

# **Robust semiparametric estimation of average causal effects in Mendelian randomization under an intermediate variable intervention**

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## **Abstract**

Mendelian randomization (MR) is a commonly used method in medical research to determine causality and address potential confounding in exposure-outcome relationships. The goal is to understand how exposure affects disease risk, but intervening directly on exposure may not always be feasible or ethical. Instead, researchers often look for a modifiable intermediate variable that is influenced by exposure and impacts the disease. This study presents a novel statistical approach for determining the average causal effect in MR studies where the intermediate variable is intervened upon across the population. The method employs a triply robust estimator and is shown to be consistent under three observed data models. Its performance is evaluated through simulations, and the study applies it to examine the impact of genetics on Alzheimer's disease risk if the status of the neurofibrillary tangle load, a potential intermediate variable, was altered.

**Keywords:** Mendelian randomization; average causal effect, robust estimation; intermediate variable intervention.