

Excessive False Positive Rate Caused by Population Stratification and Disease Rate Heterogeneity in Case-Control Association Studies

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Case-control association studies using unrelated cases and controls may suffer from the potential confounding due to population stratification. Bias and variance distortion caused by population stratification in the commonly used allele-based test could inflate the Type I error rate considerably. We find that the bias vanishes in the absence of disease rate heterogeneity and the test can be modified to yield a valid test. However, when both allele frequencies and disease rate heterogeneities are present, it is difficult to correct for this bias. We derive the explicit expressions of excessive false positive rate (EFPR) of the test due to bias and variance distortion. It turns out that this bias usually has a stronger impact on the EFPR than the variance distortion. Comprehensive simulation studies strongly support these results.

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