Dunedin Multidisciplinary Health & Development Study

Concept Paper Form

Provisional Paper Title: HDL cholesterol and changes in 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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Objective of the study:

In recent years, there has been increasing awareness that lung function is a good predictor of cardiovascular disease. Low lung function is as strong a predictor of cardiovascular mortality as high cholesterol. The mechanism for this is not known but shared risk factors for lung and heart disease are likely to explain part of the association. Smoking is the most obvious of these, but the association between low lung function and heart disease is seen in people who have never smoked, so cannot be the only explanation. Another shared risk factor could be cholesterol.

High total cholesterol and low HDL cholesterol are well known predictors of cardiovascular disease. Little is known about their effects on lungs, although there is cross-sectional evidence that HDL cholesterol and its associated apolipoprotein (a1) is associated with higher lung function in NHANES III, whereas LDL cholesterol is associated with lower lung function. HDL and apolipoprotein (a1) have anti-inflammatory effects whereas LDL contributes to oxidative stress. Hence, they may plausibly be associated with changes in lung function over time. Moreover, there is increasing interest in the use of cholesterol-lowering statins as anti-inflammatory treatments for a range of lung diseases.(Gowdy & Fessler 2012)

A few studies have analysed blood cholesterol levels and asthma/airflow obstruction. In cross-sectional analyses, higher levels of serum HDL cholesterol appear to be associated with *more* asthma and atopy in children (Shenoi et al., 1992) and atopy in adults (Schafer, et al., 2003) with the opposite associations for total and LDL cholesterol respectively. There is also evidence that ethnicity may be an effect modifier for the association in adults (Fessler, et al., 2010). Conversely, *lower* HDL in childhood has been found to be predictive of adolescent asthma with no evidence of an association for

total cholesterol or LDL (Yiallouros, et al., 2011). Rasmussen, et al. (2012) found no association between cholesterol measures at age 14 and AHR at age 20, nor cross-sectional associations at either age, after adjustment for potential confounders.

Absolute lung function is a better predictor of heart disease than measures of airflow obstruction (Agarwal, et al., 2012). Less is known about any associations, cross-sectionally or longitudinally between cholesterol and absolute levels of lung function. Cirillo, et al. (2002) found positive associations between HDL and apolipoprotein (a1) and FEV1 and negative associations between LDL and apolipoprotein (b) and FEV1.

This study will investigate associations between blood cholesterol (specifically HDL cholesterol) and subsequent decline in lung function (measured by FEV1 and FVC).

Data analysis methods:

The primary analyses will investigate HDL and HDL:total cholesterol at ages 26, 32, 38 and 45 as predictors of changes in lung function between 26 and 45 (change in FEV1 and FVC will be modeled by using age 45 values as the dependent variable while including age 26 values as a covariate in each case). Exploratory cross-sectional analyses between cholesterol and lung function at each of ages 26, 32, 38, and 45 will also be performed. All models will also be adjusted for height and sex. Further models will also be adjusted for history of smoking, asthma, and BMI. To determine the independent effects of HDL, a fully adjusted model also including LDL will be used. Interactions between variables of interest and age, sex, and ethnicity will be investigated. Standard regression diagnostics will be performed. Sensitivity analyses will be conducted where missing data may meaningfully affect results. Pregnant women will be excluded and we will also consider the role of lipid-lowering drugs use by doing sensitivity analyses excluding people taking these drugs. Analyses will be conducted using Stata with two-sided $p<0.05$ considered statistically significant in all cases.

Variables needed at which ages:

Lung function: ages 26, 32, 38, and 45
Total cholesterol, HDL, LDL, apolipoprotein (a1), apolipoprotein (b): ages 26, 32, 38, and 45
History of asthma and atopy since childhood
History of smoking since childhood
Height and weight (& BMI): ages 26, 32, 38, and 45
Statin use: ages 26, 32, 38, 45 (from medcap data for exclusion/control)

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

The interrelationship between heart disease and lung function is one of the most important but poorly understood issues in respiratory (and cardiovascular) epidemiology. Although the association is well established, there is very little research on the mechanisms. Most research has focused on established disease in elderly

people with COPD, but there is evidence that the association develops much earlier than this. If cholesterol and its subtractions can explain some of this association, this would represent a major advance in our understanding.

The literature in this area consists of case-control studies (Naveed, et al., 2012) and cross-sectional analyses (Cirillo, et al., 2002) so a longitudinal analysis on a large sample with the ability to investigate a range of potential confounders would make a substantial contribution to our understanding of this topic.

References:

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