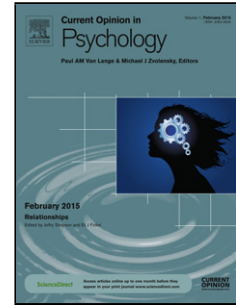


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Title: A brief tour of epidemiologic epigenetics and mental health

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Highlights:

- Epigenetic epidemiology generates much of the literature in the study of epigenetics and mental health and is a largely non-experimental field—as such, it has developed methods to contend with confounding and reverse causation
- Mendelian randomization, a technique that can minimize confounding and reverse causation, can be used to improve causal inference for the study of epigenetic epidemiology and mental health in some instances
- Whether using blood is appropriate when investigating brain phenotypes depends on the hypothesis and whether the goal is causality or to identify biomarkers
- Social scientists who specialize in behavioral and neurological phenotypes, epidemiologists with expertise in problem-solving the pitfalls of associative studies, and basic scientists with insights into biological pathways can pool their expertise and perspectives to avoid methodological snares, aid causal insight, and best frame epigenetic findings for each other, other scientists, and the public

Abstract:

The epidemiologic study of DNA methylation (DNAm) and mental health is a burgeoning area, but confounding and reverse causation remain important to know about. Whether use of non-brain tissues is appropriate when investigating brain phenotypes depends on the hypothesis and whether the goal is causality or to identify biomarkers. Look-ups of the correspondence between DNAm in blood and brain and use of Mendelian randomization (MR) can be done to follow-up, to some degree, on the causal nature of some findings. Social scientists, health methodologists (epidemiologists), and basic scientists—thinkers who view epigenetics and mental health from different perspectives—can come together in the design and framing of findings to avoid pitfalls and innovate beyond what each could do alone.

Introduction

Some epigenetic modifications of DNA are correlated with and impact gene regulation. They do this without changing DNA nucleotide sequence. The most extensively studied is DNA methylation (DNAm), the addition of a methyl group mainly at a cytosine (C) followed by a guanine (G), referred to as cytosine—p—guanine (CpG) dinucleotides (see Figure 1a).

The primary interest in DNAm¹ in relation to mental health is epidemiologic and stems from the hypothesis that adversity influences mental health via changes in DNAm—namely, DNAm *mediates* the relationship between adversity and psychopathology (Figure 2a). This

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