DUNEDIN STUDY CONCEPT PAPER

Provisional Paper Title: Validation of a quantitative index of early-life growth conditions for etiotyping developmental origins of COPD

Proposing Author: Benjamin M Smith

Author's Email: Bob Hancox, Temi Moffitt, Avshalom Caspi, Ben Williams, Karen Sugden, Anthony Ambler, Reremoana Theodore, Sandhya Ramrhaka

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

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Please describe your proposal in 2-3 pages with sufficient detail for helpful review by addressing all areas outlined below.

Objective of the study:

Chronic obstructive pulmonary disease (COPD) is a major driver of death and disability worldwide.[1] While COPD typically manifests later in life, emerging evidence suggests that exposures during early-life growth are important to COPD risk.[2–4] Investigating the relationship of early-life growth conditions and COPD in adulthood is challenging due to recall bias, selection bias and the correlated nature of adverse early-life exposures. This proposal seeks to evaluate the validity of a quantitative index of early-life growth conditions, readily deployable in adulthood, that may overcome these challenges.

A recent genome-wide association study of 5.4M adults reported a saturated map of genetic variants associated with height that accounts for over 90% of trait heritability and explains up to 45% of trait variance.[5] Since human height is determined in part by genetics and in part by early-life growth conditions, it follows that **the difference between measured height and genotype-predicted height** (**height-GaP**) **may represent a quantitative and cumulative index of adverse early-life growth conditions**. In support of this hypothesis, analysis of UKBiobank data demonstrated that a larger height-GaP deficit was associated with several *retrospectively* ascertained early-life factors known to

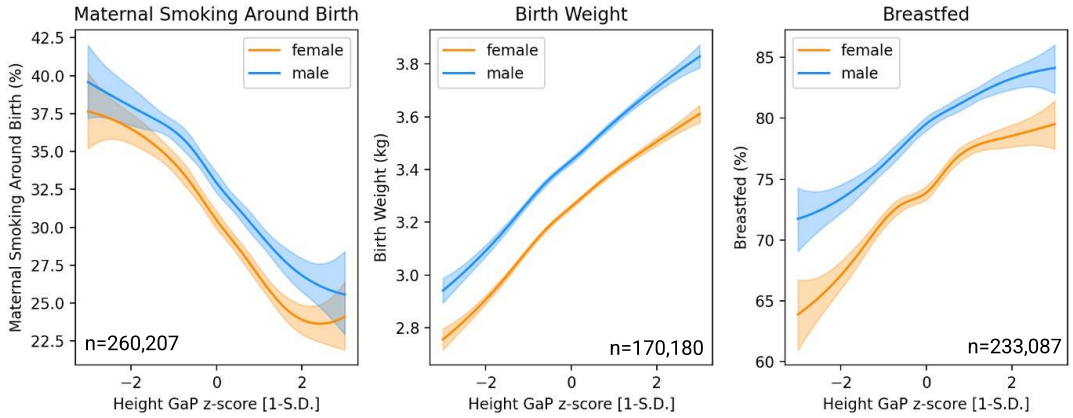

Figure. Adjusted for age, age^2, genotype-predicted height, smoking status, pack-years, pack-years^2, residential $PM_{2.5}$ concentration, and principal components of ancestry.

adversely affect growth (**Figure**), as well as subsequent all-cause and respiratory mortality.

Retrospective assessment of early-life growth conditions and potential confounding by later-life height loss limit the strength of inferences that can made from these observations and motivate the current proposal for the Dunedin Multi-Disciplinary Health and Development Study.

Objectives:

1. To determine whether height-GaP is associated with early-life growth conditions. We hypothesize that larger height-GaP deficit will be associated with prospectively ascertained early-life factors known to affect growth.

2. To determine whether height-GaP is associated with obstructive spirometry in adulthood. We hypothesize that larger height-GaP deficit will be associated with obstructive spirometry in adulthood.

Data analysis methods[1]:

Sample: All participants consenting to genotype data use and at least one measured height.

Requested variables:

Height-GaP: Standing shoeless height at all available visits, polygenic height score and principal components of genetic ancestry.

Early-life factors:

Maternal smoking during pregnancy (ascertained at participant age 9),

Gestational age,
Birthweight,
Duration of breastfeeding (ascertained at participant age 3),
Early-life weight gain (birth to age 3),
Mean childhood socioeconomic status,
Exposure to parental tobacco smoke exposure at all available visits,
Childhood asthma status at all available visits,

Lung function:

Pre- and post-bronchodilator FEV1 and FVC at all available visits.[6]

Descriptive and precision variables:

[1] A key concern for the Dunedin Study is superficial analyses of data that simply identify differences or deficits between ethnic groups or other communities where inequities exist (e.g. persons with disabilities, Pasifika peoples, members of migrant and SOGIESC (Sexual Orientation, Gender Identify and Expression and Sexual Characteristics) communities). The cumulative effect of these types of studies is stigmatising and not of benefit. Any research that identifies differences must (a) incorporate information on the broader context (e.g. historical or political factors); (b) where possible undertake additional analyses to examine the source of the difference/s, and (c) include policy recommendations for its resolution.

Sex, race-ethnicity, age at all available visits, weight at all available visits, respiratory medication use at all available visits, primary cigarette smoke exposure (status, cigarettes per day, pack-years) at all available study visits, cannabis use at all available ages, airway hyperresponsiveness at all study visits, hsCRP and IL-6 at all available visits.

Analysis plan:

Height-GaP will be computed for every visit using the corresponding measured height, but the primary analysis will use height-GaP at age 21 years – an age when the period of ontogenetic growth has ended but later-life height loss has not occurred. Height-GaP will be calculated for each participant as the difference between measured height and genotype-predicted height in cm. Genotype-predicted height will be calculated using the all-ancestry polygenic height score reported by Yengo J, *Nature* 2022.[3] Briefly, each participant's polygenic height score is calculated as the weighted sum of height-increasing alleles from the "all ancestry" weights in Supp. Table 10, Yengo, *Nature* 2022. Genotype-predicted height will be computed by fitting sex-specific linear regression models of measured height. To simplify interpretation, height-GaP values will be converted to z-scores.

For objective 1, a linear regression model of height-GaP will be fit for each of the early-life factors with adjustment for sex, genotype-predicted height and principal components of genetic ancestry. For early life factors with repeated measurements (i.e., exposure to parental tobacco smoke exposure, asthma status), a generalized linear regression model will be fit. Exploratory secondary analyses will examine height-GaP associations at earlier ages to determine when associations, if present, manifest.

For objective 2, modified Poisson regression models of airflow obstruction (defined as an FEV_1/FVC GLI-global z-score < -1.65) will be fit to estimate the association of height-GaP with airflow obstruction prevalence at age 21 years, and incidence of airflow obstruction during the adult follow-up period.[3] Models will be adjusted for sex, genotype-predicted height, principal components of genetic ancestry, childhood asthma, childhood airway hyperresponsiveness, time-varying smoking status and cigarettes smoked per day, and hsCRP. Secondary analyses will examine FEV_1/FVC GLI-global z-score < -1.264.[7]

Analyses will be performed using R. Two-sided p-values < 0.01 will be considered statistically significant.

We have adequate power based on the following assumptions:

N=750 Dunedin participants with genotype data AND at least 1 spirometry measure, two-sided alpha 0.05

Expected partial correlation	Power
0.10	78%
0.15	98%
0.20	>99%

In terms of expected partial correlations, in ALSPAC we observe partial correlations between height-GaP and early-life growth conditions ranged between 0.10 and 0.60, depending on the early-life variable (e.g., gestational age, birth weight, multiple

deprivation index, hours of household tobacco smoke exposure, months of breastfeeding, FEV1, etc…).

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

If the hypotheses are confirmed, this study will provide evidence that height-GaP can serve as a quantitative index of early-life growth conditions with potential utility for etiotyping developmental origins of COPD in adulthood.

How the paper will contribute to Māori health advancement and/or equitable health outcomes[2]

The height-gap genetic data have not been validated on Māori. Furthermore, the Dunedin Study GWAS data are based on those of NZ/European ancestry. However, the height gap is believed to arise from early life disadvantage/adverse conditions for growth. Understanding how the factors that lead to a height gap influence lung function will inform efforts to enhance health for all people, and may be especially beneficial for disadvantaged groups including Māori, because although the genetics may differ, the early-life factors that lead to adverse lung trajectories are likely to be qualitatively similar. Māori have higher rates of chronic respiratory diseases and worse outcomes from these. We know that adverse lung function trajectories often begin early in life and the aim of this proposal is to investigate the contribution of height-gap to early lung function impairment. We hope that this will help us to understand the risk factors underlying the high prevalence of lung disease in Māori and identify areas for prevention.

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[2] Helpful information can be found here: https://www.hrc.govt.nz/sites/default/files/2020-01/NZ%20Prioritisation-Framework-FA-web_0.pdf

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