CONCEPT PAPER TEMPLATE

Provisional Paper Title:	Associations between lung function and vascular health
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Objective of the study:
To assess cross-sectional and longitudinal associations between lung function and vascular health as identified by retinal photography

Data analysis methods:
Multiple linear regression using measures of retinal arteriolar and venule calibre as the dependent variables. The primary outcome variable will be the central retinal arteriolar equivalent calibre (CRAE), the central retinal venule equivalent (CRVE) calibre, and arteriolar/venule ratio (AVR). Measures of lung function (FEV1, FVC, and the FEV1/FVC ratio) will be the main predictors. Supplementary analyses will use measures of lung function (TLC, FRC, RV, DLco, and Kco) as predictors.

Initial analyses will explore cross-sectional associations at age 38. When age 45 data become available, longitudinal analyses of changes between age 38 and 45 will follow.

All analyses will be adjusted for height and sex. Additional analyses will be adjusted for potential confounders including smoking (pack years), BMI, systolic and diastolic blood pressure, and CRP. The effect of a childhood or adult asthma diagnosis will be considered and separate analyses will be conducted for those with and without these diagnoses. Supplementary analyses will also consider other measures of lung function (lung volumes and diffusion capacity) as predictors.

We will test for sex*lung function and smoking*lung function interactions and conduct separate analyses if these indicate effect modification.

Variables needed at which ages:
Lung function from age 38 and 45
Retinal microvascular calibre measures from age 38 & 45
Smoking history
Asthma diagnoses
Height & Weight & BMI
CRP

Significance of the study (for theory, research methods or clinical practice):

People with respiratory disease and poor lung function have a greatly increased risk of cardiovascular disease. The mechanism of this increased risk is poorly understood and not fully explained by smoking because even never smokers have a higher risk of cardiac death if they have poor lung function. The question that this analysis will address is whether poor lung function is associated with impaired systemic vasculopathy as indicated by retinal microvasculature measurements. Retinal blood vessel calibre and the arteriolar/venule ratio is associated with a number of cardiovascular risk factors and is an indicator of microvascular damage. A cross-sectional study of a mixed age sample of adults found

FEV_1 and FEV_1/FVC to be inversely associated with retinal venule size: smaller venules were associated with better lung function (larger venules are associated with CV risk).[1] We are not aware of any other cross-sectional or longitudinal studies.

Further, we propose to investigate possible cofounding and mediating explanations for an association if one is identified. These include common risk factors such as smoking, blood pressure, and inflammation (CRP).

Because we have identified sex differences in the association between lung function and other CVS risk factors – including BMI[2] and endothelial function[3], we will investigate sex interactions in this analysis. Also, it has been suggested that the association between lung and microvascular changes may be due to smoking[1], so we will also investigate effect modifications by smoking.

This analysis will shed light on the association between respiratory and cardiovascular health and has the potential to offer a biologically plausible explanation for the increased risk of cardiovascular disease in people with impaired lung function.

References:

1. Harris *et al*. 2012. The association of systemic microvascular changes with lung function and lung density: a cross-sectional study. PLOS One. 2012; 7: e50224
2. Sutherland *et al.* The relationship between body fat and respiratory function in young adults. Eur Respir J. 2016; 48; 734-47
3. Hancox *et al.* unpublished