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Potential of lifestyle changes for reducing the risk of developing rheumatoid arthritis: Is an ounce of prevention worth a pound of cure?

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Abstract

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

Methods: We reviewed the literature 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 towards development, such as RA-related autoimmunity or inflammatory arthritis. We summarized the evidence related to cigarette smoking, excess weight, dietary intake, physical activity, and dental health for RA risk.

Findings: Cigarette smoking has the strongest evidence base as a modifiable lifestyle behavior that increases seropositive RA risk. Smoking may increase seropositive RA risk through gene-environment interactions, increasing inflammation and citrullination locally in pulmonary/oral mucosa or systemically, and thereby inducing RA-related autoimmunity. Prolonged smoking cessation may reduce seropositive RA risk. Evidence suggests that excess weight may increase RA risk, though this effect may differ by sex, serologic status, and age at RA onset. The effect of dietary intake may also impact RA risk: overall healthier patterns, high fish/omega-3 polyunsaturated fatty acids, and moderate alcohol intake may reduce RA risk, while caffeine and sugar-sweetened soda may increase RA risk. The impact of physical activity is less clear but high levels may reduce RA risk. Periodontal disease may 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

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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 impact RA risk. Improving health behaviors may 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.

Keywords

rheumatoid arthritis; risk; prevention; lifestyle

INTRODUCTION

Lifestyle factors have been linked to the development of many chronic diseases such as cardiovascular disease and cancer. For example, the Centers for Disease Control and Prevention estimates that up to 25% of cardiovascular disease would be preventable with improved lifestyle¹. Therefore, investigations have also focused on the potential impact of lifestyle factors on rheumatoid arthritis (RA) development. RA is thought to develop in discrete preclinical phases: genetic risk, asymptomatic RA-related autoantibody-positivity, systemic inflammation, arthralgias, undifferentiated inflammatory arthritis (IA), and eventually clinical RA². 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.

This review focuses on lifestyle factors that are potentially intervenable, such as cigarette smoking, excess weight, dietary intake, physical activity, and dental hygiene. We did not include others factors that are difficult to modify, such as socioeconomic status (e.g., income, education) or female reproductive factors (e.g., 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. While 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.

METHODS

We performed a scoping review 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. We investigated risk across several established preclinical phases of RA development, termed “surrogate preclinical RA outcomes”. These include “genetic risk” based on *HLA-DRB1* shared epitope (SE) status, “RA-related autoantibody presence” defined as elevated levels anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF), systemic inflammation, arthralgias, and undifferentiated IA. We summarized the evidence, and highlighted discrepancies 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 to early symptoms to early inflammatory arthritis to clinical RA diagnosis (Figure 1)².

A central paradigm for RA pathogenesis is related to a gene-smoking interaction wherein individuals with *HLA-DRB1* SE alleles and history of heavy smoking are at very elevated risk for RA^{3–7}. Smoking is thought 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 may form neoantigens which are presented to T cells through the HLA-DRβ1 protein². This molecular interaction initiates a cascade that eventually stimulates B cells to produce anti-citrullinated protein antibodies, initially in mucosa prior to elevation in the systemic circulation⁹. Specific amino acid haplotypes at positions 11, 71, and 74 of the HLA-DRβ1 molecule greatly increase RA risk¹⁰. In a large study of three 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 positions¹¹. Blood bank studies, studies of unaffected first-degree relatives, and clinical cohorts show elevated RF or ACPA in the circulation years prior to clinical diagnosis, particularly in individuals with the SE^{12–18}. Smoking has been associated with progression from the asymptomatic phase to inflammatory joint signs among unaffected first-degree relatives¹⁹. Among seropositive individuals, those who smoke are more likely to progress to RA and in shorter duration²⁰. 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 pre-clinical phases of RA development. However, more work needs to be done to identify the distinct neoantigen(s) important in RA pathogenesis and the biology explaining the progression from asymptomatic autoimmunity to joint manifestations.

Smoking Status, Autoantibodies, and Demographics.—This association between smoking and RA has also been investigated in the context of smoking status and the nuances of serostatus and sex. Many prior studies have investigated smoking status (current vs. past

vs. never as the reference group) and RA risk^{21–30}. A meta-analysis of 16 studies showed that having ever smoked increased the odds of developing RA risk by 1.89-fold³¹. Both current (OR 1.87) and past smokers (OR 1.76) had similar associations with increased RA risk compared to never smokers³¹. Smoking is most strongly related to seropositive RA risk, in both RF-positive and ACPA-positive RA³¹. Smoking does not seem to be a risk factor for seronegative RA^{31–33}. While smoking confers increased RA risk regardless of sex, men seem to have a higher relative risk for RA from smoking than women^{31, 34}. While most of these epidemiologic analyses were performed among those with European ancestry, 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 thought to be about 20%³⁷. Another study estimated that up to 35% of risk for ACPA-positive RA could be explained by smoking³⁸. 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 risk³². A threshold above 10 pack-years appears to be important for RA pathogenesis, though 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 RA³². Studies have not convincingly showed that passive smoking is strongly related to RA risk, though 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 risk⁵². Another study suggested that high sodium intake and smoking may interact to further increase RA risk⁵³. 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 where the impact of behavior change on RA risk have been investigated. Several prospective cohort studies showed that the relative risk 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, so a modest excess risk was still possible. A subsequent Swedish cohort study suggested a reduced risk for RA with longer time since smoking cessation⁵⁴. 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-up³³. This study confirmed smoking as a strong risk factor for seropositive RA, but not seronegative RA³³. 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 quitting³³. Finally, this study suggested a reduced risk for seropositive RA with time since cessation among past smokers³³. Past smokers had about 30% reduced risk for seropositive RA 20 years after cessation³³. There was no association with smoking behavior changes and seronegative RA risk, results which are consistent with other studies showing that smoking is unlikely to be strong a risk factor for this subtype³³. This study demonstrates that a behavior change of smoking cessation may reduce risk for seropositive RA, but this was an observational study, so 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 baseline⁵⁵, but this improved and more smokers quit after a personalized medicine intervention compared to standard RA risk factor education⁵⁶, while also being reassured about risk for developing RA⁵⁷. Since 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, so 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 that are at very elevated risk of up to 50% progressing to IA or clinical RA. Even with these above caveats, smoking cessation should currently be recommended to smokers as a non-pharmacologic method to potentially reduce RA risk or delay the transition to clinical RA.

Excess weight

Body mass index (BMI) is defined as weight (in kg) per height-squared (in meters squared), and is used to set parameters for overweight (BMI 25 and <30 kg/m²), excess weight (BMI 25 kg/m²), and obesity (BMI 30 kg/m²). 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, since 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 female predominance and could explain potential differences by sex for the effect of obesity on RA risk⁶⁰. Known metabolic effects of prevalent RA on anthropometrics, such as rheumatoid cachexia and sarcopenia, also add to the rationale that BMI may impact 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 body mass index (BMI) as a measure of adiposity for risk of RA (Table 1). Two separate meta-analyses have established and quantified the association between BMI and risk of RA. A systematic review⁶¹ of 11 studies^{25, 27, 29, 62–69} investigated the association of BMI and RA risk. Obesity was associated with significantly increased risk of RA (RR 1.25, 95% CI 1.07–1.45) compared to non-obesity, defined as BMI under 30. Compared to 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 five kg/m² increase in BMI, the RR of RA was 1.03 (95% CI 1.01–1.05). A subsequent meta-analysis⁷⁰ that included many of the same studies yielded consistent results; obesity had RR 1.21 for RA (95% CI 1.02–1.44) compared to normal BMI and risk of RA increased by 13% for every five kg/m² 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.

While these meta-analyses of observational studies demonstrated 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} showed a strong association between obesity/overweight and increased RA risk compared to normal BMI, but no association among males. A subsequent population-based Danish prospective cohort study⁷¹ 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 study⁷² found stronger associations between increased BMI and waist circumference for increased risk of RA among men compared to women. However, a Swedish nested case-control study⁷³ 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 found among women. Therefore, excess weight 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-analysis⁷⁰ of the three studies^{63, 65, 68} which 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 work using the Nurses' Health Studies⁶⁸. 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 RA⁷⁰. A nested case-control study of women in the Nurses' Health Studies¹⁷ suggested that ACPA positivity prior to clinical RA diagnosis and excess weight had a statistical interaction to increase RA risk and shorten time to RA diagnosis. Prior 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.

While BMI is commonly used in epidemiologic studies due to wide availability and familiarity for easy interpretation, there may be misclassification by BMI related to age, muscular structure, and menopausal status, and the findings could be confounded. Abdominal adiposity may have more pro-inflammatory metabolic effects so may have a large impact on RA risk. Therefore, there is interest in investigating other measures of adiposity for RA risk. Lu and colleagues recently examined the effect of waist circumference as a measure of visceral adiposity on RA risk in women in the Nurses' Health Studies⁷⁴. Women with waist circumference >88 cm had increased risk of RA compared to women with waist circumference ≤88 cm (HR 1.27, 95% CI 1.10–1.47) adjusting for multiple risk factors, though the association was no longer statistically significant after adjustment for BMI⁷⁴. However, among women 55 years of age and younger, abdominal obesity was associated with seropositive RA (but not seronegative RA) even independent of BMI (HR 1.51, 95% CI 1.01–2.25)⁷⁴. A large Danish cohort study investigated bioimpedance-derived body fat percentage and waist circumference and found that both were associated with increased overall RA risk⁷¹. In subgroup analyses, there was a significant association among women, but not for men or when investigating by RA serostatus. Further investigations are underway related to adipokines and alternate measures of adiposity which may further clarify how excess weight is associated with RA.

Current evidence provides rationale for the benefits of weight loss on disease activity in established RA. A retrospective cohort study⁷⁵ of RA patients 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 2,010 individuals that underwent bariatric surgery to controls with similar weight that did not undergo bariatric surgery and without significant weight change⁷⁶. Perhaps surprisingly, there was similar incidence of RA for both groups, suggesting that marked weight loss did not have a strong effect on reducing RA risk⁷⁶. However, this study was limited by few RA outcomes and did not report on subgroups based on sex, serostatus, or age at RA diagnosis⁷⁶. More work 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}. Since RA is a prototypical inflammatory autoinflammatory disease, there is significant interest in determining whether dietary intake is associated with RA risk⁷⁹. 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 2).

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. The Mediterranean Diet is characterized by high consumption of olive oil, unrefined cereals, fruits and vegetables, spices, and a moderate amount of fish, dairy, meat, and alcohol⁸⁰. RA has lower prevalence in southern Mediterranean countries where the Mediterranean Diet originated⁸¹. The Mediterranean Diet seems to have overall health benefits^{82, 83}, including lower mortality rates from CVD 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 pressure⁸⁵. 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 studies⁸⁰. Though 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 RA⁸⁴ (adjusted OR for RA for 3rd (most adherent to Mediterranean Diet) vs. 1st 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 RA⁸⁷.

Alternative Healthy Eating Index.—Though 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 risk⁸⁸. This effect was statistically significant among women 55 years and younger (HR_{Q4 vs Q1}: 0.67; 95% CI: 0.51 to 0.88; p trend: 0.002), with the inverse association strongest for seropositive RA⁸⁸. Healthy eating patterns were based on the Alternative Healthy Eating Index (AHEI), a dietary quality score that categorized 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, 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 intake⁸⁸. These findings indicate that a generally healthy diet may reduce RA risk. Alcohol, sodium, and red/processed meat intake were the AHEI components that seemed to have the largest impact on RA risk⁸⁸.

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 risk⁸⁹. 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 (CRP), and TNF- α receptor 2)⁹⁰. Increased adherence to EDIP was associated with higher seropositive RA risk among women 55 years and younger [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 for 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 risk⁸⁹.

These positive findings are supported by prior 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 and colleagues identified several studies that found healthy eating patterns to be inversely associated with plasma CRP level, a marker of systemic inflammation^{77, 91–93}. Though 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, 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 fish, are associated with decreased RA risk^{94–97}. This effect is attributed to their anti-inflammatory properties^{97–102}. 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 eicosanoids¹⁰². As a competitive substrate for arachidonic acid, EPA suppresses inflammation⁹⁶. A similar hypothesis suggests that derivatives of EPA and docosahexaenoic acid (DHA) are competitive inhibitors of omega-6 PUFAs and consequently suppress cytokine production^{95, 97}. Thus, omega-3 PUFAs may be important in RA pathogenesis.

A meta-analysis of seven studies reported a modest and non-statistically 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)⁹⁷. This association may be partially attributed to the adverse effects of polychlorinated biphenyls (PCBs) in fish¹⁰³. 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 PCB levels in cooked fish, further demonstrating their potentially adverse effects^{104, 105}. Meanwhile, individuals who consumed oily fish or fish oil supplements had moderately decreased RA risk compared to individuals who rarely or never consumed oily fish¹⁰⁶. These findings indicate that specifically omega-3 FAs, not only fish consumption, may reduce RA risk. Additionally, a prospective cohort study found that increased fatty fish intake decreased RA risk but the association was non-significant, whereas medium fat fish consumption was significantly associated with increased RA risk¹⁰⁷. 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 risk¹⁰⁸. However, there was no association between omega-3 PUFAs and RA¹⁰⁸. Thus, additional research should be conducted to firmly establish the effect of PUFAs and RA risk.

The effect of fish consumption may also be dependent on several other factors including duration, antibody presence, and genetic status. Long-term weekly fish consumption was associated with significantly reduced RA risk, respectively¹⁰². Omega-3 PUFAs may also be important in individuals with RA-related antibody presence, particularly in those with additional genetic risk conferred from SE-positivity (Figure 2). A nested case-control study found decreased an 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 development⁹⁴. Another study investigated omega-3 PUFAs among RF or CCP positive individuals and whether the association depended on SE presence. Findings showed increasing erythrocyte-bound omega-3 PUFA levels were inversely associated with RF/CCP positivity in SE-positive, but not SE-negative individuals¹⁰⁹. 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 standard deviation increase in erythrocyte-bound omega-3 PUFAs¹⁰⁹. There was a significant association between the omega-3 PUFA docosapentaenoic acid content and reduced risk of incident IA⁹⁵. 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 by serologic status and RA risk⁵². 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 to lower levels of alcohol consumption. The mechanism behind this association¹¹⁰ may be through downregulation of the immune response¹¹¹ and decreased production of pro-inflammatory cytokines^{96, 112, 113}. However, alcohol consumption may be indicative of overall health status and be a confounding effect since those who abstain completely may suffer from chronic illness, have previously been heavy drinkers, or pre-

cursor symptoms prior to RA may have influenced drinking behaviors (reverse causation)¹¹¹. A dose-response meta-analysis of eight prospective studies (n=195,029) investigated the association between RA and alcohol consumption¹¹⁰. These findings indicate that the effect of alcohol intake is dependent on dose, duration, and sex, and is strongest in consistent intake of low to moderate doses for at least 10 years¹¹⁰. While 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 risk¹¹⁰. Compared to 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)¹¹⁰. Heavy drinking is no longer protective for RA¹¹⁰. Another meta-analysis of nine 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, 111}. Another prospective cohort study found that prolonged moderate alcohol intake modestly reduced RA risk¹¹⁴. Beer was significantly protective while wine and liquor showed a non-significant associations¹¹⁴. Former drinkers had higher RA risk than those who never drank²⁵. Overall, these findings suggest that alcohol consumption over time may be a modest intervention for RA development, but it is unclear whether this 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 status¹¹¹. The meta-analysis found a significant association between alcohol and risk reduction for ACPA-positive RA and no association for ACPA-negative RA¹¹¹. One case-control study of RF positivity found significant risk reductions for alcohol intake on both RF-positive and RF-negative RA^{111, 115}. Conversely, one prospective cohort study found no association between alcohol use and overall RA or RF-positive RA⁶⁷. 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, and have also been implicated as a potential RA risk factors. Coffee is of particular interest because it is the main dietary source of caffeine as well as a source of antioxidants¹¹⁶. Coffee intake and RA incidence was summarized in a meta-analysis of five 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 non-significant association in cohort studies¹¹⁶. 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 RA¹¹⁶. There was also a significant association between coffee and seropositive RA incidence, but not seronegative RA. While the biologic mechanisms is yet to be elucidated, these results suggest that caffeine may be linked to CCP/RF production¹¹⁶. Similarly, a prospective cohort study found that coffee and other caffeinated beverages were associated with increased RF-positive RA risk¹¹⁵. In contrast, a prospective cohort study found no association between caffeine consumption and RA risk when accounting confounding

variables such as smoking. That analysis of individual beverages including caffeinated coffee, decaffeinated coffee, and tea and RA risk, also showed no relationship¹¹⁷. Another prospective cohort study found a positive association between decaffeinated coffee and RA risk and no association between caffeinated coffee consumption and RA, but showed that decaffeinated coffee attenuated RA risk while tea reduced risk¹¹⁸. These conflicting findings demonstrate the necessity of further investigation to determine the strength of effects, if any, of caffeinated/decaffeinated beverages for RA risk.

Sugar-sweetened soda.—Since sugar-sweetened soda consumption is well established to increase other chronic inflammatory diseases, there was also interest in investigating its association with RA¹¹⁹. 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 in more detail below¹¹⁹. In the Nurses' Health Study, regular sugar-sweetened soda consumption was associated with increased RA risk compared to less frequent consumption¹¹⁹. This effect was more pronounced among seropositive RA, and no association was found between sugar-sweetened soda and seronegative RA¹¹⁹. There was no association between diet soda and RA risk¹¹⁹. 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 RA¹²⁰. A prospective cohort study found a modest association between protein consumption and elevated RA-risk, which was non-significant in the multivariable model¹²⁰. There was no association between red meat, poultry, fish, or iron and RA¹²⁰. Another prospective cohort study of overall long-term dietary quality based on AHEI score found individuals with diets low in red/processed meat consumption had significantly reduced RA risk compared to high intake. Meanwhile, a prospective cohort found that meat consumption had no association with RA¹²¹. 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 towards 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 interest¹²². However, most studies have not found an association between vitamin D and RA risk. A two-sample Mendelian randomization analysis investigating the causal association between RA and vitamin D was null¹²³. An analysis of two 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 drawn between three months and four years of RA diagnosis¹²². Another prospective cohort study showed null results in two cohorts¹²⁴. Findings from a cohort study indicate that greater dietary and supplemental vitamin D intake was associated with decreased RA risk¹²⁵. Vitamin C and antioxidants were implicated in reduced RA risk, but the mechanism was uncertain and further research is needed to confirm the results^{126–128}. The effect of carotenoids was also investigated given their anti-inflammatory properties¹²⁹. While 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 carotenoids¹²⁹. While these studies have attempted to adjust for appropriate confounders, 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, so it may be unlikely that these nutrients have a large impact on RA risk^{130, 131}.

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 pathogenesis¹³² via several immunomodulatory pathways. Physical activity is action produced by skeletal muscle movement and resulting in energy consumption¹³². Skeletal muscle contraction stimulates secretion of myokines including IL-6, IL-8, and IL-15 into the blood^{133–136}. 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; while 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 exercise¹³³. Additionally, hormones including epinephrine and norepinephrine are produced during physical activity¹³². Together, these effects tend to lower systemic inflammation and provide 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 RA¹³⁷. Women who spent >20 minutes per day/1 hour per week of leisure-time activity as compared to among women with less physical activity had decreased RA risk (RR 0.62, 95% CI 0.42–0.92)¹³⁷. Activities including household work, exercise, walking/standing at work, and walking/biking also showed decreases in RA risk¹³⁷. Similarly, a recent prospective cohort study investigated the effects of recreational physical activity and RA risk using repeated measures of physical activity over 26 years¹³⁸. Women reported time spent on recreational activities including walking, jogging, running, bicycling, swimming, tennis, and aerobics. Findings showed that in comparison to 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, showing similar trends for reduced seropositive and seronegative RA risk¹³⁸. However, another prospective cohort study found no association between leisure-time physical activity and RA, but may have been underpowered to detect a modest effect⁶⁷.

Overall, these studies suggest benefits of physical activity. 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 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 population¹³⁹. PD treatment can reduce biomarker levels important in RA pathogenesis^{140, 141}. 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.

Prior studies suggest that PD may increase RA risk compared to no PD^{141,142}. This may be due to the pathogen *Porphyromonas gingivalis* through the induction of an RA-related autoimmune response at sites of oral mucosal inflammation¹⁴². *P. gingivalis* is the only prokaryote known to express peptidylarginine deiminase (PAD), an enzyme necessary for protein citrullination, a post-translational modification from arginine to citrulline, that may lead to changes in structure, function, and potential for immunogenicity¹⁴³. 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^{144, 145}. Despite this association, most recent studies investigating PD and RA risk prior to the presentation of clinical RA have not found significant associations. In a cohort study of 9,702 men and women, Demmer and colleagues found that the prevalence and incidence of self-reported RA in patients with PD versus healthy controls were similar¹⁴⁰. Similarly, a prospective cohort study found no association between previously treated PD and RA¹⁴⁶.

Studies assessing the association between *P. gingivalis* antibodies and RA risk have drawn mixed conclusions. In two studies performed among individuals with SE 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 to controls (OR=1.68; 95% 1.12, 2.52; $p=0.012$)¹⁴⁷. However, among seropositive arthralgia patients without clinical RA, individuals who developed RA within 30 months had similar levels of anti-*P. gingivalis* compared to controls, though this small subgroup may have been underpowered to detect an association¹⁴⁸.

Studies evaluated the presence of the PAD enzyme in patients at risk for RA and also found no relationship¹⁴². In a study of PAD-encoding genes in *P. gingivalis* clinical isolates collected from RA patients and healthy controls, there was no significant difference in PAD expression between RA and non-RA controls¹⁴². Differences in protein citrullination patterns were also not statistically different between these two groups, suggesting that if *P. gingivalis* plays a role in RA onset, it is more likely to due to a post-translational

modification rather than a difference in PAD gene expression¹⁴². These findings combined suggest that PAD and *P. gingivalis* antibody levels may not be strongly predictive of RA development. Mikuls and colleagues found an association between anti-*P. gingivalis* antibodies and elevated RA risk¹⁴⁷, but this was not reproduced in studies with even larger sample sizes^{146, 148}.

No literature has assessed the direct effect that dental hygiene, such as flossing, rinsing, brushing, or attending dental visits, has on RA risk, though gingival and periodontal treatment has been associated with decreased inflammatory biomarkers important in RA pathogenesis¹⁴¹. Periodontal treatment may reduce levels of inflammatory mediators caused by periodontal infections, including IL-1 β and TNF- α ¹⁴¹. Treating gingivitis using mouthwash with essential oils alone was found to reduce levels of bacteria in the mouth by 50 percent¹⁴⁹. 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 risk¹⁴¹. Though 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.

Therefore, further longitudinal studies are 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 pre-clinical RA development. Before this type of intervention can be implemented, randomized controlled trials must be designed to determine the causal effects (Table 3). 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 relatively low incidence rates for RA in the general population. Therefore, studies restricted to subgroups at high RA risk may be preferable. These subgroups may be individuals with SE positivity, RF/ACPA positivity, imaging findings of subclinical synovitis, or undifferentiated IA. Preclinical RA surrogate outcomes to consider would be RA-related autoantibody presence/levels, incident IA, time to RA development, and joint count outcomes.

Further, more research is needed to investigate the feasibility of modifying these lifestyle factors and whether behavior change will result in reduced RA risk. In order 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 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 this paper, 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. Cigarette smoking cessation has intrinsic appeal to study given the strong evidence base for its effect on RA and available pharmacologic options. However, this may be infeasible given high rates of relapse after initial cessation and intrinsic difficulties related to 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 growing prevalence of obesity. However, it is unclear whether the amount of weight loss would be enough to impact RA risk. A randomized trial comparing bariatric surgery to 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 could be part of a multi-factorial design since 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 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 work 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 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. While the mechanisms and associations of cigarette smoking and RA development are the best established, further work 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 have 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 research could help researchers to better understand RA development, and motivate at-risk individuals to adopt healthier behaviors. Therefore, it is essential to invest time and funding to lifestyle modification trials, for an ounce of prevention is worth a pound of cure.

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Figure 1:

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

Figure 2:

Dietary intake, omega-3 PUFA intake, alcohol intake, and RA pathogenesis. Individuals at increased RA risk through the *HLA-DRB1* SE or other RA risk genes produce ACPA from immune dysregulation after neoantigen production resulting from gene-environment interactions. ACPA-positive individuals later develop arthralgias and undifferentiated inflammatory arthritis which progresses to clinically-apparent ACPA-positive RA. An overall healthy diet, especially long-term consumption omega-3 FAs and moderate alcohol, reduces the risk of producing ACPA. ACPA, anti-citrullinated protein antibodies; APC, antigen-presenting cell; RA, rheumatoid arthritis.

Figure 3:

P. gingivalis, PAD, and protein citrullination in RA pathogenesis. *Porphyromonas gingivalis*, a central initiator in the pathogenesis of periodontitis, is the only prokaryote known to express peptidylarginine deiminase (PAD), an enzyme necessary for protein citrullination. The PAD enzyme is capable of citrullinating human arginine. This post translational modification alters the peptide from a positive arginine into a polar, neutrally charged citrulline¹⁵⁰. This conformational change alters structure and may create an unrecognized epitope on citrulline, inducing an immune response, and forming neo-antigens that could result in RA development¹⁴⁷. PAD, peptidylarginine deiminase; ACPA, anti-citrullinated protein antibodies

Table 1:

Summary of the associations of measures of adiposity and risk for RA phenotypes.

Population	Measure of adiposity (exposure)	Direction for association with RA	Relative risk or odds ratio for RA (95%CI)	First author (year) of reference
Men and women	Excess weight (overweight/obese) by BMI (reference: normal BMI)	↑	RR 1.25 (1.07–1.45) RR 1.21 (1.02–1.44) RR 1.45 (1.07–1.95) OR 3.45 (1.73–6.87) OR 1.47 (1.11–1.96)	Qin B (2015) ⁶¹ Feng J (2016) ⁷⁰ Ljung L (2016) ⁷² Pedersen M (2006) ⁶³ Feng J (2016) ⁷⁰
Women	Excess weight (overweight/obese) by BMI (reference: normal BMI)	↑	RR 1.27 (1.04–1.54) RR 1.26 (1.12–1.40) HR 1.10 (1.02–1.18) HR 1.37 (1.10–1.71) OR 1.6 (1.2–2.2) HR 1.45 (1.03–2.03)	Qin B (2015) ⁶¹ Feng J (2016) ⁷⁰ Linauskas A (2018) ⁷¹ Lu B (2014) ⁶⁸ Wesley A (2013) ⁶⁵ Lu B (2018) ⁷⁴
Men	Excess weight (overweight/obese) by BMI (reference: normal BMI)	NS	HR 1.20 (0.75–1.93)	Lu B (2014) ⁶⁸
Women	Excess weight (overweight/obese) by BMI (reference: normal BMI)	↑	OR 1.78 (1.01–3.12)	Ljung L (2016) ⁷²
		↓	OR 0.33 (0.14–0.76)	Turesson C (2016) ⁷³
		↑	HR 1.05 (1.01–1.10) [‡]	Linauskas A (2018) ⁷¹
	Waist circumference >88 cm (reference: 88 cm)	↑	HR 1.25 (1.08–1.45)	Lu B (2018) ⁷⁴

* Observed for seropositive RA risk
** Observed for seronegative RA risk
‡ Observed among women aged 55 years
‡ Observed for high vs. low waist circumference
BMI, body mass index; NS, non-significant association; RA, rheumatoid arthritis.

Table 2: Summary of the associations of dietary intake patterns and individual foods/beverages and risk for RA

	Direction for association with RA	Relative risk or odds ratio for RA (95%CI)	First author (year) of reference
Dietary patterns			
Mediterranean Diet (more adherent vs. less adherent)	↓	OR 0.79 (0.65–0.96)	Johansson K (2018) ⁸²
	NS	HR 0.98 (0.80–1.20)	Hu Y (2015) ⁸⁴
Alternative Healthy Eating Index (healthy vs. unhealthy)	↓	HR 0.67 (0.51–0.88) [‡]	Hu Y (2017) ⁸⁸
Empirical Dietary Inflammatory Pattern (pro-inflammatory vs. anti-inflammatory)	↑	HR 1.38 (1.05–1.83)	Sparks JA (2019) ⁸⁹
Individual foods/beverages			
Omega-3 polyunsaturated fatty acids (high vs. low)	↓	RR 0.61 (0.40–0.93)	Di Giuseppe D (2014) ¹⁰²
	NS	HR 1.12 (0.91–1.37)	Sparks JA (2019) ⁵²
Fish (high vs. low)	↓	OR 0.8 (0.6–1.0)	Rosell M (2009) ¹⁰⁶
	NS	OR 0.78 (0.53–1.14) RR 0.91 (0.68–1.23) RR 0.96 (0.91–1.01) HR 0.93 (0.67–1.28)	Shapiro JA (1996) ¹⁰⁵ Pedersen M (2005) ¹⁰⁷ Di Giuseppe D (2014) ⁹⁷ Sparks JA (2019) ⁵²
Alcohol (moderate vs. none)	↓	RR 0.86 (0.78–0.94) OR 0.78 (0.63–0.96) HR 0.48 (0.29–0.82)	Jin Z (2014) ¹¹⁰ Scott IC (2013) ¹¹¹ Lu B (2014) ¹¹⁴
Sugar-sweetened soda (high vs. low)	↑	HR 1.63 (1.15–2.30) [*]	Hu Y (2014) ¹¹⁹
Caffeine (high vs. low)	↑	RR 2.42 (1.06–5.55) [*]	Lee YH (2014) ¹¹⁶
	NS	RR 1.1 (0.8–1.6) RR 1.04 (0.69–1.56)	Karlson EW (2003) ¹¹⁷ Mikuls T (2002) ¹¹⁸
Red/processed meat (low vs. high)	↓	HR 0.64 (0.47–0.87) [‡]	Hu Y (2017) ⁸⁸
	NS	RR 1.17 (0.89–1.55) [‡] RR 1.08 (0.77–1.53) [‡]	Benito-Garcia E (2007) ¹²⁰ Di Giuseppe D (2018) ¹²¹
Vitamin D (high vs. low)	↓	RR 0.67 (0.44–1.00)	Merlino LA (2004) ¹²⁵
	NS	OR 1.30 (0.78–2.16) RR 0.86 (0.64–1.17)	Hiraki LT (2014) ¹²² Hiraki LT (2012) ¹²⁴

* Observed for seropositive RA risk

** Observed for seronegative RA risk

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Observed among women aged 55 year
NS, non-significant association; RA, rheumatoid arthritis

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Potential interventions in hypothetical randomized controlled trials for RA prevention among seropositive individuals without RA or unaffected first-degree relatives.

Table 3:

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 (e.g., 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	Non-drinkers or low drinkers	Increase alcohol intake	Alcoholic beverages	Non-alcoholic 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

RA, rheumatoid arthritis.