Project Details	
Project Code	MRCPHS26Br Richmond
Title	Exploring mechanisms that could cause harm from vaping
Research Theme	PHS
Project Type	Dry lab
Summary	Although e-cigarettes have not been available long enough to assess their long-term effects, evidence suggests vaping may cause harm, especially in those who have never smoked. This project aims to investigate potential mechanisms of harm using a range of methods and data sources. The student will examine epigenetic changes associated with vaping, explore nicotine's causal role in health issues linked to both smoking and vaping, and identify short- and medium-term physiological and clinical effects. Large datasets and cohort studies will support this work, providing insight into the potential health impacts of vaping and contributing to evidence-based public health policy.
Description	**Background** Many people who smoke cigarettes switch to vaping to reduce their risk of smoking-related health problems, as vaping nicotine exposes users to fewer harmful chemicals and toxicants than smoking. However, the remaining/additional chemicals in vapes may pose health risks. This is especially concerning given Action on Smoking and Health (ASH) youth surveys estimate that 390,000 11–17-year-olds vape, including 1.8% of never-smokers in this age group. The ASH 2024 survey estimated around 5.6 million adults in Great Britain vape. Of these, ~3 million are ex-smokers, ~2.2 million also smoke, and ~0.6 million have never smoked. These figures indicate a substantial portion of the population may be at risk from vaping, but the long-term health effects remain uncertain due to the relative novelty of these products. Vapes (e-cigarettes) began gaining popularity in the UK around 2013, primarily among smokers attempting to quit. Thus, we lack the long-term data on exclusive vapers needed to understand the health impacts of extended use without prior exposure to tobacco smoke. However, we can use biomarkers and various statistical methods to explore potential mechanisms that could lead to harm. DNA methylation is an epigenetic change characterised by the addition of a methyl group to a DNA nucleotide. These changes do not change the underlying DNA, but can turn genes on or off. Smoking is associated with epigenetic changes that likely cause some smoking-related health outcomes. Previous work has identified both overlapping and distinct epigenetic changes associated with smoking and vaping. Recently, a study partially using the same data found that methylation patterns associated with vaping are consistent with DNA methylation changes seen in people who later develop lung cancer. This highlights that vaping could cause DNA methylation changes that could in turn cause cancer. DNA methylation is just one example of a mechanism that could indicate what long-term vaping-related health outcomes we may expect to observe in the future. It is widely accepted that nicotine itself is addictive but not an important driver of smoking-related harm. However, with the rise in popularity of nicotine vaping among young people in the US and UK over the past

	decade, there has been a greater demand for understanding the impact of nicotine without exposure to cigarette smoke. We have developed a model using a method called multivariable Mendelian randomisation that can be used to disentangle the effects of nicotine from the effects of other constituents of tobacco smoke. This model allows us to look at the direct effect of regular nicotine use over decades, which we will not be able to observe among vapers for many years. Understanding the biological and clinical mechanisms that could cause harm from vaping is important to identify potential risks to vapers in the future. Although we are confident that, compared to smoking, vaping will be less harmful overall, vapers need to know what the potential risks are. Using complex, harmonised data from internationally recognised cohort studies (e.g., ALSPAC), applying sophisticated techniques in longitudinal data analysis and predictive modelling, we can triangulate evidence with different sources of bias to more confidently infer whether causal relationships exist. **Aims and objectives** This project aims to better understand how vaping might lead to poor health outcomes by identifying the underlying biological and clinical mechanisms involved. To achieve this, the student will focus on four key objectives: Biomarker identification 1. Conduct a systematic review and meta-analysis of studies exploring the associations between vaping and DNA methylation. 2. Investigate how DNA methylation changes over time with vaping use (with and without a history of smoking) using multi-level modelling in a cohort of e-cigarette users. Statistical approaches 3. Triangulate evidence from an array of statistical methods (e.g., machine learning, G-methods, observational analyses) to identify clinical and biological differences that are associated with vaping versus not vaping. They will then use the same methods to investigate if these differences are associated with potential health risks. The analysis will be conducted using large datasets (e.g., Our Future Health (n =~1,740,000), the Avon Longitudinal Study of Parents (n=~14,000) and linked health records (the Clinical Practice Research Datalink, n=~18,000,000). 4. Separate the effects of nicotine from the other constituents of tobacco smoke by conducting genome-wide association studies stratified by smoking status and then using multivariable Mendelian randomisation to explore the impact of nicotine on potential health outcomes related to vaping. These analyses will be conducted using UK Biobank (n=~500,000) or Our Future Health. **Ownership and steer of the project** The student will shape this project by identifying which potential health outcomes and relevant mechanisms to focus on. The student will have access to saliva samples from a longitudinal study in the US and will be able to choose an alternative relevant analysis to conduct with these samples if desired.

Supervisory Team	
Lead Supervisor	
Name	Dr Rebecca Richmond
Affiliation	Bristol
College/Faculty	
Department/School	Faculty of Health and Life Sciences
Email Address	Rebecca.Richmond@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Jasmine Khouja
Affiliation	Bath
College/Faculty	Department of Psychology
Department/School	Jasmine.khouja@bristol.ac.uk
Co-Supervisor 2	
Name	Dr Gemma Taylor
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Bristol Medical School – Population Health Science
Co-Supervisor 3	
Name	Professor Matthew Suderman
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Bristol Medical School – Population Health Science