CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author:

Provisional Paper Title:	Associations between endothelial and lung function
Proposing Author:	Bob Hancox
Other Contributors:	Michael Williams, Richie Poulton, Avshalom Caspi, Temi Moffitt, Malcolm Sears, +? Others
Potential Journals:	
Intended Submission Date	December 2017

Please keep one copy for your records and return one to the proposing author

B. To be completed by potential co-authors:

[xx] Approved [ ] Not Approved [ ] Let's discuss, I have concerns

Comments: Fascinating question, so glad you will study it! Neither lung function nor endothelial function are in my area of expertise,

but I was able to help with financial support for the respiratory data collection in the past, so I guess that makes me a stakeholder, and thank you for sharing this concept paper with me. I don't need to be involved in creating the paper, and I will be happy with an acknowledgement.

Please check your contribution(s) for authorship:

- [x] Conceptualising and designing the longitudinal study
- [ ] Conceptualising and collecting one or more variables
- [ ] Data collection
- [ ] Conceptualizing and designing this specific paper project
- [ ] Statistical analyses
- [ ] Writing
- [ ] Reviewing manuscript drafts
- [ ] Final approval before submission for publication
- [x] Acknowledgment only, I will not be a co-author

Signature: Temi

Date: 25 july 2017

CONCEPT PAPER TEMPLATE

Provisional Paper Title:	Associations between endothelial and lung function
Proposing Author:	Bob Hancox
Author's Phone, Fax or E-mail:	bob.hancox@otago.ac.nz
Date:	25/7/17
P.I. Sponsor (if the proposing author is a student or colleague of an original PI)	

Objective of the study:
To assess cross-sectional associations between endothelial function and lung function at age 38

Data analysis methods:
Multiple linear regression using endothelial function assessed by peripheral arterial tonometry (PAT) at age 38 as the dependent variable and measures of lung function (FEV1, FVC, and the FEV1/FVC ratio) as the main predictors. All analyses will be adjusted for height and sex.

Additional analyses will be adjusted for potential confounders including smoking, BMI. 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. Blood eosinophils and CRP are both associated with lung function in this cohort and could be potential mediating factors. Nitric Oxide is a key mediator of endothelial function and the mediating effect of exhaled NO will also be investigated.

Supplementary analyses will also consider other measures of lung function (lung volumes and diffusion capacity) as predictors.

Variables needed at which ages:
Lung function from age 38
Endothelial function from age 38 (Framingham-reactive hyperemia index)
Smoking history
Asthma diagnoses
Height & Weight
CRP
Eosinophils

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. This is not explained by smoking- even never smokers have a higher risk of cardiac death if they have poor lung function. Endothelial dysfunction is one possible shared risk factor for poor cardiovascular and respiratory health. There are plausible mechanisms by which inflammatory airways disease leads to endothelial dysfunction in the pulmonary circulation. Conversely, the integrity of the pulmonary endothelium may influence airway inflammation.[1] Assessing the pulmonary endothelium is very difficult, but there is evidence that COPD and Asthma both have altered endothelial function in the systemic circulation suggesting that these diseases may have systemic as well as pulmonary endothelial effects.[1-3] Evidence is sparse, however, and It is unknown whether an association between pulmonary function and systemic endothelial function exists in healthy people and/or those with mild or early disease or the extent to

which these associations are confounded by common risk factors such as smoking. This analysis will shed light on this association and has the potential to offer an explanation for the increased risk of cardiovascular disease in people with impaired lung function.

References:

1. Green CE, Turner AM. The role of the endothelium in asthma and chronic obstructive pulmonary disease (copd). *Respiratory Research* 2017; 18: 20.
2. Yildiz P, Oflaz H, Cine N*, et al.* Endothelial dysfunction in patients with asthma: The role of polymorphisms of ace and endothelial nos genes. *The Journal of asthma : official journal of the Association for the Care of Asthma* 2004; 41: 159-66.
3. Ye C, Younus A, Malik R*, et al.* Subclinical cardiovascular disease in patients with chronic obstructive pulmonary disease: A systematic review. *QJM* 2017; 110: 341-9.