Metabolic pathways mediating the relationships of physical activity and acute exercise response

Background and Rationale:

Nayor et al. (2021) showed that changes in physical activity are associated with better cardiorespiratory fitness and Nayor et al. (2020) identified metabolites essential to the pathways of cardiorespiratory fitness. An important next step is understanding the role of the circulating metabolome in the association of physical activity and cardiorespiratory fitness. Does more physical activity result in a metabolic profile that results in higher peak VO2, maximal oxygen consumption during exercise? Causal mediation analysis (Baron & Kenny 1986; Robins & Greenland 1992; Pearl 2001; Lok 2016) can decompose the total effect of physical activity on Peak VO2 into: the indirect effect of physical activity, the exposure, on Peak VO2, the outcome, through the metabolic profiles, the mediator, and the direct effect of physical activity on peak VO2 through all other pathways.

In addition to the relevant clinical implications, as a doctoral thesis-related work this project will propose a methodological solution to causal mediation estimation in the presence of a high dimensional mediator. Vanderweele et al. (2014) extends causal mediation analysis to multiple mediators. Application of their proposed methodology to a high dimensional mediator without further modification would result in estimates with high variances and poor predictions. We propose two solutions to address the dimensionality problem: 1. Reduce the dimensionality of the metabolites using principal components analysis then proceed with the estimation methodology as usual or 2. Introduce regularization with elastic net penalties to the estimation accomplishing both control for variance inflation and variable selection. We will limit modeling assumptions by using a semi-parametric estimator of the indirect and direct effects (Lok 2016; Lok & Bosch 2021). Since this is thesis-related research, we expect that the methodology will evolve.

Causal mediation analysis requires adjusting for confounders between the metabolites and Peak VO2. Since physical activity is not (and cannot be) randomized we need to additionally adjust for confounders of physical activity, metabolites, and peak VO2. We will use the set of confounders used in Nayor et al. (2021) and Nayor et al. (2020) to adjust for the confounding.

Specific aim:

The aim of this project is to determine how much of the effect of physical activity on peak vo2 is mediated by the metabolome.

Study Sample:

All individuals with available CPFE, metabolites (HILIC metabolites), and actical data from Gen 3 exam 3, NOS, and Omni 2 exam 3.

Data Requested:

We will only use existing data. Any new variable created will be submitted to FHS data management for future use.

CPET outcome variable:

Peak VO2

Actical exposure variables:

1. Minutes spent in moderate to vigorous physical activity (MVPA)
2. Met physical activity guidelines (at least 150 minutes spent in MVPA)

Metabolite mediator variables:

All baseline metabolites variables used in Nayor (2020).

Confounders:

1. Age
2. Sex
3. BMI
4. Smoking status
5. Resting SBP
6. Season of actical wear
7. Wear time
8. Geographic location
9. Cohort
10. Hypertension
11. CVD
12. Diabetes

References:

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