Air pollution may increase susceptibility to ulcerative colitis through epigenetic alterations involving CXCR2 and the MHC class III region

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Abstract

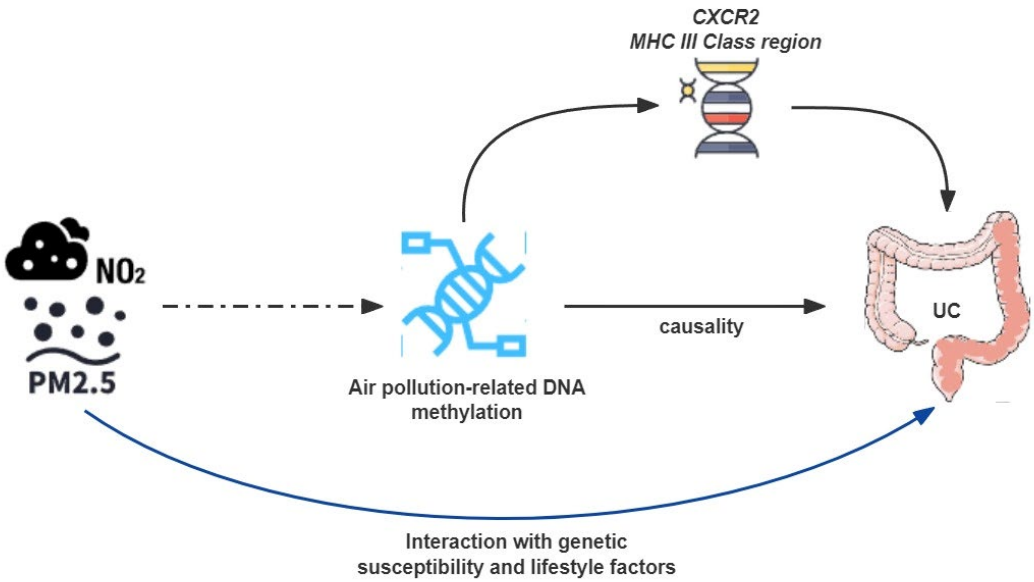
Objective: Environmental factors are involved in the development of inflammatory bowel disease (IBD). Recent provocative data have linked air pollution (i.e., $PM_{2.5}$ PM_{10}, NO_x) with ulcerative colitis (UC), but not Crohn's disease (CD). Deoxyribonucleic acid (DNA) methylation is the most widely investigated epigenetic change that could explain the impact of gene-environment interaction in disease development. However, its potential role in the association between air pollution and IBD has not yet been explored. This study aims to confirm this association, explore interactions with genetics, deprivation, lifestyle, and urbanization and explore potential epigenetic mechanisms.

Methods: We conducted a systematic literature review to summarize previous studies on air pollutants and the risk of UC and CD. Then, we identified 454,402 individuals in UK Biobank, examined associations of air pollution with incident IBD and its interaction with genetics and lifestyle by applying a Cox regression. Next, epigenetic Mendelian randomization (MR) analyses were conducted to examine causal association between air pollution-related DNA methylation and UC risk. Lastly, those loci identified from epigenetic MR were further validated by genome-wide DNA methylation analysis, co-localization and gene expression analyses.

Results: In analysis of participants in UK Biobank, with a mean follow-up of 13.2 years, we found that higher exposures to NO_x (HR=1.21, 95%CI 1.06-1.38), NO_2 (HR=1.19, 95%CI=1.04-1.36), $PM_{2.5}$ (HR=1.19, 95%CI=1.04-1.36) and combined air pollution score (HR=1.24, 95%CI=1.08-1.42) were associated with incident UC but not CD. NO_x, NO_2, $PM_{2.5}$, PM_{10} exposures were associated with urbanization and deprivation. Interactions with genetics and lifestyle factors including diet were also observed. In MR analysis, we found 5 and 22 methylated CpG sites related to $PM_{2.5}$ and NO_2 exposure to be significantly associated with UC. DNA methylation alterations at *CXCR2* and susceptible loci within MHC class III region (AGPAT*1, TNXB, TNF*), were validated in the genome-wide DNA methylation analysis, co-localization analysis and gene expression analysis of colonic tissue.

Conclusion: We provide further evidence that air pollution is implicated in the pathogenesis of late-onset UC. We demonstrate interaction with urbanization and deprivation; the effect is influenced by genetic susceptibility and some lifestyle factors. The effects of air pollution on UC may be mediated by epigenetic alterations in specific genetic determinants including *CXCR2* and genes within the MHC class III region.

Keywords: inflammatory bowel disease; air pollution; DNA methylation; Mendelian randomization; MHC III region



Graphic abstract