

# **Bidirectional mediation to quantify direct and indirect effects with application to Obesity and Diabetes**

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**Abstract:** Obesity and type 2 diabetes are major public health issues with known interdependence. Genetic variants have been associated with obesity, type 2 diabetes, or both; thus, we hypothesize that some single nucleotide polymorphisms (SNPs) associated with both conditions may be mediated through obesity to affect type 2 diabetes or vice versa. We propose a framework for bidirectional mediation analyses. Simulations show that this approach accurately estimates the parameters, whether the mediation is unidirectional or bidirectional. In many scenarios, when the mediator is regressed on the initial variable and the outcome is regressed on the mediator and the initial variable, the resulting residuals are correlated because of other unmeasured covariates not in the model. We show that the proposed model provides accurate estimates in this scenario, too. We applied the proposed approach to investigate the mediating effects of SNPs associated with type 2 diabetes and obesity using genetic data from the Multi-Ethnic Study of Atherosclerosis cohort. Specifically, we used body mass index as a measure for obesity and fasting glucose as a measure for type 2 diabetes. We evaluated the top 6 SNPs associated with both body mass index and fasting glucose. Two SNPs (rs3752355 and rs6087982) had indirect effects on body mass index mediated through fasting glucose (0.2677; 95% confidence interval (CI) [0.0007, 0.6548] and 0.3301; 95% CI [0.0881, 0.8544], respectively). The remaining four SNPs (rs7969190, rs4869710, rs10201400 and rs12421620) directly affect body mass index and fasting glucose without mediating effects.