To date, most research examining the associations between maternal smoking during pregnancy (MSP) and offspring behavior problems has focused on externalizing outcomes (e.g., aggression), with fewer examining internalizing outcomes (e.g., anxiety, depression). Findings on the association between MSP and offspring internalizing behavior problems are inconsistent. While some support an association, others do not. A key source for this inconsistency is methodological differences across studies, particularly in their ability to control for potential confounding influences. In particular, confounding caused by differences between women who smoke while pregnant and others. Genetically informed studies are increasingly used to study the relationship between MSP and offspring internalizing behavior outcomes, particularly designs that compare siblings discordant for MSP. Yet this design has not been used to investigate the association between MSP and offspring internalizing disorders. We utilized a within-family design to investigate the association between MSP and an important internalizing problem, major depression, by mid-adulthood.