

Informed metabolic network analysis implicates disrupted energy metabolism in young adults from low socioeconomic backgrounds

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Emerging research documents the significant association between socioeconomic status (SES) and indicators of metabolic health: for example, higher SES is associated with improved metabolic control, reduced incidence of diabetes complications, and improved cardiovascular health. In fact, a considerable body of evidence suggests a link between socioeconomic disparities and risk of metabolic syndrome (MetS), a cluster of physiological and biochemical disorders that includes elevated fasting glucose, high blood pressure, dyslipidemia, and abdominal obesity. These interrelated components are partially responsible for an increased risk of type 2 diabetes, cardiovascular diseases and all-cause mortality. Metabolic pathways are also altered in SES – associated chronic conditions and aging. This relationship is mediated by social and behavioral factors suggesting that SES is a crucial determinant of metabolic health outcomes. Tailored interventions addressing these disparities and their mechanisms are thus essential for enhancing metabolic health across different socioeconomic groups.

Despite this progress, the mechanisms by which socioeconomic gradients disrupt one or more of the connected human pathologies of MetS remain poorly understood. In this study, we address these drawbacks by investigating the changes in the global genome scale metabolic network in humans as a consequence of socioeconomic inequalities. We leverage transcriptomic data from 4,543 young adults in the transcriptomic subsample of the National Longitudinal Study of Adolescent to Adult Health (Add Health). The data are derived from the largest nationally-representative study of young adults, who are ostensibly healthy but at-risk for later health challenges. First, the analytic strategy analyzes genes whose expression varied significantly by the early adulthood socioeconomic composite score using a linear model analysis. Second, we project the magnitude of change of the SES – differentially expressed genes (SES – DEG) onto Recon3D, a human genome-scale metabolic model (GEM) that can help uncover the molecular basis of the metabolic perturbations. Additionally, we incorporate SES – differential serum creatine, glucose, and, triglyceride concentrations, into the same framework. Lastly, we infer steady – state differential metabolic flux profiles to analyze the altered physiology using constraint-based modelling (CBM) approaches and optimization principles that maximizes the consistency of the predicted flux profiles and the observed differential gene expression and differential metabolite concentrations.

Our analysis revealed a repression of the cellular carbohydrate and energy metabolism in adults with low socioeconomic positions, particularly in metabolic flux profiles in the glycolysis, citric acid cycle and oxidative phosphorylation. Besides the cellular energetic crisis, our results further showed disruptions in the amino acid and lipid metabolic pathways. Interestingly, type 2 diabetes and cardiovascular diseases have also been linked to a repression in cellular energy generation. Thus, our results link metabolic perturbation to socioeconomic inequalities and subsequently to risk of metabolic syndrome. These changes in metabolic pathways are likely major conduits by which SES affects an array of metabolic-related, SES-graded diseases.