Principal Investigator

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Summary of research
Smoking, caffeine, Mendelian randomisation, cardiovascular disease

Application Lay Summary:

1a: This research aims to investigate whether observed associations between caffeine and smoking and health outcomes are causal. We will use Mendelian randomisation methods, using genetic variants associated with caffeine consumption and smoking as proxies for measured exposures. We will investigate the role of caffeine consumption and smoking in the following outcome measures: cardiovascular and metabolic disease (including diagnoses of coronary heart disease, stroke and diabetes and intermediate traits such as glucose, lipids and blood pressure), mental health outcomes (including diagnoses of depression, anxiety, psychosis and dementia), cognitive function, lung function, asthma and allergy, kidney function, liver function and thyroid function.

1b: The proposed research will help to further understanding of the role of caffeine consumption and smoking in disease outcomes, which will inform prevention and treatment strategies. Knowledge of causal effects of caffeine will help to inform public health messages regarding caffeine intake. Knowledge of
the causal effects of smoking will be important for strategies for reducing the harmful effects of smoking in those unable to quit. This work may also contribute to the development of novel treatments by identifying pathways through which caffeine intake and smoking contribute to disease.

1c: We will use Mendelian randomisation methods to look at the associations of genetic variants that are associated with caffeine consumption and smoking behaviour with health outcomes of interest. Due to the way that genes are passed from parents to offspring, which is essentially random, genetic variants that are associated with caffeine intake or smoking behaviour will not be associated with other lifestyle factors (unlike reported caffeine consumption and smoking). Additionally, health outcomes cannot affect the genes that an individual is born with so we do not need to worry about the possibility of reverse causality.

1d: This work will be undertaken in the full cohort, N=500,000.

PROJECT EXTENSION - APPROVED 09.01.2017:
"Within the scope of the initial proposal, which aims to investigate the causal nature of a number of observational associations with substance use, we would like to extend the list of mental health outcomes to also include neuroticism and ADHD.

Recreational substance use is seen at higher prevalence in populations with ADHD compared to the general population. Understanding causality in these association is notoriously problematic due to our reliance on observational studies. Mendelian randomization uses genetic instruments for modifiable exposures to investigate the causal nature of observational associations. We wish to investigate whether risk of ADHD is causally associated with substance use, in particular caffeine and cigarette use. We also wish to investigate whether caffeine and cigarette use causally predict risk of ADHD.

In addition, we would like to extend the proposal to look at the association between mental health outcomes (including schizophrenia and neuroticism) and cognition.
Associations are consistently seen between cigarette use and a number of mental health outcomes including psychosis and neuroticism, although direction of causation is not known. There is also a large body of literature showing association between cognitive function and these outcomes. There has been some suggestion, for example, that high rates of smoking in schizophrenia could be to alleviate cognitive impairment from both the disorder and anti-psychotic medication side-effects, as nicotine has been posited as a cognitive enhancer. We aim to investigate whether associations between cigarette use, cognition and mental health outcomes are causal, using Mendelian randomization.

**PROJECT EXTENSION - APPROVED 02.05.2017**
Scope of application 9142 updated so that it includes Mendelian randomisation studies of smoking and coffee on all lifestyle and health outcomes in UK Biobank, rather than just the stated outcomes.