Review

Potential of Lifestyle Changes for Reducing the Risk of Developing Rheumatoid Arthritis: Is an Ounce of Prevention Worth a Pound of Cure?

Alessandra Zaccardelli, BS[1]; H. Maura Friedlander, BA[1]; Julia A. Ford, MD[1,2]; and Jeffrey A. Sparks, MD, MMSc[1,2]

[1]*Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA; and* [2]*Harvard Medical School, Boston, MA, USA*

ABSTRACT

Purpose: Lifestyle may be important in the development of rheumatoid arthritis (RA). Therefore, changing behaviors may delay or even prevent RA onset. This article reviews the evidence basis for the associations of lifestyle factors with RA risk and considers future directions for possible interventions to reduce RA risk.

Methods: The literature was reviewed for cross-sectional studies, case-control studies, cohort studies, and clinical trials investigating potentially modifiable lifestyle factors and RA risk or surrogate outcomes on the path toward development such as RA-related autoimmunity or inflammatory arthritis. The evidence related to cigarette smoking, excess weight, dietary intake, physical activity, and dental health for RA risk were summarized.

Findings: Cigarette smoking has the strongest evidence base as a modifiable lifestyle behavior for increased seropositive RA risk. Smoking may increase seropositive RA risk through gene−environment interactions, increasing inflammation and citrullination locally in pulmonary/oral mucosa or systemically, thereby inducing RA-related autoimmunity. Prolonged smoking cessation may reduce seropositive RA risk. Evidence suggests that excess weight can increase RA risk, although this effect may differ according to sex, serologic status, and age at RA onset. TDietary intake may also affect RA risk: overall healthier patterns, high fish/omega-3 polyunsaturated fatty acid consumption, and moderate alcohol intake may reduce RA risk, whereas caffeine and sugar-sweetened soda consumption might increase RA risk. The impact of physical activity is less clear, but high levels may reduce RA risk. Periodontal disease might induce citrullination and RA-related autoimmunity, but the effect of dental hygiene behaviors on RA risk is unclear. Although the effect size estimates for these lifestyle factors on RA risk are generally modest, there may be relatively large public health benefits for targeted interventions given the high prevalence of these unhealthy behaviors. With the exception of smoking cessation, the impact of behavior change of these lifestyle factors on subsequent RA risk has not been established. Nearly all of the evidence for lifestyle factors and RA risk were derived from observational studies.

Implications: There are many potentially modifiable lifestyle factors that may affect RA risk. Improving health behaviors could have large public health benefits for RA risk given the high prevalence of many of the RA risk-related lifestyle factors. However, future research is needed to establish the effects of lifestyle changes on RA risk or surrogate outcomes such as RA-related autoimmunity or inflammatory arthritis. (*Clin Ther*. 2019;41:1323−1345) © 2019 Published by Elsevier Inc.

Key words: lifestyle, prevention, rheumatoid arthritis, risk.

INTRODUCTION

Lifestyle factors have been linked to the development of many chronic diseases such as cardiovascular disease

Accepted for publication April 11, 2019
https://doi.org/10.1016/j.clinthera.2019.04.021
0149-2918/$ - see front matter

and cancer. For example, the Centers for Disease Control and Prevention estimates that up to 25% of cardiovascular disease could be preventable with improved lifestyle.[1] Therefore, investigations have also focused on the potential impact of lifestyle factors on rheumatoid arthritis (RA) development. RA is believed to develop in discrete preclinical phases: genetic risk, asymptomatic RA-related autoantibody positivity, systemic inflammation, arthralgias, undifferentiated inflammatory arthritis (IA), and eventually clinical RA.[2] Studies have investigated whether lifestyle factors are associated with overall risk, and some have examined whether behaviors may affect transitions between these preclinical RA phases.

The current review focuses on lifestyle factors that are potentially intervenable, including cigarette smoking, excess weight, dietary intake, physical activity, and dental hygiene. We did not include other factors that are difficult to modify, such as socioeconomic status (eg, income, education) or female reproductive factors (eg, parity, breastfeeding, menopause) despite research showing associations with RA risk. Investigating lifestyle factors for RA risk also provides insight into the biologic mechanisms contributing to RA pathogenesis, and we highlighted some of these advances. We also describe the heterogeneity for RA risk according to genotype, sex, RA-related autoantibody status at diagnosis, and age at RA onset. Finally, we discuss evidence for behavior change and RA risk and summarize remaining research gaps. Although accumulating evidence indicates that modifying lifestyle may potentially delay or even prevent RA development, this possibility remains uncertain. More research is needed to establish the causal relationship between various risk factors and RA progression. Furthermore, trials are needed to determine the effects of behavior changes on RA risk. This knowledge may help prevent RA, an intervention which is more effective and feasible than curing the disease.

MATERIALS AND METHODS

A scoping review was performed to collate and present the available literature in a narrative review paper. We searched PubMed and included cross-sectional studies, case-control studies, cohort studies, clinical trials, and meta-analyses investigating potentially modifiable lifestyle patterns and RA risk. Risk was investigated across several established preclinical phases of RA development, termed "surrogate preclinical RA outcomes." These include "genetic risk" based on *HLA-DRB1* shared epitope status, "RA-related autoantibody presence" defined as elevated levels of anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF), systemic inflammation, arthralgias, and undifferentiated IA. The evidence was summarized and discrepancies highlighted among studies related to cigarette smoking, excess weight, dietary intake, physical activity, and dental health for RA risk.

RA RISK-RELATED BEHAVIORS

Cigarette Smoking

Smoking and RA Development

Cigarette smoking is the best-established behavioral risk factor for RA. Smoking may exert effects on RA risk throughout all of the transitions between preclinical phases of development, specifically from genetic risk to asymptomatic autoimmunity, early symptoms, early inflammatory arthritis, and, finally, clinical RA diagnosis (Figure 1).[2]

A central paradigm for RA pathogenesis is related to a gene−smoking interaction wherein individuals with *HLA-DRB1* shared epitope alleles and history of heavy smoking are at very elevated risk for RA.[3−7] Smoking is believed to confer these biologic effects by aberrantly activating immune cells and stimulating production of pro-inflammatory cytokines. This inflammatory milieu may induce citrullination of proteins, perhaps in the lungs through peptidyl arginine deiminase.[2,8] This action may form neoantigens that are presented to T cells through the HLA-DRβ1 protein.[2] This molecular interaction initiates a cascade that eventually stimulates B cells to produce anti-citrullinated protein antibodies, initially in mucosa before elevation in the systemic circulation.[9] Specific amino acid haplotypes at positions 11, 71, and 74 of the HLA-DRβ1 molecule greatly increase the risk of RA.[10] In a large study of 3 different populations, smoking interacted at these particular amino acid haplotype positions to increase RA risk, further suggesting that smoking may induce neoantigen production that physically interacts with the molecule at those positions.[11] Blood bank studies, studies of unaffected first-degree relatives, and

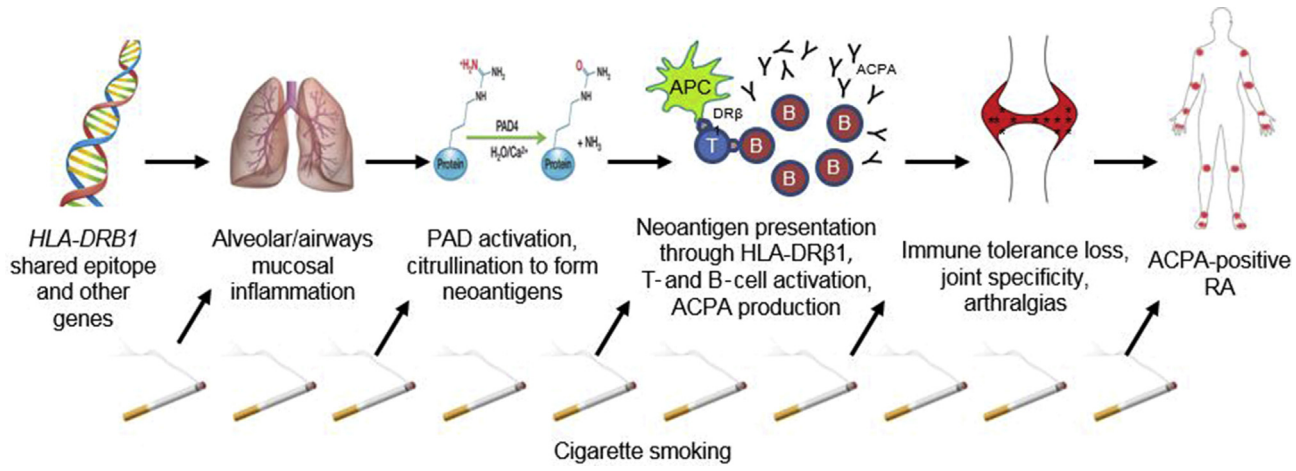

Figure 1. Paradigm for smoking and development of rheumatoid arthritis (RA). Smoking induces inflammation at mucosal surfaces, perhaps in the lung. Among genetically predisposed individuals, aberrant citrullination occurs through peptidylarginine deiminase (PAD), which may form neoantigens. This action activates T cells and then B cells to produce autoantibodies such as anti-citrullinated protein antibodies (ACPA). After autoimmunity, joint specificity and clinical symptoms appear that are more likely to occur among smokers.

clinical cohorts show elevated RF or ACPA in the circulation years before clinical diagnosis, particularly in individuals with the shared epitope.[12–18]

Smoking has been associated with progression from the asymptomatic phase to inflammatory joint signs among unaffected first-degree relatives.[19] Among seropositive individuals, those who smoke are more likely to progress to RA and in shorter duration.[20] Therefore, the identification of smoking as a potent risk factor for RA at these crucial points has revealed biologic insights into RA pathogenesis and increased the understanding of transitions between the preclinical phases of RA development. However, more research must be conducted to identify the distinct neoantigens important in RA pathogenesis and the biology explaining the progression from asymptomatic autoimmunity to joint manifestations.

Smoking Status, Autoantibodies, and Demographic Characteristics

The association between smoking and RA has also been investigated in the context of smoking status and the nuances of serostatus and sex. Many previous studies have investigated smoking status (current vs past vs never as the reference group) and risk of RA.[21–30] A meta-analysis of 16 studies showed that having ever smoked increased the odds of developing RA risk by 1.89-fold.[31] Both current (odds ratio [OR], 1.87) and past (OR, 1.76) smokers had similar associations with increased RA risk compared with never smokers. Smoking is most strongly related to seropositive RA risk, in both RF-positive and ACPA-positive RA. Smoking does not seem to be a risk factor for seronegative RA.[31–33] Although smoking confers increased RA risk regardless of sex, men seem to have a higher relative risk (RR) for RA from smoking than women.[31,34] Most of these epidemiologic analyses were performed among subjects with European ancestry, but smoking has also been shown to be a risk factor for RA in diverse populations.[35,36] Given the high worldwide prevalence of smoking, the population-attributable risk for smoking for RA is believed to be ~20%.[37] Another study estimated that up to 35% of risk for ACPA-positive RA could be explained by smoking.[38] These studies primarily examined individual categories of smoking status rather than behavior changes of quitting or starting smoking.

Smoking Intensity and Duration

Several studies have also investigated smoking intensity and duration as well as passive smoking for RA risk. Smoking pack-years as a measure of smoking duration seems most strongly related to RA risk.[32] A threshold above 10 pack-years seems to be important for RA pathogenesis, although large studies have detected modestly elevated RA risk at even lower pack-year thresholds.[32,35,39,40] There is also a correlation between duration of smoking with increased risk for RA.[32] Studies have not convincingly reported that passive smoking is strongly related to RA risk, although a modest association is still possible.[41,42]

Smoking and Other Environmental Factors

Additional studies have investigated other inhalants such as pollution[43–45] and silica[46–49] and RA risk. Smokeless tobacco has not been associated with RA risk, suggesting that inhalants, not nicotine, confer risk for RA.[50,51] However, no strong evidence demonstrating the relationship between other inhalants such as cigar smoking, marijuana (or illicit drugs) smoking, vaping, or e-cigarettes and RA risk has emerged. Other studies have investigated possible diet–smoking interactions for RA risk. High fish intake may attenuate the strong association of smoking with RA risk.[52] Another study suggested that high sodium intake and smoking may interact to further increase RA risk.[53] More research is needed to understand the complex interactions between smoking as an established RA risk factor and other genetic, epigenetic, and environmental exposures.

Smoking Cessation

Smoking is also one of the few lifestyle risk factors in which the impact of behavior change on RA risk has been investigated. Several prospective cohort studies showed that the RR for RA became similar to never smokers after 10–20 years of smoking cessation.[32,39] However, there were relatively few individuals with this lengthy duration of sustained smoking cessation, and thus a modest excess risk was still possible. A subsequent Swedish cohort study suggested a reduced risk for RA with longer time since smoking cessation.[54] Recently, smoking cessation and RA risk was investigated in a large investigation using the Nurses' Health Studies that had biennial measures of smoking cessation during up to 40 years of prospective follow-up.[33] This study confirmed smoking as a strong risk factor for seropositive RA but not seronegative RA. This study also reported a modestly elevated risk for seropositive RA even after 30 years of prolonged smoking cessation, suggesting that smoking may induce irreversible changes in the immune system that can lead to RA even decades after quitting. Finally, this study suggested a reduced risk for seropositive RA with time since cessation among past smokers. Past smokers had an ~30% reduced risk for seropositive RA 20 years after cessation. There was no association with smoking behavior changes and seronegative RA risk, results that are consistent with other studies showing that smoking is unlikely to be a strong risk factor for this subtype. This study shows that a behavior change of smoking cessation may reduce risk for seropositive RA, but this was an observational study, and thus the results may be confounded.

Overall, these studies provide moderate evidence that smoking cessation could reduce seropositive RA risk. However, a randomized clinical trial would be needed to prove a causal relationship between smoking cessation and reduced RA risk. A trial showed that few first-degree relatives knew that smoking was an RA risk factor at baseline,[55] but this knowledge improved and more smokers quit after undergoing a personalized medicine intervention compared with standard RA risk factor education[56] while also being reassured about risk for developing RA.[57] Because most studies suggest that RA risk is gradually reduced over many years after smoking cessation, a trial powered to detect effects on RA risk would likely require a large sample size with lengthy follow-up, and thus may not be feasible. A more realistic alternative study design could investigate surrogate RA-related outcomes such as RA-related autoantibody presence/levels or could be restricted to seropositive individuals who are at a very elevated risk of up to 50% progressing to IA or clinical RA. Even with these caveats, smoking cessation should currently be recommended to smokers as a nonpharmacologic method to potentially reduce RA risk or delay the transition to clinical RA.

Excess Weight

Body mass index (BMI) is defined as weight (in kilograms) per height-squared (in meters squared), and it is used to set parameters for overweight (BMI $\geq$25 and <30 kg/m^2), excess weight (BMI $\geq$25 kg/m^2), and obesity (BMI $\geq$30 kg/m^2). Although excess weight is a

less established RA risk factor than smoking, there is growing interest in understanding the connection between excess weight and disease risk, as the prevalence of overweight and obesity is increasing worldwide at an alarming rate.

Previous research studies on weight and RA risk have investigated excess weight, overweight, and obesity. There are several potential biologic mechanisms by which excess weight may affect RA risk. Obesity is considered an inflammatory condition with increased levels of pro-inflammatory cytokines secreted by adipocytes, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which have been implicated in RA pathogenesis and are current therapeutic targets.[58,59] Obesity is also associated with a relative increase in estrogen levels, which likely plays a major role in RA pathogenesis given the female predominance and could explain potential differences according to sex for the effect of obesity on RA risk.[60] Known metabolic effects of prevalent RA on anthropometrics such as rheumatoid cachexia and sarcopenia also add to the rationale that BMI may affect RA risk. There may be complex interactions of excess weight with other potential metabolic factors for RA risk such as dietary intake and physical activity.

Most studies have investigated BMI as a measure of adiposity for risk of RA (Table I). Two separate meta-analyses have established and quantified the association between BMI and risk of RA. A systematic review[61] of 11 studies[25,27,29,62–69] investigated the association of BMI and RA risk. Obesity was associated with a significantly increased risk of RA (RR, 1.25; 95% CI, 1.07−1.45) compared with nonobesity, defined as BMI <30 kg/m^2. Compared with the reference group of normal weight, overweight (pooled RR, 1.15; 95% CI, 1.03−1.29) and obesity (pooled RR, 1.31; 95% CI, 1.12−1.53) were modestly associated with increased RA risk. In the dose−response analysis, for every 5 kg/m^2 increase in BMI, the RR of RA was 1.03 (95% CI, 1.01−1.05). A subsequent meta-analysis[70] that included many of the same studies yielded consistent results; obesity had an RR of 1.21 for RA (95% CI, 1.02−1.44) compared with normal BMI, and the risk of RA increased by 13% for every 5 kg/m^2 increase in BMI (RR, 1.13; 95% CI, 1.01−1.26). However, these studies compared static categories of BMI, but none investigated weight or BMI change over time for RA risk.

Although these meta-analyses of observational studies showed that obesity and overweight may increase overall RA risk, there is less consensus about possible differences based on sex. Subgroup analyses of women[61,70] found a strong association between obesity/overweight and increased RA risk compared with normal BMI but no association among male subjects. A subsequent population-based Danish prospective cohort study[71] similarly showed that increasing BMI was associated with increased RA risk as well as other markers of adiposity among women but not men. However, several other subsequent studies have yielded discrepant results. A Swedish cohort study[72] found stronger associations between increased BMI and waist circumference for increased risk of RA among men compared with women. However, a Swedish nested case-control study[73] found that overweight and obesity were actually protective against development of RA among men (OR for overweight/obesity, 0.33; 95% CI, 0.14−0.76), with no significant association reported among women. Excess weight therefore seems to affect RA risk differently in men and women, and further investigations are needed to clarify conflicting findings, particularly among men.

Whether excess weight and obesity affect RA risk based on serologic status is also unclear. In a subgroup meta-analysis[70] of the 3 studies[63,65,68] that phenotyped RA based on ACPA or RF status, the positive association between excess BMI and RA risk was present only for seropositive RA. This positive association between increased BMI and seropositive RA was mainly driven by research using the Nurses' Health Studies.[68] In contrast, there was a strong positive association between obesity and RA risk only for seronegative RA in the meta-analysis (RR, 1.47; 95% CI, 1.11−1.96; reference group normal BMI) regardless of sex, with no significant association for seropositive RA.[70] A nested case-control study of women in the Nurses' Health Studies[17] suggested that ACPA positivity before clinical RA diagnosis and excess weight had a statistical interaction to increase RA risk and shorten time to RA diagnosis. Previous research suggests that seropositive individuals with excess weight are more likely to develop RA than those with seropositivity and normal weight. Further research may clarify the differences between seronegative and seropositive RA risk with respect to excess weight.

Although BMI is commonly used in epidemiologic studies due to wide availability and familiarity for easy interpretation, there may be misclassification by BMI

Table I. Summary of the associations of measures of adiposity and risk for rheumatoid arthritis (RA) phenotypes.

Population	Measure of Adiposity (Exposure)	Direction for Association With RA	HR, RR, or OR for RA (95% CI)	Author (Year) of Reference
Men and women	Excess weight (overweight/obese) according to BMI (reference: normal BMI)	↑	RR, 1.25 (1.07–1.45)	Qin et al (2015)[61]
			RR, 1.21 (1.02–1.44)	Feng et al (2016)[70]
			RR, 1.45 (1.07–1.95)	Ljung et al (2016)[72]
			OR, 3.45 (1.73–6.87)*	Pedersen et al (2006)[63]
			OR, 1.47 (1.11–1.96)*	Feng et al (2016)[70]
Women	Excess weight (overweight/obese) according to BMI (reference: normal BMI)	↑	RR, 1.27 (1.04–1.54)	Qin et al (2015)[61]
			RR, 1.26 (1.12–1.40)	Feng et al (2016)[70]
			HR, 1.10 (1.02–1.18)	Linauskas et al (2018)[71]
			HR, 1.37 (1.10–1.71)†	Lu et al (2014)[68]
			OR, 1.6 (1.2–2.2)*	Wesley et al (2013)[65]
			HR, 1.45 (1.03–2.03)†,‡	Lu et al (2018)[74]
		NS	HR, 1.20 (0.75–1.93)	Lu et al (2014)[68]
Men	Excess weight (overweight/obese) according to BMI (reference: normal BMI)	↑	OR, 1.78 (1.01–3.12)	Ljung et al (2016)[72]
		↓	OR, 0.33 (0.14–0.76)	Turesson et al (2016)[73]
Women	Waist circumference >88 cm (reference: ≤88 cm)	↑	HR, 1.05 (1.01–1.10)§	Linauskas et al (2018)[71]
		↑	HR, 1.25 (1.08–1.45)	Lu et al (2018)[74]

BMI = body mass index; HR = hazard ratio; NS = nonsignificant association; OR = odds ratio; RR = relative risk.
* Observed for seronegative RA risk.
† Observed for seropositive RA risk.
‡ Observed among women aged ≤55 years.
§ Observed for high versus low waist circumference.

related to age, muscular structure, and menopausal status, and the findings could be confounded. Abdominal adiposity may have more pro-inflammatory metabolic effects and thus could have a large impact on RA risk. There is interest therefore in investigating other measures of adiposity for RA risk. Lu et al[74] recently examined the effect of waist circumference as a measure of visceral adiposity on RA risk in women in the Nurses' Health Studies. Women with waist circumference >88 cm had an increased risk of RA compared with women with waist circumference ≤88 cm (hazard ratio [HR], 1.27; 95% CI, 1.10–1.47) adjusting for multiple risk factors, although the association was no longer statistically significant after adjustment for BMI. However, among women aged ≤55 years, abdominal obesity was associated with seropositive RA (but not seronegative RA) even independent of BMI (HR, 1.51; 95% CI, 1.01–2.25). A large Danish cohort study investigated bioimpedance-derived body fat percentage and waist circumference and found that both factors were associated with increased overall RA risk.[71] In subgroup analyses, there was a significant association among women but not for men or when investigating

according to RA serostatus. Further investigations related to adipokines and alternate measures of adiposity are underway, which may further clarify how excess weight is associated with RA.

Current evidence provides the rationale for the benefits of weight loss on disease activity in established RA. A retrospective cohort study[75] of patients with RA who underwent bariatric surgery showed marked improvements in RA disease activity in patients after substantial weight loss. However, there is a paucity of literature investigating the impact of weight loss or gain on RA risk. A recent abstract examined the effect of weight loss after bariatric surgery on incident RA. The Swedish Obese Study matched 2010 individuals who underwent bariatric surgery with control subjects with similar weight who did not undergo bariatric surgery and with no significant weight change.[76] Perhaps surprisingly, there was a similar incidence of RA for both groups, suggesting that marked weight loss did not have a strong effect on reducing RA risk. However, this study was limited by few RA outcomes and did not report on subgroups based on sex, serostatus, or age at RA diagnosis. More research is needed to provide evidence supporting that a behavior change of weight loss may reduce RA risk or, conversely, to show that weight gain may increase RA risk. Clinical trials enrolling individuals with excess weight into weight loss strategies assessing for surrogate preclinical RA outcomes, including RA-related autoantibody positivity and inflammatory arthritis, could be feasible.

Dietary Intake

The beneficial health effects of dietary patterns have been established in many chronic diseases, often through modulating levels of systemic inflammation.[77,78] Because RA is a prototypical inflammatory autoinflammatory disease, there is significant interest in determining whether dietary intake is associated with RA risk.[79] Dietary intake may be analyzed from a whole diet or individual food/beverage item or nutrient perspective, each providing insight on the dynamic effects of food in disease development (Table II).

Dietary Patterns

Researchers have investigated the effects of overall dietary patterns on chronic disease risk. Analyzing overarching food consumption patterns has advantages because foods and beverages are not eaten in isolation, and these patterns could be implemented broadly to those at risk. Therefore, studying dietary intake as a whole may be more important for RA risk rather than assessing individual foods/beverages.

Mediterranean Diet

Several investigations have focused on the potential anti-inflammatory benefits of the Mediterranean diet. This diet is characterized by high consumption of olive oil, unrefined cereals, fruits and vegetables, spices, and a moderate amount of fish, dairy, meat, and alcohol.[80] RA has lower prevalence in southern Mediterranean countries where the Mediterranean diet originated.[81] The Mediterranean diet seems to have overall health benefits,[82,83] including lower mortality rates from cardiovascular disease and lower incidence of other fatal diseases.[77,84] Past studies suggest these benefits may be mediated through the reduction of inflammatory markers, lipid levels, and blood pressure.[85] These anti-inflammatory effects provided rationale for investigation into the effects of the Mediterranean diet on RA risk.

A systematic review evaluated the effects of the Mediterranean diet on the prevention and management of RA in prospective human studies.[80] Although the studies suggested that the Mediterranean diet may reduce pain and symptoms in patients already diagnosed with RA, there was insufficient evidence to establish the Mediterranean diet as preventative for RA development. Both prospective studies found that there was no significant association between the Mediterranean diet adherence and an altered risk of seropositive or seronegative RA[84] (adjusted OR for RA for the third tertile [most adherent to Mediterranean diet] vs the first tertile [least adherent], 0.88; 95% CI, 0.66−1.16).[86] However, a recent case-control study suggested that increasing adherence to the Mediterranean diet was associated with reduced RA risk, particularly among men and for seropositive RA.[82]

Alternative Healthy Eating Index

Although the Mediterranean diet is the most commonly studied diet pattern for RA risk, the effects of healthy eating have also been a focus of RA prevention research. In the Nurses' Health Study, long-term healthy eating patterns were modestly associated with reduced RA risk.[87] This effect was

Table II. Summary of the associations of dietary intake patterns and individual foods/beverages and risk for rheumatoid arthritis (RA).

Variable	Direction for Association With RA	HR, RR, or OR for RA (95% CI)	Author (Year) of Reference
Dietary patterns			
Mediterranean diet (more adherent vs less adherent)	↓	OR, 0.79 (0.65–0.96)	Johansson et al (2018)[82]
	NS	HR, 0.98 (0.80–1.20)	Hu et al (2015)[84]
Alternative Healthy Eating Index (healthy vs unhealthy)	↓	HR, 0.67 (0.51–0.88)†	Hu et al (2017)[87]
Empirical dietary inflammatory pattern (pro-inflammatory vs anti-inflammatory)	↑	HR, 1.38 (1.05–1.83)	Sparks et al (2019)[88]
Individual foods/beverages			
Omega-3 polyunsaturated fatty acids (high vs low)	↓	RR, 0.61 (0.40–0.93)	Di Giuseppe et al (2014)[101]
	NS	HR, 1.12 (0.91–1.37)	Sparks et al (2019)[52]
Fish (high vs low)	↓	OR, 0.8 (0.6–1.0)	Rosell et al (2009)[105]
	NS	OR, 0.78 (0.53–1.14)	Shapiro et al (1996)[104]
		RR, 0.91 (0.68–1.23)	Pedersen et al (2005)[106]
		RR, 0.96 (0.91–1.01)	Di Giuseppe et al (2014)[96]
		HR, 0.93 (0.67–1.28)	Sparks et al (2019)[52]
Alcohol (moderate vs none)	↓	RR, 0.86 (0.78–0.94)	Jin et al (2014)[109]
		OR, 0.78 (0.63–0.96)	Scott et al (2013)[110]
		HR, 0.48 (0.29–0.82)	Lu et al (2014)[113]
Sugar-sweetened soda (high vs low)	↑	HR, 1.63 (1.15–2.30)*	Hu et al (2014)[118]
Caffeine (high vs low)	↑	RR, 2.42 (1.06–5.55)*	Lee et al (2014)[115]
	NS	RR, 1.1 (0.8–1.6)	Karlson et al (2003)[116]
		RR, 1.04 (0.69–1.56)	Mikuls et al (2002)[117]
Red/processed meat (low vs high)	↓	HR, 0.64 (0.47–0.87)†	Hu et al (2017)[87]
	NS	RR, 1.17 (0.89–1.55)‡	Benito-Garcia et al (2007)[119]
		RR, 1.08 (0.77–1.53)‡	Di Giuseppe et al (2018)[120]
Vitamin D (high vs low)	↓	RR, 0.67 (0.44–1.00)	Merlino et al (2004)[124]
	NS	OR, 1.30 (0.78–2.16)	Hiraki et al (2014)[121]
		RR, 0.86 (0.64–1.17)	Hiraki et al (2012)[123]

HR = hazard ratio; NS = nonsignificant association; OR = odds ratio; RR = relative risk.
* Observed for seropositive RA risk.
† Observed among women aged ≤55 years.
‡ Observed for high vs. low red/processed meat.

statistically significant among women aged ≤55 years ($HR_{Q4\ vs\ Q1}$, 0.67; 95% CI, 0.51−0.88; $P_{trend} = 0.002$), with the inverse association strongest for seropositive RA. Healthy eating patterns were based on the Alternative Healthy Eating Index (AHEI), a dietary quality score that categorizes foods/beverages/nutrients consistently associated with chronic disease risk through previous consensus. Healthy components of the AHEI (higher intake, decreasing risk) include fruits, vegetables, whole grains, nuts, long-chain fatty acids, polyunsaturated fatty acids (PUFAs), and moderate alcohol consumption. Unhealthy components of the AHEI (higher intake, increasing risk) include sugar-sweetened beverages, red/processed meats, *trans* fats, and sodium intake. These findings indicate that a generally healthy diet may reduce risk of RA. The AHEI components that seemed to have the largest impact on RA risk were alcohol, sodium, and red/processed meat intake.

Empirical Dietary Inflammatory Pattern

Another prospective study using the Nurses' Health Studies investigated whether long-term adherence to the empirical dietary inflammatory pattern (EDIP) was associated with RA risk.[88] The EDIP classified food/beverage groups as either anti-inflammatory or pro-inflammatory based on their correlations with serum inflammatory biomarkers (IL-6, C-reactive protein, and TNF-α receptor 2).[89] Increased adherence to EDIP was associated with higher seropositive RA risk among women aged ≤55 years (HRs across EDIP quartiles [95% CIs], 1.00 [reference], 1.14 [0.86−1.51], 1.35 [1.03−1.77], and 1.38 [1.05−1.83]; $P_{trend} = 0.01$). This association was attenuated after adjustment for BMI, with an estimated 41.8% proportion of the EDIP effect mediated by BMI (95% CI, 10.3−81.8), emphasizing the complex interactions between dietary intake and BMI for RA risk.[88]

These positive findings are supported by previous studies that have found an inverse relationship between healthy diet and systemic inflammation. In a review of observational and interventional studies assessing the effect of a "prudent" diet high in fruits, vegetables, legumes, whole grains, poultry and fish, Giugliano et al identified several studies that found healthy eating patterns to be inversely associated with plasma C-reactive protein level, a marker of systemic inflammation.[77,90–92] Although these findings are not specific to RA risk, they provide further support that a healthy diet may be effective at lowering RA risk through decreased systemic inflammation.

Other Dietary Patterns

Many individuals may inquire about the effects of other specific dietary patterns on RA risk. However, there is currently no strong literature on the effects of the vegetarian, pescatarian, Paleo, ketogenic, South Beach, Atkins, and gluten-free diets for RA risk.

Individual Foods/Beverages

Investigating the role of diet from a purely holistic approach neglects the accumulating evidence that specific food and beverage items have direct immunomodulatory effects and may therefore be important in RA development. Individual dietary items that have garnered interest for RA risk include fish intake and omega-3 PUFAs as well as alcohol, caffeine, sugar-sweetened soda, red meat, and vitamins/supplements.

Fish Intake/Omega-3 PUFAs

There is some evidence that increased consumption of omega-3 PUFAs, often found in dark meat and fish, are associated with decreased RA risk.[93–96] This effect is attributed to their anti-inflammatory properties.[96–101] One proposed mechanism is that long-chain eicosapentaenoic acid (EPA) derived from omega-3 PUFAs is a homolog of arachidonic acid; while arachidonic acid produces pro-inflammatory eicosanoids, EPA engenders anti-inflammatory eicosanoids.[101] As a competitive substrate for arachidonic acid, EPA suppresses inflammation.[95] A similar hypothesis suggests that derivatives of EPA and docosahexaenoic acid are competitive inhibitors of omega-6 PUFAs and consequently suppress cytokine production.[94,96] Thus, omega-3 PUFAs may be important in RA pathogenesis.

A meta-analysis of 7 studies reported a modest and nonstatistically significant inverse association between fish consumption and RA risk. As fish consumption increased, RA risk decreased by 4% (RR, 0.96; 95% CI, 0.19−1.01).[96] This association may be partially attributed to the adverse effects of polychlorinated biphenyls in fish.[102] A population-based case-control study found that baked or broiled fish (but not total fish) decreased RA risk. This association may be due

to reduced polychlorinated biphenyl levels in cooked fish, further illustrating their potentially adverse effects.[103,104] Meanwhile, individuals who consumed oily fish or fish oil supplements had moderately decreased RA risk compared with individuals who rarely or never consumed oily fish.[105] These findings indicate that specifically omega-3 fatty acids, not only fish consumption, may reduce RA risk. In addition, a prospective cohort study found that increased fatty fish intake decreased RA risk but the association was nonsignificant, whereas medium fat fish consumption was significantly associated with increased RA risk.[106] A nested case-control study recently investigated the potential association of omega-6 PUFAs and RA risk and found a significant inverse association between omega-6 PUFAs and reduced RA risk[107]; however, there was no association between omega-3 PUFAs and RA. Thus, additional research should be conducted to firmly establish the effect of PUFAs and risk of RA.

The effect of fish consumption may also depend on several other factors, including duration, antibody presence, and genetic status. Long-term weekly fish consumption was associated with significantly reduced RA risk.[101] Omega-3 PUFAs may also be important in individuals with RA-related antibody presence, particularly in those with additional genetic risk conferred from shared epitope positivity (Figure 2). A nested case-control study found a decreased inverse association between erythrocyte-bound omega-3 PUFA levels (as a relatively long-term measure of dietary intake) and ACPA positivity, indicating omega-3 PUFAs may prevent RA antibody development.[93] Another study investigated omega-3 PUFAs among RF- or cyclic citrullinated peptide (CCP)-positive individuals and whether the association depended on shared epitope presence. Findings showed increasing erythrocyte-bound omega-3 PUFA levels were inversely associated with RF/CCP positivity in shared epitope−positive, but not shared epitope−negative, individuals.[108] Among CCP- and RF-positive individuals subtyped for *HLA-DR4* and *HLA-DRB1* alleles, increasing omega-3 FA levels lowered risk for IA as another preclinical surrogate outcome, with a 91% decrease in odds of IA for every SD increase in erythrocyte-bound omega-3 PUFAs. There was a significant association between the omega-3 PUFA docosapentaenoic acid content and reduced risk of incident IA.[94] Thus, the impact of omega-3 PUFAs on RF/CCP levels may be enhanced in those at high genetic risk for RA, suggesting that omega-3 PUFAs are important in the transition from RA-related autoantibody positivity to IA. However, more research is needed to quantify possible protection of omega-3 PUFAs on RA, especially considering other studies that showed null results. For example, the largest study prospectively (n = 166,013 women) investigating fish consumption over 30 years of follow-up recently found no association between fish consumption or dietary/supplemental marine omega-3 PUFAs with RA risk, even when stratifying data according to serologic status and RA risk.[52] More research may be needed to firmly establish the potentially protective relationship between omega-3 PUFA intake and RA risk.

Alcohol Consumption

There is evidence that moderate alcohol intake may reduce RA risk compared with lower levels of alcohol consumption. The mechanism behind this association[109] may be through downregulation of the immune response[110] and decreased production of pro-inflammatory cytokines.[95,111,112] However, alcohol consumption might be indicative of overall health status and be a confounding effect because those who abstain completely may be experiencing chronic illness, have previously been heavy drinkers, or pre-cursor symptoms before RA may have influenced drinking behaviors (reverse causation).[110] A dose−response meta-analysis of 8 prospective studies (n = 195,029) investigated the association between RA and alcohol consumption.[109] These findings indicate that the effect of alcohol intake depends on dose, duration, and sex and is strongest in consistent intake of low to moderate doses for at least 10 years. Although there was no statistically significant association between high alcohol consumption and RA risk, low to moderate consumption conferred significant protection (RR, 0.86; 95% CI, 0.78−0.94), suggesting a U-shaped curve for RA risk. Compared with women who did not drink, women who consumed low to moderate alcohol had a 19% reduction in RA risk (RR, 0.81; 95% CI, 0.75−0.92).[109] Heavy drinking is no longer protective for RA. Another meta-analysis of 9 studies found that alcohol drinkers had lower RA risk (OR, 0.78; 95% CI, 0.63−0.96). One case-control study found that long-term drinking was associated with lower RA risk.[25,110] Another prospective cohort

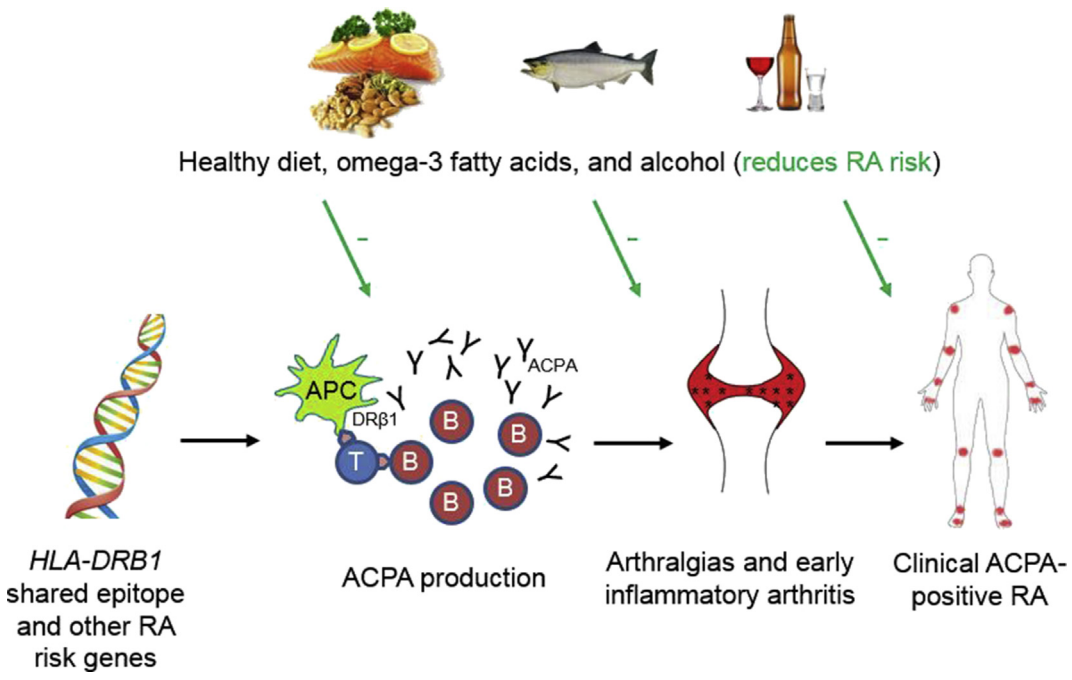

Figure 2. Dietary intake, omega-3 polyunsaturated fatty acid intake, alcohol intake, and rheumatoid arthritis (RA) pathogenesis. Individuals at increased RA risk through the *HLA-DRB1* shared epitope or other RA risk genes produce anti-citrullinated protein antibody (ACPA) from immune dysregulation after neoantigen production resulting from gene–environment interactions. ACPA-positive individuals later develop arthralgias and undifferentiated inflammatory arthritis, which progress to clinically apparent ACPA-positive RA. An overall healthy diet, especially long-term consumption of omega-3 fatty acids and moderate alcohol, reduces the risk of producing ACPA. APC = antigen-presenting cell.

study found that prolonged moderate alcohol intake modestly reduced risk of RA.[113] Beer was significantly protective, whereas wine and liquor showed a nonsignificant associations. Former drinkers had higher RA risk than those who never drank.[25] Overall, these findings suggest that alcohol consumption over time may be a modest intervention for RA development, but it is unclear whether this finding is dependent on duration or type of alcohol and at what phase of preclinical RA development that alcohol may exert effects.

The meta-analysis also investigated whether RA risk and alcohol consumption is dependent on ACPA/RF status.[110] The meta-analysis found a significant association between alcohol and risk reduction for ACPA-positive RA and no association for ACPA-negative RA. One case-control study of RF positivity found significant risk reductions for alcohol intake on both RF-positive and RF-negative RA.[110,114] Conversely, one prospective cohort study found no association between alcohol use and overall RA or RF-positive RA.[67] These findings suggest an interaction between alcohol and RA antibodies, but further research is needed to determine the precise point of interaction. Alcohol intervention studies for RA risk are likely infeasible related to ethical considerations but could be a component of dietary pattern intervention.

Caffeine Intake

Coffee, tea, soda, and other caffeinated beverages have also been implicated as potential RA risk factors. Coffee is

of particular interest because it is the main dietary source of caffeine as well as a source of antioxidants.[115] Coffee intake and RA incidence were summarized in a meta-analysis of 5 studies, which found a significant association for increased caffeine intake increasing RA risk in case-control studies (RR, 1.201; 95% CI, 1.058−1.361) and a nonsignificant association in cohort studies. There was an overall significant association between coffee consumption and seropositive RA (RR, 2.42; 95% CI, 1.060−5.554; $P = 0.036$), but no association between tea consumption and RA. There was also a significant association between coffee and seropositive RA incidence but not seronegative RA. Although the biologic mechanisms have yet to be elucidated, these results suggest that caffeine may be linked to CCP/RF production. Similarly, a prospective cohort study found that coffee and other caffeinated beverages were associated with increased RF-positive RA risk.[114] In contrast, a prospective cohort study reported no association between caffeine consumption and RA risk when accounting for confounding variables such as smoking; that analysis of individual beverages including caffeinated coffee, decaffeinated coffee, and tea and RA risk also showed no relationship.[116] Another prospective cohort study found a positive association between decaffeinated coffee and RA risk and no association between caffeinated coffee consumption and RA, but it did show that decaffeinated coffee attenuated RA risk while tea reduced risk.[117] These conflicting findings illustrate the necessity of further investigation to determine the strength of effects, if any, of caffeinated/decaffeinated beverages for RA risk.

Sugar-Sweetened Soda

Because sugar-sweetened soda consumption is well established to increase other chronic inflammatory diseases, there was also interest in investigating its association with RA.[118] It is possible that RA risk from sugar may be derived from an increased risk of periodontal infectious disease, which has been implicated in RA pathogenesis, discussed later in more detail. In the Nurses' Health Study, regular sugar-sweetened soda consumption was associated with increased RA risk compared with less frequent consumption. This effect was more pronounced among seropositive RA, and no association was found between sugar-sweetened soda and seronegative RA. There was no association between diet soda and RA risk. Other studies are needed to replicate these findings implicating sugar-sweetened soda and RA risk.

Red/Processed Meat

Red meat and protein may be associated with development of inflammatory polyarthritis, encouraging research on the relationship between red meat and RA.[119] A prospective cohort study found a modest association between protein consumption and elevated RA risk, which was nonsignificant in the multivariable model. There was no association between red meat, poultry, fish, or iron and RA. Another prospective cohort study of overall long-term dietary quality based on AHEI score found that individuals with diets low in red/processed meat consumption had significantly reduced RA risk compared with those with high intake. Meanwhile, a prospective cohort found that meat consumption had no association with RA.[120] The association between red meat and RA remains unclear, and further research is needed to elucidate its proposed effects.

Vitamins and Supplements

Growing attention has been directed toward research of supplements, including vitamin D, vitamin C, and antioxidants, and risk for RA. Vitamin D has known immunomodulatory properties, which may be important in RA development and has garnered much research interest.[121] However, most studies have not found an association between vitamin D and RA risk. A 2-sample Mendelian randomization analysis investigating the causal association between RA and vitamin D was null.[122] An analysis of 2 prospective cohorts found no association between vitamin D levels and RA diagnosis in one cohort and a significant inverse association among a subset of women in the second cohort with blood sampled between 3 months and 4 years of RA diagnosis.[121] Another prospective cohort study showed null results in 2 cohorts.[123] Findings from a cohort study indicate that greater dietary and supplemental vitamin D intake was associated with decreased RA risk.[124] Vitamin C and antioxidants were implicated in reduced RA risk, but the mechanism was uncertain, and further research is needed to confirm the results.[125–127] The effect of carotenoids was also investigated given their anti-inflammatory properties.[128] Although there was no significant association among specific levels of carotenoids and RA risk using a nested case-control

design, there was a decrease risk for seronegative RA (57%) among individuals with high levels of carotenoids.

These studies have attempted to adjust for appropriate confounders, but intake and serum levels of vitamins/supplements may be highly confounded by other healthy behaviors that can be difficult to measure. Overall, there is little evidence that vitamin and supplement intake may affect RA risk. A well-designed, recent, large 2 × 2 factorial design, placebo-controlled, randomized trial testing the efficacy of vitamin D and marine omega-3 PUFAs on cancer and cardiovascular disease found no effect, and thus it may be unlikely that these nutrients have a large impact on RA risk.[129,130]

Other Individual Foods/Beverages

Despite popular intrigue and some evidence of anti-inflammatory effects, there is no strong literature linking dietary items such as nightshade, turmeric, and blueberries with RA risk.

Physical Activity

Physical activity may contribute to RA pathogenesis[131] via several immunomodulatory pathways. Physical activity is action produced by skeletal muscle movement and resulting in energy consumption. Skeletal muscle contraction stimulates secretion of myokines, including IL-6, IL-8, and IL-15, into the blood.[132–135] Physical activity may also cause modulations in levels of T_{h1}/T_{h2} cells associated with RA development. The effect of these fluctuations is intensity dependent; although prolonged exercise decreases T_{h1} levels, strenuous exercise may stimulate T_{h1} cell production. Natural killer cell levels also increase after brief, intense exercise and in response to chronic exercise.[132] In addition, hormones, including epinephrine and norepinephrine, are produced during physical activity.[131] Together, these effects tend to lower systemic inflammation and provide a rationale that physical activity could protect against RA. However, physical activity, adiposity, and dietary intake are all interrelated, making it difficult to understand which of these factors may be independently contributing to RA pathogenesis.

A population-based prospective study found that physical activity was protective for RA.[136] Women who spent >20 min per day/1 h per week of leisure-time activity compared with women with less physical activity had decreased RA risk (RR, 0.62; 95% CI, 0.42–0.92). Activities including household work, exercise, walking/standing at work, and walking/biking also showed decreases in RA risk. Similarly, a recent prospective cohort study investigated the effects of recreational physical activity and RA risk using repeated measures of physical activity over 26 years.[137] Women reported time spent on recreational activities, including walking, jogging, running, bicycling, swimming, tennis, and aerobics. Findings showed that compared with low physical activity levels, increasing cumulative total hours of recreational physical activity significantly reduced RA risk (HR, 0.67; 95% CI, 0.47–0.98). This effect was also investigated based on serologic status, finding similar trends for reduced seropositive and seronegative RA risk. However, another prospective cohort study found no association between leisure-time physical activity and RA, but it may have been underpowered to detect a modest effect.[67]

Overall, these studies suggest benefits of physical activity for reducing RA risk. Modifying this behavior may be an effective intervention, but further research is needed to provide a stronger evidence basis for a biologic effect on RA risk.

Dental Health

Periodontal disease (PD) is a chronic oral inflammatory disease that can cause bone erosions and increases inflammation both locally and systemically. Given the similarities with RA, several researchers are interested in the potential link between PD and RA. There is abundant epidemiologic evidence that PD and RA often affect a similar population.[138] PD treatment can reduce biomarker levels important in RA pathogenesis.[139,140] Theoretically, PD prevention via dental health behaviors could therefore have effects on RA risk. However, a causal relationship between periodontal treatment and RA prevention remains unclear.

Previous studies suggest that PD may increase RA risk compared with no PD.[140,141] This may be due to the pathogen *Porphyromonas gingivalis* through the induction of an RA-related autoimmune response at sites of oral mucosal inflammation.[141] *P gingivalis* is the only prokaryote known to express peptidylarginine deiminase (PAD), an enzyme necessary for protein citrullination, a posttranslational modification from arginine to

citrulline, that may lead to changes in structure, function, and potential for immunogenicity.[142] As already detailed, this protein modification is likely central to RA pathogenesis given the importance of ACPA. Therefore, oral mucosa may serve as an originating site for RA development (Figure 3).

Several studies have established a higher prevalence of PD in patients with existing RA.[143,144] Despite this association, most recent studies investigating PD and RA risk before the presentation of clinical RA found no significant associations. In a cohort study of 9702 men and women, Demmer et al[139] reported that the prevalence and incidence of self-reported RA in patients with PD versus healthy control subjects were similar. Similarly, a prospective cohort study found no association between previously treated PD and RA.[145]

Studies assessing the association between *P gingivalis* antibodies and RA risk have drawn mixed conclusions. In 2 studies performed among individuals with shared epitope positivity and those with first-degree relatives affected with RA, anti−*P gingivalis* antibody concentrations were significantly associated with the high-risk group, individuals who were positive for ACPA or for two or more RF assays, compared with control subjects (OR, 1.68; 95% CI, 1.12−2.52; $P = 0.012$).[146] However, among seropositive arthralgia patients without clinical RA, individuals who developed RA within 30 months had similar levels of anti−*P gingivalis* compared with control subjects, although this small subgroup may have been underpowered to detect an association.[147]

Studies evaluated the presence of the PAD enzyme in patients at risk for RA and also found no relationship.[141] In a study of PAD-encoding genes in *P gingivalis* clinical isolates collected from patients with RA and healthy control subjects, there was no significant difference in PAD expression between patients with RA and non-RA control subjects. Differences in protein citrullination patterns were also not statistically different between these 2 groups, suggesting that if *P gingivalis* plays a role in RA onset, it is more likely to be due to a posttranslational modification rather than a difference in PAD gene expression. These findings combined suggest that PAD and *P gingivalis* antibody levels may not be strongly predictive of RA development. Mikuls et al[146] found an association between anti−*P gingivalis* antibodies and elevated RA risk, but this finding was not reproduced in studies with even larger sample sizes.[145,147]

No literature has assessed the direct effect that dental hygiene, such as flossing, rinsing, brushing, or attending dental visits, has on RA risk, although gingival and periodontal treatment has been associated with decreased inflammatory biomarkers important in RA pathogenesis.[140] Periodontal treatment may reduce levels of inflammatory mediators caused by periodontal infections, including IL-1β and TNF-α. Treating gingivitis using mouthwash with essential oils alone was found to reduce levels of bacteria in the mouth by 50%.[148] However, due to the multifactorial etiology of both PD and RA, there is currently no straightforward method to measure the direct effects of reduced oral bacteria on RA risk.[140] Although dental hygiene promotes general bacterial reduction and a decreased inflammatory response, there is no convincing research that supports a direct relationship between improving dental hygiene habits and reducing RA risk.

Further longitudinal studies are therefore necessary to assess the precise role, if any, that dental hygiene, *P gingivalis*, and PAD enzymes play in the development of RA. Despite the epidemiologic similarities between PD and RA, and the intriguing biology potentially linking both, further research is needed to establish the connection.

Future Directions

With growing interest in preventative medicine and accumulating knowledge on identifying lifestyle RA risk factors, it is possible that lifestyle modification could delay or even prevent RA. These could be adjusted to fit individual characteristics such as sex, genotype, and current state of preclinical RA development. Before this type of intervention can be implemented, randomized controlled trials must be designed to determine the causal effects (Table III). An ideal study design would consider the impact of sex, serostatus, and genotype, as well as the potential interactions between the behaviors themselves. However, testing for impact on overall RA risk would likely require a large sample size with many years of follow-up given the relatively low incidence rates for RA in the general population. Therefore, studies restricted to subgroups at high RA risk may be preferable. These subgroups could be individuals with shared epitope positivity, RF/ACPA positivity, imaging findings of subclinical synovitis, or undifferentiated IA. Preclinical RA surrogate outcomes to consider would be RA-related

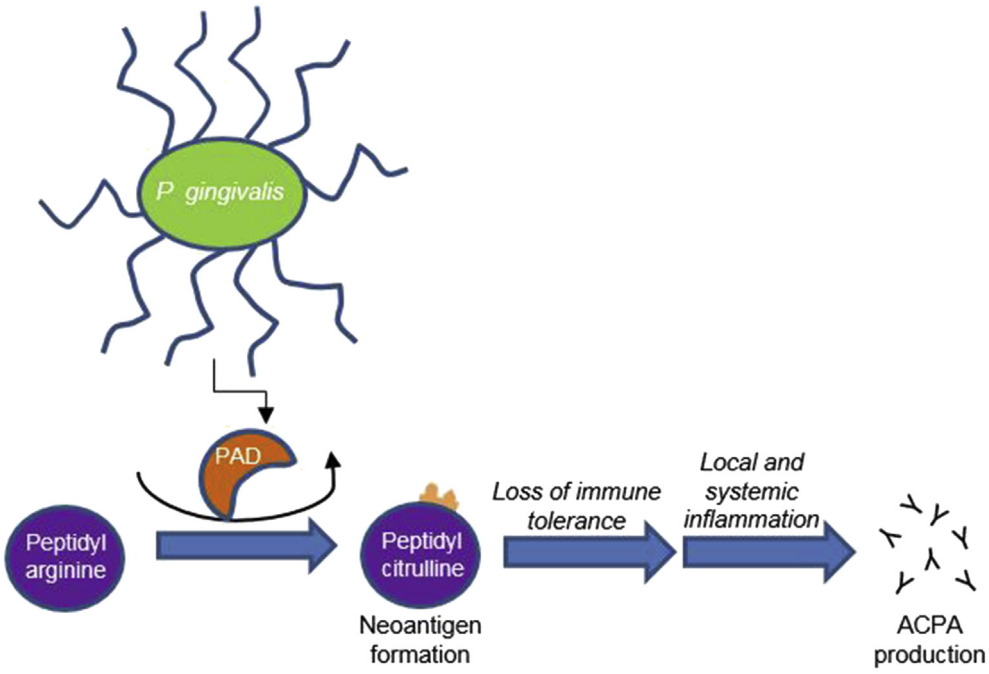

Figure 3. *Porphyromonas gingivalis*, peptidylarginine deiminase (PAD), and protein citrullination in rheumatoid arthritis pathogenesis. *P gingivalis*, a central initiator in the pathogenesis of periodontitis, is the only prokaryote known to express PAD, an enzyme necessary for protein citrullination. The PAD enzyme is capable of citrullinating human arginine. This posttranslational modification alters the peptide from a positive arginine into a polar, neutrally charged citrulline.[149] This conformational change alters structure and may create an unrecognized epitope on citrulline, inducing an immune response, and forming neoantigens that could result in development of rheumatoid arthritis.[146] ACPA = anti-citrullinated protein antibody.

autoantibody presence/levels, incident IA, time to RA development, and joint count outcomes.

Furthermore, additional research is needed to investigate the feasibility of modifying these lifestyle factors and whether behavior change will result in reduced RA risk. To firmly establish the associations between individual lifestyle factors and RA risk, a randomized controlled trial, likely with many years of follow-up, would be needed. A possible study design would be to identify seropositive individuals without RA or unaffected first-degree relatives (to enrich the event rate or progression to RA and improve motivation to enroll) and excess weight. These at-risk individuals could be randomized to receive a pharmacologic therapy for weight loss or placebo. A factorial design could also test several hypotheses simultaneously by also including arms for physical activity and dietary programs with attention control. During the trial, participants would be monitored for RA signs/symptoms, changes in levels of RA-related antibodies and systemic inflammation, and development of clinical RA. Researchers may face challenges in designing, recruiting, and implementing other interventions to significantly modify other behaviors discussed in the current article, such as smoking and alcohol consumption, both of which may have ethical considerations.

This review detailed research gaps and next steps needed for observational studies. Randomized trials are needed to truly establish a causal effect of lifestyle factors on RA risk. Cessation of cigarette smoking has intrinsic appeal to study given the strong evidence base for its effect on RA and available pharmacologic options. However, this approach may be infeasible given the high rates of relapse after initial cessation and intrinsic difficulties related to

Table III. Potential interventions in hypothetical randomized controlled trials for rheumatoid arthritis (RA) prevention among seropositive individuals without RA or unaffected first-degree relatives.

Lifestyle Factor	Population	Targeted Behavior Change	Intervention(s)	Comparator(s)	Feasibility	Comments
Smoking	Smokers	Smoking cessation	Nicotine patch Pharmacologic	Placebo	Potentially feasible	All would require counseling on smoking cessation, may have ethical considerations; likely to have high rates of smoking relapse; recruitment and retention may be difficult
Excess weight	Overweight/ obese	Weight loss	Pharmacologic Bariatric surgery	Placebo Waitlist/calorie restriction program	Feasible Relatively infeasible	Blinding possible for pharmacologic trial but unclear if modest weight loss would be sufficient to affect RA risk; bariatric surgery vs medical weight loss intervention may be difficult to recruit and unable to blind
Dietary intake	All	Dietary change	"RA risk reduction" diet (eg, Mediterranean) Calorie restriction	"Sham"/control diet Normal calorie diet	Potentially feasible	Blinding and adherence difficult; unclear composition of control diet; may be part of a factorial design to test several hypotheses
Alcohol	Nondrinkers or low volume drinkers	Increase alcohol intake	Alcoholic beverages	Nonalcoholic beverages	Infeasible	Blinding not possible; ethical considerations
Physical activity	All	Increase physical activity	Physical activity program	Attention control	Potentially feasible	May be incorporated as part of dietary or weight loss trial to test several hypotheses using a factorial design
Dental hygiene	All	Increase brushing Increase flossing Deep dental cleanings Increase frequency of visits to dental providers	Dental hygiene equipment Incentives for dental care Program encouraging visits to dental providers	Attention control	Potentially feasible	Unlikely to have powerful effects on RA risk but may yield mechanistic insight

adherence in this population. There may also be ethical considerations related to offering placebo to smokers who are interested in quitting. Other options would include novel behavior interventions for smoking cessation, but attention would be needed to ensure that the control arm reflects standard of care, and blinding would not be possible in these designs, both of which could affect results. Another option would be to consider pharmacologic weight loss interventions among those who are obese and at elevated RA risk related to genetics or RA-related autoimmunity. This study could be blinded and placebo controlled and may be feasible given the growing prevalence of obesity. However, it is unclear whether the amount of weight loss would be enough to affect RA risk. A randomized trial comparing bariatric surgery versus a waitlist control (unblinded) may be a possibility but still may require large sample size and lengthy follow-up. Physical activity and dietary intake trials seem less feasible than a weight loss trial, or they could be part of a multifactorial design because all are intrinsically intertwined. There may be appeal to pursue trials of individual nutrients, such as vitamin D or omega-3 PUFAs, for RA risk but again these trials are likely to require large sample sizes with lengthy follow-up. The lack of benefit in trials of these supplements for other chronic disease may limit the appeal to pursue for RA risk. Lastly, much more research is needed to establish the epidemiology and biologic mechanisms linking PD and RA risk. The data are too sparse and inconsistent to consider dental hygiene intervention studies for RA risk, but novel microbiome studies targeting *P gingivalis* and other microbes would be an exciting direction for assessment of RA risk.

CONCLUSIONS

Lifestyle factors such as cigarette smoking, excess weight, dietary intake, physical activity, and dental hygiene may play important roles in RA pathogenesis. Although the mechanisms and associations of cigarette smoking and RA development are the best established, further research is needed to identify and quantify associations of excess weight, dietary intake, physical activity, and dental hygiene on RA risk. The current research is epidemiologic in nature and thus has intrinsic pitfalls, including selection bias, recall bias, small sample size, limited follow-up, potential for unmeasured confounding, and reliance on surrogate outcomes that may not always accurately predict progression to RA. These restrictions make it difficult to establish a causal pathway between risk factors and RA incidence. Based on these current limitations, randomized trials of lifestyle interventions are needed to establish a causal relationship with RA and to make it possible for providers to recommend lifestyle changes to high-risk individuals.

Thus, measuring the impact of healthy lifestyle on RA progression is difficult because of barriers to effectively implementing behavior change as well as intrinsic challenges in isolating individual behaviors. RA prevention trials for weight loss, increasing physical activity, optimizing dietary intake, and improving dental hygiene are all relatively feasible and could yield important results elucidating the biologic mechanisms for RA pathogenesis. The results of this work could help researchers to better understand RA development and motivate at-risk individuals to adopt healthier behaviors. It is therefore essential to invest time and funding to lifestyle modification trials, for an ounce of prevention is worth a pound of cure.

ACKNOWLEDGMENTS

Dr. Sparks is supported by the National Institutes of Health (grant numbers K23 AR069688, L30 AR066953, P30 AR070253, and P30 AR072577) and the Rheumatology Research Foundation K Supplement Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard University, its affiliated academic health care centers, or the National Institutes of Health. All authors were involved in drafting the article or revising it critically for important intellectual content. All authors contributed to the study conception/design, literature search, creation figures/tables, and writing. AZ drafted the final manuscript. JAS, MF, and JAF provided edits and all approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest regarding the content of this article.

The funders had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript.

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Address correspondence to: Jeffrey A. Sparks, MD, MMSc, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, 60 Fenwood Road, #6016U, Boston, MA 02115, USA. E-mail: jsparks@bwh.harvard.edu