

Environmental confounding in gene-environment interaction studies

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Abstrak

We show that, in the presence of uncontrolled environmental confounding, joint tests for the presence of a main genetic effect and gene-environment interaction will be biased if the genetic and environmental factors are correlated, even if there is no effect of either the genetic factor or the environmental factor on the disease. When environmental confounding is ignored, such tests will in fact reject the joint null of no genetic effect with a probability that tends to 1 as the sample size increases. This problem with the joint test vanishes under gene-environment independence, but it still persists if estimating the gene-environment interaction parameter itself is of interest. Uncontrolled environmental confounding will bias estimates of gene-environment interaction parameters even under gene-environment independence, but it will not do so if the unmeasured confounding variable itself does not interact with the genetic factor. Under gene-environment independence, if the interaction parameter without controlling for the environmental confounder is nonzero, then there is gene-environment interaction either between the genetic factor and the environmental factor of interest or between the genetic factor and the unmeasured environmental confounder. We evaluate several recently proposed joint tests in a simulation study and discuss the implications of these results for the conduct of gene-environment interaction studies.