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Where There's Smoke, There's a Joint: Passive Smoking and Rheumatoid Arthritis

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Among the established risk factors associated with developing rheumatoid arthritis (RA), smoking remains one of the leading environmental exposures associated with disease onset. One meta-analysis of ten studies found that the risk of developing RA increased by 26% among those who smoked 1–10 pack-years, and nearly doubled among those with more than 20 pack-years, compared to never smokers[1]. Studies that closely examine smoking and development of RA continue to be important, as it is a modifiable risk factor that can significantly reduce the burden of disease in the population.

Despite the extensive body of literature on smoking and RA, less is known regarding the impact of passive and active smoking throughout the life-course on the development of incident RA. Ideally, examining this research question requires longitudinal data captured in disease-free individuals with sufficient follow-up time, which is not commonly available. Additionally, detailed information beyond "ever" vs "never" smoking is valuable in that the window of exposure susceptibility can be assessed, offering insight into how different exposures accumulate over the life-course, as these are not singular risk factors, but rather correlated variables that may contribute both directly and indirectly to the development of RA through various pathways.

Yoshida et al. use the Nurses' Health Study II (n~90,000) and a life-course epidemiology approach to examine three passive smoking exposures on RA onset: 1) maternal smoking during pregnancy; 2) parental smoking during childhood; and 3) adult passive smoking. Analyses also accounted for personal (active) smoking, as earlier-life experiences of passive smoking could potentially influence the uptake of later-life personal smoking, which itself is a risk factor for RA onset. The life-course epidemiology approach is appropriate given how correlated the smoking variables are to each other, which can potentially accumulate to increase the risk of disease in adulthood and act through a number of pathways. Therefore, the analysis calculated both the direct and indirect effect of passive smoking, accounting for the time ordering of variables across the lifespan and controlling for time-varying

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covariates. Results demonstrated that early-life inhaled exposures, such as passive cigarette smoking, were associated with adult-onset seropositive RA, even after controlling for later-life personal smoking. Further, the effect of childhood passive smoking exposure was especially pronounced among “ever” adult smokers, similar to previous studies[2].

The study by Yoshida et al. is unique in that it teases apart smoking exposure with use of multiple variables and utilizes robust statistical analyses, including inverse probability weighted controlled direct effect models (a type of marginal structural model)[3,4]. These models were developed to account for confounding in observational studies and have demonstrated the ability to mimic randomized clinical trial results. As a clinical trial of exposure to passive smoking in childhood as a risk factor for development of RA in adulthood is not feasible or ethical, investigation of this issue must use observational data. The use of the life-course epidemiology approach and the state-of-the-art statistical models used in this study provide the best evidence to date regarding the association between passive smoking and RA development.

While a role for passive smoking aligns with previous work and the mucosal paradigm of RA pathogenesis[5], several unknowns remain. For example, residual confounding of factors such as socioeconomic status and/or other social determinants of health (e.g., poverty, poor diet) that are correlated with active and passive smoking may increase the risk of autoimmune disease and cannot be ruled out. Smoking also increases the risk of infections[6,7] and periodontal disease[8], which in turn could increase the risk of RA[9]. As the authors note, smoking may also induce epigenetic changes years before symptoms develop in individuals genetically susceptible to RA. Lastly, there may be interaction effects with other factors, such as anti-citrullinated protein antibodies and rheumatoid factor, which were not explored in this analysis.

Although the specific mechanism remains unexplained, the research by Yoshida et al. adds additional evidence to the literature suggesting that reducing exposure to passive smoking during early years may reduce risk of RA in adulthood. Looking forward, interventions should focus on not only reducing personal smoking habits but also secondhand smoke exposure in children, especially those at risk for autoimmune conditions (e.g., familial susceptibility). Smoking harms nearly every organ of the body, and remains the leading cause of preventable disease, disability, and death in the United States[10]. Additionally, over 40% of U.S. children aged 3–11 years are exposed to secondhand smoke[11]. Intervening on this important public health issue will not only potentially reduce the risk of RA, but also reduce the impact of other debilitating chronic diseases.

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