

Project Details	
Project Code	MRCNMH25Ba Taylor
Title	What are the biological mechanisms underlying the association between smoking, smoking cessation and mental health: a triangulation approach using machine learning, mendelian randomisation, and g-methods applied to multiple biological cohort studies.
Research Theme	Neuroscience & Mental Health
Summary	What are the biological mechanisms underlying the association between smoking, smoking cessation, and mental health? A growing body of evidence supports smoking as a causal risk factor for poorer mental health, and there is evidence for long-term improvements in mental health following smoking cessation. However, less is known about the mechanisms underlying this association. This PhD project will examine hypothesized biological mechanisms, such as inflammation markers. The PhD candidate will receive training in various methodological approaches, including techniques from genetic epidemiology, machine learning, and G-methods to reduce residual and time-varying confounding.
Description	<p><b>Background:</b> Smoking is the world's leading cause of preventable illness and death. One in every two people who smoke will die of a smoking-related disease unless they quit. Smoking prevalence has decreased markedly in the general population but remains disproportionately higher in people with mental illness, leading to significant disparities in morbidity and mortality.</p> <p>There is evidence indicating that smoking causes mental ill health, and cessation improves mental health; however, little is known about the causal biological pathways underlying this association. There is preliminary evidence suggesting that smoking can damage neurological systems and oxidative stress pathways, and it is possible that these systems return to normal functioning after sustained smoking cessation. All studies on this topic are likely to face issues with unmeasured and time-varying confounders. Therefore, we propose an innovative approach to: a) provide evidence for the biological basis of the association between smoking (and cessation) and mental health, and b) address potential biases from confounding and time-varying confounders using novel methods.</p> <p><b>Aims and Method:</b> The student will apply a triangulation approach across their program of work to strengthen causal inference by comparing different approaches with assumed unrelated sources of bias. The student will work with multiple data sources from different populations (NHANES, United States; IMAGEN, multiple countries across Europe; UK Biobank, United Kingdom), and compare effect estimates derived from traditional modeling (regression, generalized linear models) to estimates derived from novel and more sophisticated approaches, including G-methods, machine learning, adjustment for genetic risk to exposure, and Mendelian Randomization. This triangulation approach not only leads to more robust conclusions but additionally provides an excellent training opportunity for the student in a variety of methods.</p> <p>The student will have the opportunity to take full ownership of both the methodological and theoretical aspects of the project. This type of</p>

	<p>project offers an extensive range of research decisions, such as selecting variables for biological data, selecting specific biomarkers, neurological systems, mental health outcomes, or time-varying confounders. Students will be empowered to explore various modeling approaches and select methods based on their scientific rationale and training needs. They will be able to choose from a variety of techniques, including G-methods and machine learning, tailoring their approach to best fit the project’s objectives. Additionally, the student will have the opportunity to shape the patient and public involvement aspect of the project. This includes selecting platforms and crafting messaging that align with their personal interests and career objectives.</p> <p><b>The student will undertake four main studies:</b></p> <p>Study 1: A systematic review and meta-analysis of studies examining possible causal biological mechanisms for the association between smoking, smoking cessation, and mental health (e.g., inflammation pathways).</p> <p>Study 2: A cross-sectional and longitudinal mediation and moderation analysis using pre-existing data from cohort studies with biological data (IMAGEN, UK Biobank, NHANES) to examine the association between smoking, smoking cessation, and mental health, and potential mediators and moderators of the relationship (e.g., inflammation markers). Exposure will be smoking status, outcome will be depression and anxiety scores. Mediators and moderators will be inflammation markers such as cytokines, corticosteroids, and neurotrophins, and we can examine the possibility of investigating other potential biological mediators/moderators. The student can also explore examining dose-response relationships in exposure, such as smoking heaviness.</p> <p>Study 3: Re-examine the longitudinal associations in Study 2 using IMAGEN and NHANES, employing methods to overcome issues of residual and time-varying confounding, including G-methods (e.g., inverse probability weighted marginal structural models, G estimation of a structural nested model), machine learning (e.g., to examine patterns in time-varying confounding).</p> <p>Study 4: Re-examine the cross-sectional associations in Study 2 using UK Biobank with adjustment for genetic risk factors, and Multivariable Mendelian Randomization approach to overcome residual confounding.</p> <p><b>International Impact:</b> These findings will significantly improve our understanding of the mechanisms through which tobacco harms mental health and if these harms are reversible after smoking cessation. This information will have important implications for the development of bespoke individual-level interventions and public health interventions (e.g., specific messaging around the benefits of cessation on one’s mental health) for this population to improve smoking cessation, as well as important policy and healthcare implications in the UK and around the globe. The importance of targeted messaging was recently highlighted in the UK Government’s Khan Review “Making Smoking Obsolete.</p>
<b>Supervisory Team</b>	
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