8. COSTENBADER KH, FESKANICH D, MANDL LA, KARLSON EW: Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. *Am J Med* 2006; 119(6): 503.e1-503.e9. https://doi.org/10.1016/j.amjmed.2005.09.053
9. SHAN M, CHENG H-F, SONG L-Z *et al*.: Lung myeloid dendritic cells coordinately induce TH1 and TH17 responses in human emphysema. Science Translational Medicine 2009, 1(4), 4ra10. https://doi.org/10.1126/scitranlsmed.3000154
10. PREVENTION (US): Chemistry and toxicology of cigarette smoke and biomarkers of exposure and harm. in how tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General; Centers for Disease Control and Prevention (US), 2010.
11. GLOSSOP JR, DAWES PT, MATTEY DL: Association between cigarette smoking and release of tumour necrosis factor α and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2006; 45(10): 1223-29. https://doi.org/10.1093/rheumatology/kel094
12. LEE S-H, GOSWAMI S, GRUDO A *et al*.: Antielastin autoimmunity in tobacco smoking-induced emphysema. *Nat Med* 2007; 13(5): 567-69. https://doi.org/10.1038/nm1583
13. SAEVARSDOTTIR S, REZAEI H, GEBOREK P *et al*.: Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial. *Ann Rheum Dis* 2015; 74(8): 1509-14. https://doi.org/10.1136/annrheumdis-2013-204601
14. GWINNUTT JM, VERSTAPPEN SMM, HUMPHREYS JH: The impact of lifestyle behaviours, physical activity and smoking on morbidity and mortality in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2020; 34(2): 101562. https://doi.org/10.1016/j.berh.2020.101562
15. SAEVARSDOTTIR S, WEDRÉN S, SEDDIGHZADEH M *et al*.: Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: Observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. *Arthritis Rheum* 2011; 63(1): 26-36. https://doi.org/10.1002/art.27758
16. CUPPEN BV, JACOBS JW, TER BORG EJ *et al*.: Necessity of TNF-alpha inhibitor discontinuation in rheumatoid arthritis is predicted by smoking and number of previously used biological DMARDs. *Clin Exp Rheumatol* 2017; 35(2): 221-28.
17. HAMANN PDH, PAULING JD, MCHUGH N, SHADDICK G, HYRICH K; BSRBR-RA CONTRIBUTORS GROUP: Predictors, demographics and frequency of sustained remission and low disease activity in anti-tumour necrosis factor-treated rheumatoid arthritis patients. *Rheumatology* (Oxford) 2019; 58(12): 2162-69. https://doi.org/10.1093/rheumatology/kez188
18. LIU X, TEDESCHI SK, BARBHAIYA M *et al*.: Impact and timing of smoking cessation on reducing risk of rheumatoid arthritis among women in the nurses' health studies. *Arthritis Care Res* 2019; 71(7): 914-24. https://doi.org/10.1002/acr.23837
19. KAPLAN GG, HUBBARD J, KORZENIK J *et al*.: The inflammatory bowel diseases and ambient air pollution: a novel association. *Am J Gastroenterol* 2010; 105(11): 2412-9. https://doi.org/10.1038/ajg.2010.252
20. OIKONEN M, LAAKSONEN M, LAIPPALA P *et al*.: Ambient air quality and occurrence of multiple sclerosis relapse. *Neuroepidemiology* 2003; 22(1): 95-99. https://doi.org/10.1159/000067108
21. ZHAO C-N, XU Z, WU G-C *et al*.: Emerging role of air pollution in autoimmune diseases. *Autoimmun Rev* 2019; 18(6): 607-14. https://doi.org/10.1016/j.autrev.2018.12.010
22. BAMBINO K, CHU J: Chapter Nine - Zebrafish in Toxicology and Environmental Health. In *Current Topics in Developmental Biology*. Sadler KC (Ed.), Zebrafish at the Interface of Development and Disease Research; Academic Press, 2017; vol. 124, pp 331-67. https://doi.org/10.1016/bs.ctdb.2016.10.007
23. MIKULS TR, PAYNE JB, DEANE KD, THIELE GM: Autoimmunity of the lung and oral mucosa in a multisystem inflammatory disease: The spark that lights the fire in rheumatoid arthritis? *J Allergy Clin Immunol* 2016; 137(1): 28-34. https://doi.org/10.1016/j.jaci.2015.10.024
24. CHEN R, LI H, CAI J *et al*.: Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction. *Environ Health Perspect* 2018; 126(1): 017007. https://doi.org/10.1289/ehp1447
25. WILSON WE, SUH HH: Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. *J Air Waste Manag Assoc* 1997; 47(12): 1238-49. https://doi.org/10.1080/10473289.1997.10464074
26. POPE CA 3RD, DOCKERY DW: Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc* 2006; 56(6): 709-42. https://doi.org/10.1080/10473289.2006.10464485
27. ALEX AM, KUNKEL G, SAYLES H, FLAUTERO ARCOS JD, MIKULS TR, KERR GS: Exposure to ambient air pollution and autoantibody status in rheumatoid arthritis. *Clin Rheumatol* 2020; 39(3): 761-68. https://doi.org/10.1007/s10067-019-04813-w
28. JAAKKOLA JJK: Case-crossover design in air pollution epidemiology. *Eur Respir J Suppl* 2003; 40: 81s–85s. https://doi.org/10.1183/09031936.03.00402703
29. LEWER D, PETERSEN I, MACLURE M. The case-crossover design for studying sudden events. *BMJ Med* 2022; 1(1): e000214. https://doi.org/10.1136/bmjmed-2022-000214
30. ADAMI G, VIAPIANA O, ROSSINI M *et al*.: Association between environmental air pollution and rheumatoid arthritis flares. *Rheumatology* (Oxford) 2021; 60(10): 4591-97. https://doi.org/10.1093/rheumatology/keab049
31. ADAMI G, ROSSINI M, VIAPIANA O *et al*.: Environmental air pollution is a predictor of poor response to biological drugs in chronic inflammatory arthritides. *ACR Open Rheumatology* 2021; 3(7): 451-56. https://doi.org/10.1002/acr2.11270
32. REZAYAT AA, NILOUFAR J, MIR NOURBAKHSH SH *et al*.: The effect of air pollution on systemic lupus erythematosus: a systematic review and meta-analysis. *Lupus* 2022; 31(13): 1606-18. https://doi.org/10.1177/09612033221127569
33. ADAMI G, PONTALTI M, CATTANI G *et al*.: Association between long-term exposure to air pollution and immune-mediated diseases: a population-based cohort study. *RMD Open* 2022; 8(1): e002055. https://doi.org/10.1136/rmdopen-2021-002055
34. BERNATSKY S, SMARGIASSI A, BARNABE C *et al*.: Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. *Environ Res* 2016; 146: 85-91. https://doi.org/10.1016/j.envres.2015.12.021
35. CHANG K-H, HSU C-C, MUO C-H *et al*.: Air pollution exposure increases the risk of rheumatoid arthritis: A longitudinal and nationwide study. *Environ Int* 2016; 94: 495-99. https://doi.org/10.1016/j.envint.2016.06.008
36. ANDERSON R, MEYER PWA, ALLY MMTM, TIKLY M: Smoking and air pollution as pro-inflammatory triggers for the development of rheumatoid arthritis. *Nicotine Tob Res* 2016; 18(7): 1556-65. https://doi.org/10.1093/ntr/ntw030
37. BRITO-ZERÓN P, FLORES-CHÁVEZ A, NG W-F *et al*.: Exposure to air pollution as an environmental determinant of how Sjögren's disease is expressed at diagnosis. *Clin Exp Rheumatol* 2023; 41(12): 2448-57. https://doi.org/10.55563/clinexprheumatol/p1r1j4
38. ROESER A, SESE L, CHASSAGNON G *et al*.: The association between air pollution and the severity at diagnosis and progression of systemic sclerosis-associated interstitial lung disease: results from the retrospective ScleroPol study. *Respir Res* 2023; 24(1): 151. https://doi.org/10.1186/s12931-023-02463-w
39. ZHAO W-M, WANG Z-J, SHI R *et al*.: Environmental factors influencing the risk of ANCA-associated vasculitis. *Front Immunol* 2022; 13: 991256. https://doi.org/10.3389/fimmu.2022.991256
40. KWON D, CHOE YJ, KIM S-Y, CHUN BC, CHOE S-A: Ambient air pollution and Kawasaki disease in Korean children: a study

of the national health insurance claim data. *J Am Heart Assoc* 2022; 11(9): e024092. https://doi.org/10.1161/jaha.121.024092
41. TERAO C, HASHIMOTO M, FURU M *et al*.: Inverse association between air pressure and rheumatoid arthritis synovitis. *PLoS One* 2014; 9(1): e85376. https://doi.org/10.1371/journal.pone.0085376
42. SCHERER HU, HÄUPL T, BURMESTER, GR: The etiology of rheumatoid arthritis. *J Autoimmun* 2020; 110: 102400. https://doi.org/10.1016/j.jaut.2019.102400
43. WANG M, CHEN J, LIN X *et al*.: High humidity aggravates the severity of arthritis in collagen-induced arthritis mice by upregulating xylitol and L-pyroglutamic acid. *Arthritis Res Ther* 2021; 23(1): 292. https://doi.org/10.1186/s13075-021-02681-x
44. KONDO Y, ABE S, TOKO H *et al*.: Effect of climatic environment on immunological features of rheumatoid arthritis. *Sci Rep* 2023; 13(1): 1304. https://doi.org/10.1038/s41598-022-27153-3
45. CUTOLO M, SMITH V, PAOLINO S, GOTELLI E: Involvement of the secosteroid vitamin D in autoimmune rheumatic diseases and COVID-19. *Nat Rev Rheumatol* 2023; 19(5): 265-87. https://doi.org/10.1038/s41584-023-00944-2
46. LIN J, LIU J, DAVIES ML, CHEN W: Serum vitamin D level and rheumatoid arthritis disease activity: review and meta-analysis. *PloS One* 2016; 11(1): e0146351. https://doi.org/10.1371/journal.pone.0146351
47. ADAMI G, ROSSINI M, BOGLIOLO L *et al*.: An exploratory study on the role of vitamin D supplementation in improving pain and disease activity in rheumatoid arthritis. *Mod Rheumatol* 2019; 29(6): 1059-62. https://doi.org/10.1080/14397595.2018.1532622
48. DUPUIS ML, PAGANO MT, PIERDOMINICI M, ORTONA E: The role of vitamin D in autoimmune diseases: could sex make the difference? *Biol Sex Differ* 2021; 12: 12 https://doi.org/10.1186/s13293-021-00358-3
49. FASSIO A, GATTI D, ROSSINI M *et al*.: Effects on serum inflammatory cytokines of cholecalciferol supplementation in healthy subjects with vitamin D deficiency. *Nutrients* 2022; 14(22): 4823. https://doi.org/10.3390/nu14224823
50. MORI H, SAWADA T, NISHIYAMA S *et al*.: Influence of seasonal changes on disease activity and distribution of affected joints in rheumatoid arthritis. *BMC Musculoskelet Disord* 2019; 20(1): 30. https://doi.org/10.1186/s12891-019-2418-2
51. HANSEN AL, AMBROZIAK G, THORNTON D *et al*.: Vitamin D supplementation during winter: effects on stress resilience in a randomized control trial. *Nutrients* 2020; 12(11): 3258. https://doi.org/10.3390/nu12113258
52. CUTOLO M, STRAUB RH: Sex steroids and autoimmune rheumatic diseases: state of the art. *Nat Rev Rheumatol* 2020; 16(11): 628-44. https://doi.org/10.1038/s41584-020-0503-4
53. HAHN J, COOK NR, ALEXANDER EK *et al*.: Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* 2022; 376: e066452. https://doi.org/10.1136/bmj-2021-066452
54. COSTENBADER KH, COOK NR, LEE I-M *et al*.: Vitamin D and marine n-3 fatty acids for autoimmune disease prevention: outcomes at two years after VITAL trial completion. *Arthritis Rheumatol* 2024. https://doi.org/10.1002/art.42811
55. PAN Q, CHEN J, GUO L *et al*.: Mechanistic insights into environmental and genetic risk factors for systemic lupus erythematosus. *Am J Translat Res* 2019; 11(3): 1241-54.
56. AMIT M, MOLAD Y, KISS S, WYSENBEEK AJ: Seasonal variations in manifestations and activity of systemic lupus erythematosus. *Br J Rheumatol* 1997; 36(4): 449-52. https://doi.org/10.1093/rheumatology/36.4.449
57. YANG J, LU Y-W, PAN H-F *et al*.: Seasonal distribution of systemic lupus erythematosus activity and its correlation with climate factors. *Rheumatol Int* 2012; 32(8): 2393-99. https://doi.org/10.1007/s00296-011-1971-2
58. WANG W, LI Y, MENG X: Vitamin D and neurodegenerative diseases. *Heliyon* 2023; 9(1): e12877. https://doi.org/10.1016/j.heliyon.2023.e12877
59. ANWAR MJ, ALENEZI SK, ALHOWAIL AH: Molecular insights into the pathogenic impact of vitamin D deficiency in neurological disorders. *Biomed Pharmacother* 2023; 162: 114718. https://doi.org/10.1016/j.biopha.2023.114718
60. RADIĆ M, KOLAK E, ĐOGAŠ H *et al*.: Vitamin D and Sjögren's disease: revealing the connections – a systematic review and meta-analysis. *Nutrients* 2023; 15(3): 497. https://doi.org/10.3390/nu15030497
61. NIKIPHOROU E, PHILIPPOU E: Nutrition and its role in prevention and management of rheumatoid arthritis. *Autoimmun Rev* 2023; 22(7): 103333. https://doi.org/10.1016/j.autrev.2023.103333
62. BÄCKLUND R, DRAKE I, BERGSTRÖM U, COMPAGNO M, SONESTEDT E, TURESSON C: Diet and the risk of rheumatoid arthritis – a systematic literature review. *Semin Arthritis Rheum* 2023; 58: 152118. https://doi.org/10.1016/j.semarthrit.2022.152118
63. MCKELLAR G, MORRISON E, MCENTEGART A *et al*.: A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. *Ann Rheum Dis* 2007; 66(9): 1239-43. https://doi.org/10.1136/ard.2006.065151
64. ASTERIOU E, GKOUTZOURELAS A, MAVROPOULOS A, KATSIARI C, SAKKAS LI, BOGDANOS DP: Curcumin for the management of periodontitis and early ACPA-positive rheumatoid arthritis: killing two birds with one stone. *Nutrients* 2018; 10(7): 908. https://doi.org/10.3390/nu10070908
65. GIOIA C, LUCCHINO B, TARSITANO MG, IANNUCCELLI C, DI FRANCO M: Dietary habits and nutrition in rheumatoid arthritis: can diet influence disease development and clinical manifestations? *Nutrients* 2020; 12(5): 1456. https://doi.org/10.3390/nu12051456
66. MCINNES IB, SCHETT G: The pathogenesis of rheumatoid arthritis. *New Engl J Med* 2011: 365(23): 2205-19. https://doi.org/10.1056/nejmra1004965
67. OLIVIERO F, SPINELLA P, FIOCCO U, RAMONDA R, SFRISO P, PUNZI L: How the Mediterranean diet and some of its components modulate inflammatory pathways in arthritis. *Swiss Med Wkly* 2015; 145: w14190. https://doi.org/10.4414/smw.2015.14190
68. ALUNNO A, NIKIPHOROU E, PHILIPPOU E *et al*.: Nutrition in RMDs: is it really food for thought? Focus on rheumatoid arthritis. *BMC Rheumatol* 2020; 4: 10. https://doi.org/10.1186/s41927-020-0113-4
69. ALPÍZAR-RODRÍGUEZ D, FINCKH A, GILBERT B: The role of nutritional factors and intestinal microbiota in rheumatoid arthritis development. *Nutrients* 2020; 13(1): 96. https://doi.org/10.3390/nu13010096
70. CALDER PC: Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans* 2017, 45(5), 1105-15. https://doi.org/10.1042/bst20160474
71. SAIDANE O, SEMERANO L, SELLAM J: Could omega-3 fatty acids prevent rheumatoid arthritis? *Joint Bone Spine* 2019; 86(1): 9-12. https://doi.org/10.1016/j.jbspin.2018.05.007
72. GIOXARI A, KALIORA AC, MARANTIDOU F, PANAGIOTAKOS DP: Intake of ω-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Nutrition* 2018; 45: 114-24. e4. https://doi.org/10.1016/j.nut.2017.06.023
73. VADELL AK, BÄREBRING L, HULANDER E, GJERTSSON I, LINDQVIST HM, WINKVIST A: Anti-inflammatory diet in rheumatoid arthritis (ADIRA) – a randomized, controlled crossover trial indicating effects on disease activity. *Am J Clin Nut* 2020; 111(6): 1203-13. https://doi.org/10.1093/ajcn/nqaa019
74. CHEN Y, MA C, LIU L *et al*.: Analysis of gut microbiota and metabolites in patients with rheumatoid arthritis and identification of potential biomarkers. *Aging* (Albany NY) 2021; 13(20): 23689-701. https://doi.org/10.18632/aging.203641
75. BERNARD NJ: Rheumatoid arthritis: Prevotella copri associated with new-onset untreated RA. *Nat Rev Rheumatol* 2014; 10(1): 2. https://doi.org/10.1038/nrrheum.2013.187
76. VALDES AM, WALTER J, SEGAL E, SPECTOR TD: Role of the gut microbiota in nutrition and health. *BMJ* 2018; 361: k2179. https://doi.org/10.1136/bmj.k2179
77. CUTOLO M, NIKIPHOROU E: Nutrition and diet in rheumatoid arthritis. *Nutrients* 2022; 14(4): 888. https://doi.org/10.3390/nu14040888
78. MASLINSKA M, KOSTYRA-GRABCZAK K, KRÓLICKI L, KWIATKOWSKA B: The role of the microbiome in Sjogren's syndrome. *Crit Rev Immunol* 2021; 41(6): 13-26. https://doi.org/10.1615/critrevimmunol.2022043083
79. MIELIAUSKAITĖ D, KONTENIS V: Insights into microbiota in Sjögren's syndrome. *Medicina* 2023; 59(9): 1661. https://doi.org/10.3390/medicina59091661
80. ZHANG L, QING P, YANG H, WU Y, LIU Y, LUO Y: Gut microbiome and metabolites in systemic lupus erythematosus: link, mechanisms and intervention. *Front Immunol* 2021; 12: 686501. https://doi.org/10.3389/fimmu.2021.686501
81. PHILIPPOU E, PETERSSON SD, RODOMAR C, NIKIPHOROU E: Rheumatoid arthritis and dietary interventions: systematic review of clinical trials. *Nutr Rev* 2021; 79(4): 410-28. https://doi.org/10.1093/nutrit/nuaa033