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# Air pollution and multiple sclerosis risk

Based on epidemiological studies MS is likely to be a preventable disease or at least a proportion of new cases will be preventable (Dobson and Giovannoni, 2019). We the MS community, therefore, should be doing intervention studies to assess whether reduced exposure to potentially modifiable risk factors reduces the risk of getting MS. However, many environmental exposures, associated with an increased risk of getting MS, don't lend themselves to interventional studies (Ramagopalan et al., 2010). These include smoking (Handel et al., 2011), passive smoking (Wang et al., 2019), organic solvent exposure (Gerhardsson et al., 2020) and air pollution (Hayes and Ntambi, 2020; Noorimotlagh et al., 2020) all of which are inhaled. How inhaled pollutants cause MS is unknown (Hayes and Ntambi, 2020; Noorimotlagh et al., 2020)). However, it has always been argued that air pollution may work by acting as an atmospheric filter for ultraviolet light and hence increases one's risk of getting MS by reducing ultraviolet (UV) light exposure, in particular UVB exposure, which is the important component of the UV spectrum for vitamin D synthesis in the skin (Mousavi et al., 2019; Noorimotlagh et al., 2020). The air pollution-UVB filter hypothesis supports vitamin D insufficiency as the causal factor in MS (Noorimotlagh et al., 2020).

All these airbourne exposures, however, do not necessarily contribute to vitamin D insufficiency, but rather cause inflammation and oxidative damage, particularly in the lungs. We, therefore, favour a competing 'lung hypothesis' of how environmental pollutants contribute to one's risk of getting MS. The latter implies that inflammation in the lungs changes or alters proteins via a process called post-translational modification, which converts normal proteins into highly immunogenic autoantigens that trigger autoimmune disease, or the inflammation acts as a non-specific stimulant to lower the threshold of developing MS or autoimmunity.

Interestingly, oral tobacco or exposure to smokeless tobacco through the use of snus lowers one's risk of getting MS compared to inhaled tobacco smoke (Waubant et al., 2019), which also supports the lung hypothesis of MS risk. In an adaptively transferred experimental autoimmune encephalomyelitis (EAE) model of MS, T-cells blasts do not efficiently enter the CNS but only gain the capacity to enter the CNS after residing transiently within the lung tissues (Odoardi et al., 2012). In this model T-cell blasts pass through bronchus-associated lymphoid tissues and lung-draining mediastinal lymph nodes before re-entering the circulation and migrating to the CNS (Odoardi et al., 2012). Effector T cells appear to be reprogrammed in the lung and fundamentally change their gene-expression profile indicating that the lung contributes to the activation of autoaggressive T cells and enables them to migrate to the CNS to induce autoimmune disease. Based on these pieces of evidence it appears that the lungs may be an important niche for triggering autoimmunity. Importantly, there is support for the lung hypothesis in rheumatoid arthritis (Sparks and Karlson, 2016). However, to the best of our knowledge outside of animal models, the evidence for the lung hypothesis playing a major role in MS remains speculative. Saying this who wouldn't want to breathe clean air if one of the benefits is a potentially lower risk of developing MS and other autoimmune diseases?

A study in this issue from Padua in Italy shows quite a strong correlation (r = -0.89) between exposure to particulate matter in the air less than 2.5 micrometres (PM2.5) and the prevalence of MS (Scartezzini et al., 2020). Seeing an r-value or correlation coefficient close to 0.9 is hard to ignore, but one should not be tempted to interpret this relationship between particulate air pollution and MS prevalence as being causal. The association between air pollution and MS prevalence may not necessarily be biological. One could imagine a link between air pollution and better access to healthcare, for example, which would lead to improved survival and hence a higher prevalence of MS.

Another hypothesis is the 'sunshine hypothesis'; rather than vitamin D insufficiency, it is the reduction in exposure to sunshine that is the causal factor in MS (Lucas and Rodney Harris, 2018). The only way to separate out whether sun exposure itself or reduced vitamin D is the causal factor is to do a randomised vitamin D supplementation trial and to control for ambient background sun exposure when analysing the data. Interestingly in relation to the sunshine versus the vitamin D debate, a recent German study using sun-exposure measures for vitamin D and latitude, showed correlations between vitamin D levels or latitude and MS disease severity in two cohorts of patients (Ostkamp et al., 2021). High serum vitamin D levels was associated with a reduced MS severity score (MSSS), reduced risk for relapses, and lower disability accumulation over time (Ostkamp et al., 2021). As expected low latitude was associated with higher vitamin D levels, lower MSSS, fewer gadolinium-enhancing lesions, and lower disability accumulation (Ostkamp et al., 2021). In interferon-β–treated subjects the association of latitude with disability was lacking (Ostkamp et al., 2021). These investigators then used the photosensitivity-associated genomic variant MC1R as a proxy for sunlight exposure. In carriers of MC1R:rs1805008 (T) variant, who reported increased sunlight sensitivity, lower latitude was associated with higher MRI activity, whereas for non-carriers there was less MRI activity at lower latitudes (Ostkamp et al., 2021). To back-up these epidemiological observations, which indicate that sunshine itself plays a role, the investigators looked at the effect of ultraviolet (UV)-phototherapy on the transcriptome of immune cells from MS subjects from an earlier study. Phototherapy induced a vitamin D and type I interferon signature that was most apparent in monocytes but was also detected in B and T cells (Ostkamp et al., 2021). Although these data do not prove that vitamin D or sunshine are the causal factors, it at least

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provides evidence for clinically relevant immunological effects of sunlight exposure and illustrates how difficult it will be to disentangle vitamin D's effects from that of sunlight itself on the immune system.

In conclusion, it seems that air pollution is a risk factor for developing MS. Whether the effects of air pollution are via direct effects on the immune system as a result of lung inflammation or indirectly via its effect on filtering sunlight is unclear. Now more than ever we need additional population-based and well-designed migration studies to replicate and hopefully support the Padua study's findings. In particular, the incidence of MS, rather than the prevalence of MS, should be used. As alluded to above, the prevalence of MS confounded by other factors that are increasing the life expectancy of people with MS. In parallel, we would urge the international MS community to get together to start vitamin D supplementation trials with the aim of trying to prevent MS. These trials are critical in answering the question whether it is low vitamin D, low sunlight exposure or both that are the causal risk factors in the pathogenesis of MS.

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