Ever since smoking was first identified as a risk factor for rheumatoid arthritis (RA),1 growing evidence has implicated the respiratory mucosa in RA pathogenesis.2–4 Respiratory exposures now associated with increased risk of RA include air pollution,5–6 respiratory tract diseases,7–11 passive smoking,12 13 and importantly, occupational inhalants14 such as silica dust and asbestos,15 textile dust,16 brick and concrete laying,17 pesticides18 and military burn pits.19 Another revolution in understanding RA pathogenesis occurred when a strong interaction between smoking and human leucocyte antigen shared epitope (HLA-SE) alleles to increase risk of anticitrullinated peptide antibody (ACPA) positive RA by 21-fold.20 A subsequent study found a similar strong (39-fold) interaction between textile dust and the HLA-SE alleles for ACPA-positive RA risk.16 Together, these helped form the basis for the respiratory mucosal origins paradigm for RA pathogenesis. However, the interaction between genes and other respiratory exposures remains less studied despite the fact that it may offer critical insights to RA pathogenesis and prevention.

In *Annals of the Rheumatic Diseases*, Tang et al studied 4033 RA cases from the Epidemiological Investigation of RA (EIRA) dataset to identify the effect of 32 occupational inhalable exposures on RA risk, including their interactions with smoking and RA risk genes.21 A total of 17 occupational inhalable agents (16 of which were independent of each other) had associations with increased risk of ACPA-positive RA, with insecticides and fungicides showing the strongest associations (OR 2.10 for each). Exposure to any agent increased the risk of ACPA-positive RA by 1.25-fold, with a stronger association in men than women (OR 1.66 vs 1.13). Importantly, both the number and duration of exposures exhibited a dose–response effect on RA risk. In addition, they observed a gene–environment interaction for RA risk for certain inhalants including gasoline engine exhaust (attributable proportion (AP) 0.52), asbestos (AP 0.44), carbon monoxide (AP 0.23) and quartz dust (AP 0.43). This interaction was stronger when using the Genetic Risk Score (GRS) based on genome-wide markers compared with only HLA-SE alleles. When adding smoking status, triple-exposed (inhalants, smoking, and high GRS) individuals had an 18-fold increased risk of ACPA-positive RA compared with triple-unexposed individuals. Smoking also interacted with certain agents to increase RA risk including carbon monoxide (AP 0.30) and detergents (AP 0.25) for ACPA-positive RA risk. The authors conclude that occupational inhalants may serve as triggers for RA, so reducing these exposures and smoking is warranted, especially for genetically vulnerable individuals.

The above findings provide several important implications regarding RA pathogenesis and prevention. First, each occupational inhalable agent had a unique profile of the way it interacted with RA risk genes and with smoking. For example, gasoline exhaust, carbon monoxide and asbestos had strong statistical interactions with the RA-risk genes for increased risk of RA, whereas other inhalants including detergents and pulp or paper dust did not. In contrast, certain agents such as detergents and carbon monoxide interacted with smoking in a statistically significant manner to increase RA risk, whereas several other inhalants did not. These unique interactions suggest that if the relationship between inhalable agents and RA is indeed causal, they may do so via distinct pathways.

Another important finding related to RA pathogenesis was that the individual inhalable agents and their interactions showed a strong association for ACPA-positive RA, but not ACPA-negative RA. On the one hand, this is somewhat surprising since prior studies of both occupational inhalants15–17 and respiratory diseases7–8 showed that they were associated with both ACPA-positive and ACPA-negative RA, approximately equally. On the other hand, smoking has long been known to be associated stronger with ACPA-positive RA,2 20 Furthermore, prior studies of interactions with genes have only shown positive interaction for ACPA-positive RA as well.16 20 22 23 This stronger link between genetic interactions and ACPA-positive RA may simply reflect the fact that ACPA-positive RA has much stronger heritability24 25 and genetic risk26 than ACPA-negative RA. Overall, these findings further support the growing notion that ACPA-positive may represent a distinct and more homogeneous entity compared with ACPA-negative RA.

A third key finding to note relating to RA pathogenesis was the positive relationship observed between dose and duration of occupational inhaled exposures and RA risk. The authors also noted that risk of developing RA increased as duration of exposure to any agents elongated. Interestingly, however, the data shown in the corresponding figure follow a U-shaped association than a linear one, with the strongest associations seen for inhalant exposures occurring approximately 8–15 years before RA onset. This timing also coincides with the timing of autoantibody development in RA.27 28 It also coincides with prior studies of air pollutants29 and respiratory tract diseases30 showing that exposures 10 or more years before RA onset were most associated with RA risk. Thus, the findings for dose and duration of exposure may provide further support for a true association between these agents and RA. They also provide further evidence that RA pathogenesis likely begins many years before clinical onset for most patients.

In addition to informing RA pathogenesis, this study by Tang et al also provides several important implications for RA prevention. Due to its comprehensive assessment of exposures, it identified novel associations between several common and preventable exposures and RA including detergents and gasoline engine exhaust. In addition, this study provides further support for regulating agents with known associations with RA including carbon monoxide6 and asbestos.7 Finally, the fact that no single exposure dominated RA risk is not surprising and suggests that preventing RA will require a multimodal approach.
Indeed, several specific public policy implications directly follow from the results of this study. First, environmental health initiatives should reduce public exposure to ambient pollutants including carbon monoxide and gasoline exhaust. Second, occupational health initiatives should mitigate occupational hazards including detergents and asbestos. Third, public health initiative should continue to reduce cigarette smoking. While we agree with the authors that such interventions would have the strongest effect for the genetically vulnerable, this information is not currently available for most. Thus, such interventions are likely best performed on a global basis.

Strengths of this study include its large sample size and combination of smoking, genetic and detailed occupational exposures in one population-based dataset along with ACPSA status. There are also several important limitations to consider. Although the population-based study is a strength, results may not generalise especially out of White and/or Swedish populations. For example, this study found no gene–environment interaction for occupational exposure to asbestos and silica and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study. RMD Open 2019;5:e000978.

In conclusion, this important study by Tang et al demonstrated that several common, occupational inhalable agents are associated with increased risk of ACPSA-positive RA, especially in the context of RA risk alleles and smoking. These findings further implicate the respiratory tract mucosa in ACPSA-positive RA pathogenesis and impress the need for public policy initiatives related to occupational inhalants to prevent RA.

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REFERENCES


