DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Oxidative stress and lung function

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P.I. Sponsor:
(if the proposing author is a student or colleague of an original PI)

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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:
To assess cross-sectional associations between a broad range of lung function measures and blood markers of oxidative stress at age 45.

To further explore whether accelerated lung function decline during early-mid adulthood is associated with oxidative markers at age 45.

Data analysis methods:
Linear regression of lung function at age 45 using markers of oxidative stress as the main predictors. Lung function will be defined as percent of predicted value to each person as a function of their age, height, and sex. Oxidative stress markers will be transformed to approximate normal distributions if necessary.

Initial analyses will be adjusted for sex and investigate effect-modification by sex. Further analyses will adjust for smoking, asthma, and BMI.

This will be an exploratory analysis: multiple measures of lung function and multiple markers of oxidative stress will be investigated. No adjustments will be made for multiple statistical analyses, but the pattern of associations (if any) will be investigated.

If cross-sectional associations are found, further regression analyses will investigate whether decline in lung function since age 32 is associated with markers of oxidative stress at age 45 (using decline in lung function as the independent variable). The analyses will adjust for sex, smoking, asthma, and BMI and test for effect modification as above.

Variables needed at which ages:
Lung function at age 45:
Spirometry: FEV1, FVC, FEV1/FVC ratio
Lung volumes: TLC, FRC, RV
Gas transfer: DLco, DLco/VA, VA

Changes in lung function between age 32 and 45

Oxidative markers: Protein carbonyl, Prdx2 basal, Prdx2 challenge, GDF15, Allantoin

Sex, height, weight, smoking history, cannabis use, respiratory symptoms, and asthma diagnosis.

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

The lungs receive the entire cardiac output, have a very large surface area for gas exchange, and have the highest tissue concentration of oxygen of any internal organ. The lungs may therefore be particularly vulnerable to oxidative stress, such that systemic production of reactive oxygen species (ROS) could lead to lung damage. [1]

Oxidative damage, has been implicated in many diseases, including COPD and Asthma.[2] Chronic lung infections (such as in COPD) may further increase ROS due to immune activation.[3] The main cause of COPD is cigarette smoking, and this appears to impair antioxidant activity, although oxidative stress has been shown to persist long after smoking cessation.[4] ROS species are also implicated in asthma – partly due to underlying eosinophilic inflammation.[2, 5, 6]

There is, however, little epidemiological research on oxidative stress and respiratory dysfunction in humans, although some studies have suggested associations.[7] A study of 1265 apparently healthy Japanese adults (mean age 57 ±12 years) found an association between spirometric lung function, reactive oxygen metabolites, and myocardial microdamage (troponin I concentrations).[8]

Oxidative stress could plausibly help to explain the well-established, but poorly understood link between impaired lung function and cardiac disease/all cause mortality. ROS are also associated with impaired heart function and could be either a mediator of the association, or a common cause of both lung and heart disease.[8, 9]

Oxidative stress has been implicated in endothelial function and in a previous investigation of the Dunedin study cohort, we have established associations between lung and endothelial function: an association that was stronger in women than men.[10]

In view of the paucity of evidence from population-based studies, we propose an exploratory analysis. Evidence of an association between oxidative stress and lung function would have implications for further research into the causes of chronic lung disease and the associations between lung and cardiovascular diseases. It may also lead to therapeutic investigations into antioxidant therapy for lung disease.

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