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Smoking and Multiple Sclerosis: A Matter of Global Importance

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The aetiology of multiple sclerosis (MS) arises from the interaction of multiple different genetic and environmental risk factors [1]. Large-scale genome-wide association studies have identified multiple genetic risk loci but by far the most important association in MS susceptibility is with the class II *human leukocyte antigen* (HLA) region, specifically *HLA-DRB1*1501* bearing haplotypes [2]. The environmental factors most consistently associated with risk of MS are Epstein-Barr virus infection, particularly infectious mononucleosis, cigarette smoking and low vitamin D lev-

els [1]. However, these data largely stem from studies in North American and European populations.

In this edition of *Neuroepidemiology*, Maghzi et al. [3] report the results of a well-powered sibling case-control study of cigarette smoking and MS in Iran. MS in Iran is gaining attention due to reports of a recent substantial prevalence increase [4]. If true, causal factors may be more easily discovered in this population. The authors found that smoking history was associated with MS risk.

Overall this is a similar finding to that reported by a previous case-control study conducted in multiple centres across Iran [5]. However, there are a number of unexplained discrepancies; Maghzi et al. report a positive association with a history of smoking drawn almost exclusively from the association observed in men since the frequency of smoking amongst women in the study was very low. In contrast, the other Iranian study found that smoking was significantly associated with MS susceptibility only in women and not in men. The two studies are quite similar in demographical characteristics and, indeed, the controls used in the first study were often family members, but the smoking rate in females reported by Maghzi et al. is much lower than that seen

Fig. 1. Forest plot of smoking history and MS risk. The risk ratios, 95% confidence intervals (CI) and p values are calculated using the inverse variance (IV) with random effects model in Review Manager 5.1. Study details are reported in Alonso et al. [5].

in the previous study. Previously no significant interaction between gender and the contribution of smoking to MS susceptibility had been seen [6]. It is currently unclear why the results of these two studies differ and further analysis will be important to resolve this discrepancy.

The most recent meta-analysis examining the effect of past or current smoking on MS susceptibility reported a risk ratio of 1.52 (95% confidence interval 1.39–1.66, $p < 0.00001$) [6]. Incorporating the results of Maghzi et al. into this meta-analysis provides further evidence that this association is robust across multiple study designs and geographical regions. The updated risk ratio is 1.57 (95% confidence interval 1.41–1.76, $p < 0.00001$; fig. 1).

The most interesting questions arising from these studies are: how does smoking interact with other established risk factors to lead to the development of MS and what molecular mechanism underlies the effect on MS risk?

Recent studies are just beginning to shed light on the first of these questions. The risk associated with high antibody titres against Epstein-Barr virus is higher in ever smokers than never smokers [7]. There is also evidence that smoking interacts with *HLA* alleles to determine MS susceptibility [8]. Even larger cohort and case-control studies will be needed to establish the precise extent of the interactions that exist between different genetic and environmental risk factors.

MS is not alone amongst autoimmune conditions in its association with smoking; other conditions in which cigarette smoking increases disease risk include rheumatoid arthritis, Grave's disease, Crohn's disease, Goodpasture's syndrome, thromboangiitis obliterans, primary biliary cirrhosis, systemic sclerosis and fibromyalgia [9]. In the particular case of rheumatoid arthritis, smoking appears to exert its effect on susceptibility by citrullination of the autoantigen α -enolase [10]. It may be that a similar molecular pathway exists for MS but studies are hampered by the lack of a definitively identified autoantigen. Regardless of the specific molecular mechanism involved, epidemiological studies have shown that it is constituents of cigarette smoke rather than the nicotine that are likely to be responsible for the effect on MS susceptibility. This is supported by the selective association between cigarette smoking and MS risk *not* observed with the use of tobacco-containing snuff [11].

Case-control and cohort studies have established a firm association between cigarette smoking and MS susceptibility. Identification of the molecular mechanism behind this association is urgently required. However, more immediately, public health measures targeting smoking cessation may aid in reducing the prevalence of this often devastating disease.

Disclosure Statement

The authors have no conflicts of interest to declare.

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