Effect of adolescent socioeconomic conditions and health-related behaviors on chronic diseases in adulthood

Study protocol for a PhD thesis

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1. Overarching goal

Our overarching goal is to assess the mechanisms by which adolescent health-related behaviors mediate the effect of parental socioeconomic conditions on chronic disease in adulthood and to rank the relative impact of socioeconomic policy interventions compared to behavioral policy interventions at that early life period in reducing the burden of chronic disease in adulthood.

2. Background

Chronic diseases such as cardiometabolic diseases (CMD) and cancers are major causes of death and disability worldwide. Globally, they constitute about two thirds (64%) of total burden of disease in 2019. In high-income countries, this proportion is even higher [1]. These diseases have been shown to exhibit a social gradient, whereby those with poorer socioeconomic conditions, typically measured by income level, occupation or educational attainment, have worse health status and higher mortality than those with better socioeconomic conditions [2-4].

Notably, parental socioeconomic conditions in early life (e.g. during preconception, gestation, infancy, childhood and adolescence) have an important effect on the development of chronic diseases in later life [5]. Indeed, empirical evidence have demonstrated that disadvantageous socioeconomic conditions in early life are related to higher incidence of chronic diseases in adulthood compared to favorable early life socioeconomic conditions [6-9]. Additionally, following the framework of social-to-biological transitions or biological embedding [10], various biological processes have been shown to embody social gradients in disease [11-14].

Adolescence, in particular, is a period of rapid development, both biologically and psychosocially. Many important health-related behaviors such as smoking and alcohol use are initiated during this period with effects lasting well into adulthood [15]. These health-related behaviors during adolescence have been found to be strong predictors of the development of chronic diseases in adulthood [16, 17]. Additionally, unhealthy behaviors in adolescence can have an effect on the biological mechanisms of aging at the DNA level, manifesting as accelerated epigenetic aging in adulthood [18]. These health-related behaviors have been found to be important mediators in the pathway between early life parental socioeconomic conditions and health in later life [19, 20].

However, the mechanisms by which health-related behaviors during adolescence mediate the relationship between parental socioeconomic conditions during adolescence and chronic diseases in adulthood are unknown. One potential mechanism is differential exposure, whereby disadvantageous socioeconomic conditions (e.g. having low household income) increase exposure to unhealthy behaviors. At the same time, groups across different socioeconomic levels (e.g. low vs. high household income) may experience different effects of health-related behaviors, which constitute the mechanism known as differential susceptibility [21, 22]. Importantly, increased susceptibility to specific health behaviours among those having experienced disadvantaged parental socioeconomic conditions will imply a prioritization of preventive policies targeting these susceptible population groups in order to mitigate socioeconomic inequalities in chronic diseases. Ranking the relative importance of socioeconomic policy interventions compared to behavioral policy interventions aiming at reducing chronic diseases would also guide public health policy prioritization.

For this PhD thesis, we aim to assess the mediating role of health-related behaviors in adolescence for the effect of parental socioeconomic conditions on 1) chronic diseases in adulthood and 2) biological aging, and we aim to 3) rank the impact of hypothetical population interventions on the adolescent socioeconomic conditions and health-related behaviors for reducing chronic diseases in adulthood. We will be using data from a nationwide ongoing cohort which contains extensive socioeconomic, behavioral and biomarkers data across a follow up period spanning adolescence to adulthood, using causal inference approaches. Findings from this project will help decide on the design and allocation of resources for real-world preventive strategies on chronic diseases.

3. Methods

This project will use causal inference methods, specifically by adopting a framework based on potential outcomes and directed acyclic graphs (DAGs) [23]. We will practice Open Science principles to improve the accountability and reproducibility of research. This may include publishing a protocol on the Open Science Framework and online sharing of scripts [24, 25].

3.1. Cohort

We will use data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), an ongoing population-based longitudinal cohort study conducted in the United States (US). This cohort is nationally representative of the US, with initial data collection completed in 1994 and 1995. Since then, four follow up periods of data collection have been completed, most recently at Wave V in 2016 to 2018 [26]. An overview of the study population and the variables of interest proposed to be used in this project is provided in Table 1.

Table 1 : Overview of the Add Health study population and variables of interest

Study population	Adolescents aged 12 – 19 years old in the United States in 1994 – 1995 (n=20,745 in Wave I)
Exposure variables	Parental income during adolescence, offspring health-related behaviors during adolescence
Outcome variables	Chronic disease morbidities, cardiometabolic health markers, epigenetic clocks at ages 32 – 42 in 2016 – 2018 (n=5,381 in Wave V)

3.2. Exposures and mediators

3.2.1. Socioeconomic conditions will be assessed by parental income. We will focus on parental income during adolescence, adjusting for household size and composition by applying equivalence scales which enable comparing households with different sizes and composition [27].

3.2.2. Adolescent health behaviors that will be investigated are cigarette smoking, alcohol consumption (high intake or binge drinking), leisure physical activity (based on questions about frequency, intensity and estimated duration of exercise), sleep duration/quality and dietary habits (frequency of vegetable and fruit consumption). We will consider analyses by single health-related behavior and by cluster of health-related behaviors.

3.3. Health Outcomes

3.3.1. Chronic diseases such as CMD and cancers, as they constitute the major contributors to the burden of chronic diseases. Information on these diseases will be measured through self-report and biomarkers. Analyses will be run separately for CMD and cancers.

3.3.2. Biological aging as captured by DNA methylation signatures will be investigated. This outcome will be assessed using various scores of epigenetic ageing called epigenetic clocks, which are predictors of CMD, cancers, and all-cause mortality [28].

4. Specific Aims

4.1. Aim 1: Assess the mechanisms by which health-related behaviors in adolescence mediate the effect of parental socioeconomic conditions on chronic disease in adulthood

4.1.1. Hypothesis: Health-related behaviors in adolescence mediate the effect of parental socioeconomic conditions on chronic diseases in adulthood through both differential exposure and differential susceptibility.

4.1.2. Statistical analysis: We will conduct a counterfactual-based mediation analysis decomposing the total effect of parental income on adult health into three components being the controlled direct effect (representing the effect of parental income when everyone has no unhealthy behaviors in adolescence potentially counter to the fact), the portion attributable to differential exposure to the unhealthy behaviors in adolescence, and the portion attributable to interaction (the effect of the additive interaction between the exposure and the mediator, indicating differential susceptibility) [21, 29]. All potential measured confounders will be identified, and to guide the statistical analyses, we will construct DAGs using an evidence synthesis approach [30].

4.2. Aim 2: Assess the mechanisms by which health-related behaviors in adolescence mediate the effect of parental socioeconomic conditions on biological aging

4.2.1. Hypothesis: Health-related behaviors in adolescence mediate the effect of parental socioeconomic conditions on biological aging through both differential exposure and differential susceptibility.

4.2.2. Statistical analysis: The same counterfactual-based analysis will be carried out for this aim as for Aim 1, with epigenetic clocks as the outcome.

4.3. Aim 3: Simulate population interventions on adolescent socioeconomic conditions and health behaviors to rank their impact for reducing chronic diseases in adulthood

4.3.1. Hypothesis: Population interventions aimed at reducing the prevalence of adolescent disadvantaged socioeconomic conditions reduce the risk of developing chronic diseases in adulthood to a larger degree than those that mitigate unhealthy behaviors in adolescence.

4.3.2. Statistical analysis: Hypothetical population-level interventions will be simulated by a counterfactual scenario of reduced risk factor prevalence in the population. The amount of potential reduction in chronic diseases will be estimated by comparing the hypothetical counterfactual scenario with the factual or observed risk factor distribution [31]. We will rank these effects across risk factors, specifically comparing when i) halving the prevalence of low parental income in early life and ii) halving the prevalence of one or multiple unhealthy behaviors. We will also consider ranking the effect of counterfactual reduction of social factors (e.g. state provision of child-related welfare payments for low income families) and unhealthy behaviors for mitigating income inequalities in chronic diseases using population attributable fraction metrics [32].

5. Limitations

The counterfactual approach to mediation analysis relies on strong identifying assumptions, among which is no unmeasured confounding. Given the observational nature of our data, unmeasured confounding cannot be excluded. To partially overcome this, we will identify the minimal set of measured confounding using DAGs. We may also consider using negative controls to triangulate evidence [33]. We will also consider an alternative assessment of differential vulnerability by estimating joint effects, which are based on fewer identifying assumptions [34].

Our estimates could also be biased due to potential misclassification of exposure and differential misclassification of health-related behaviors. Additionally, with regard to Aim 2, although epigenetic scores of aging have been shown to be predictive of morbidity and mortality, there is insufficient evidence of their causal effect on these outcomes [35-37]. We will monitor the literature for evidence of novel potential causal epigenetic clocks which may be useful for our research [38].

6. Strengths

The main strength of this project is that it uses a cohort with long and regular follow ups and nationally representative of the US. The Add Health cohort has been followed up for more than 20 years and has assessed participants more than five times during their life, providing repeated measures. The health outcomes measured in this cohort are assessed with state-of-the-art technologies, reducing the likelihood of potential measurement error. Additionally, we will provide observational evidence on both chronic diseases and biological correlates of these diseases.

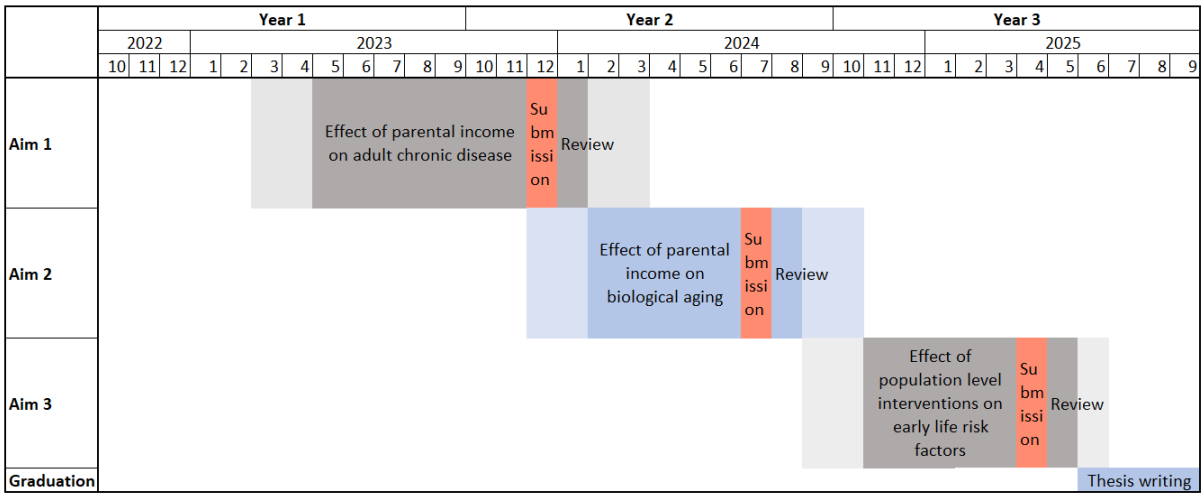
Furthermore, the contemporary counterfactual-based methods allow for greater understanding of the underlying mechanisms of the effect of early childhood exposures on adult health outcomes by decomposing the effects of differential exposure and differential susceptibility. This can have significant implications on the decision of whether preventive intervention strategies should be targeted to specific susceptible groups or directed at the entire population [21]. Additionally, the results of the simulations in Aim 3 will provide valuable insights for policymakers in prioritizing strategies to improve population health without running experimental interventions which can be costly and require long periods of study which can make them unfeasible.

7. Expected Outcomes and Public Health Context

This project is expected to produce three peer-reviewed papers, all of which are original research papers. These papers will make up the bulk of the PhD thesis.

This project will contribute to the existing literature by providing novel empirical evidence on the mechanisms by which early life socioeconomic conditions cause impairments in health due to chronic diseases in adulthood across the US population. The evidence generated from this project will aid public health policymaking by providing a comparison of the effect of alternative population policy interventions on early life socioeconomic conditions or health-related behavioral risk factors on health in adulthood. This would be useful for decisions regarding the allocation of resources as policy interventions which produce greater effect on improving population health could be prioritized.

8. Estimated Timeline



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