## Editorial

# Next Steps Toward Understanding the Relationship Between Cigarette Smoking and Depression/Anxiety Disorders: A Lifecourse Perspective

Substantial research attention has been dedicated to longitudinal studies estimating the relationship between smoking and depression and anxiety disorders over the past two decades. In this issue, Fluharty et al.<sup>1</sup> provide a succinct and thorough systematic review of longitudinal studies that have examined the relationship of smoking to depression/anxiety disorders, as well as the relationship of depression/anxiety disorders to smoking. Understanding where the weight of evidence lies in terms of: (1) the direction of effect; and (2) conclusions that can be drawn on the underlying mechanisms of these relationships is critical to moving the field forward. This applies both in terms of implications for clinical treatment and from a public health perspective via the potential impact on tobacco control at a population level. The authors conclude that the results offer substantial, yet somewhat inconsistent, evidence supporting a relationship in both directions while, in contrast, providing relatively little information on possible mechanistic pathways explaining these links. In order to move the field forward both in terms of understanding the direction(s) of these relationships and uncovering mechanistic pathways, there are several new avenues that seem to hold promise.

First, depression/anxiety disorders and smoking are not fixed states. Major depression is thought to be episodic, with recurrence in the majority but not all cases, and anxiety disorders tend to be persistent, though level of persistence and age of onset tends to vary widely depending on the specific anxiety disorder. Overall, both tend to wax and wane, remit, and relapse, over time. Longitudinal studies with measurements of both smoking and depression/anxiety disorders at multiple time points over several decades (ideally from early adolescence into older adulthood) could help to capture the truly dynamic and fluctuating relationship of these relations over the life course. Second, the study by Duhde et al.<sup>2</sup>, also in this issue, as well as prior work on trauma, suggests that various exposures and discrete life events (eg, stress and traumatic events) may interact with other factors to provoke changes in smoking and/or depression/anxiety status over time. A better understanding of the impact of such events on the interactive relationship between smoking and depression/anxiety over time is clearly needed. Third, the potential role of various environmental exposures and individual factors on the relationship between smoking and depression/anxiety may be different in adolescence (the highest period of risk for both) compared with midlife. This point is relevant to the conclusion that results to date are inconsistent, and may provide another explanation. For instance, several studies cited by Fluharty and colleagues found no link between smoking and subsequent depression.3-6 However, these appear to have included either unique samples (eg, medical students) or covered only the period from adolescence into young adulthood.

The onset of depression tends to be later than several anxiety disorders (eg, phobias). Therefore, these findings may not be truly null, but merely incomplete in the sense that the relationship between smoking and depression/anxiety may genuinely differ at different stages of life. Fourth, it is reasonable to consider the possibility that there are critical periods from a biological perspective. Exposure to smoking and/or the onset of depression/anxiety disorder at different ages may result in a different neurobiological impact, thereby conferring potentially varying effects on risk of depression/anxiety among those exposed to smoking at specific ages/critical periods, as well as the reverse. More work to understand this dynamic may help shed light on potential biological pathways. Fifth, there are strong links between heavy alcohol consumption and/or consistent drug use and mental health problems,<sup>7</sup> and these behaviors are common among smokers.8 While many studies adjust for alcohol and illicit drug use disorders, fewer have adjusted for exposure to heavy drinking and/ or consistent drug use that does not meet diagnostic criteria. Sixth, many studies lack ethical/racial diversity (many are drawn from populations of predominantly Northern European descent) and therefore relatively little is known about the potential heterogeneity of these relationships across demographic subgroups. As we see increasingly strong patterning of smoking prevalence by socioeconomic status, and among vulnerable subgroups, exploring this heterogeneity may shed new light on differences in the relationship between depression/ anxiety disorders and smoking by various subgroups.

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In addition to these important directions, several promising findings are reported in this issue that could help to address the question of causality between smoking and depression/anxiety. Tidey et al.9 found a decrease in depressive symptoms among those with higher depression symptoms at baseline which is consistent with longitudinal work in the population suggesting that quitting smoking leads to decreased recurrence of depression.<sup>10</sup> Further, their study isolates a potentially causal agent in nicotine. The use of reduced nicotine cigarettes in future work seems promising toward further understanding potentially causal pathways between smoking and depression/anxiety. Second, Mendelian randomization studies may also be useful in next steps as a promising and intriguing avenue. In this issue, Skov-Ettrup et al.<sup>11</sup> did not find a link suggestive of a causal relationship between high tobacco consumption and increased risk of psychological distress, consistent with previous work using this approach.<sup>12</sup> However, this could be related in part to examination of psychological distress, which is related to mental health, although it is not an anxiety or mood disorder, per se. As such, use of this method with full diagnostic measures of mental disorders would be of interest as a next step.

In sum, Fluharty and colleagues summarize the longitudinal literature to date effectively, and here we have discussed some next steps that may help move the field forward in answering the question or direction and mechanism in terms of smoking and depression/anxiety disorders. The potential clinical impact is clear, and moving from an individual to population level with this question seems equally urgent in terms of potential impact on mental health and physical health for millions of individuals. Ultimately, if there were adequate evidence of a causal link between smoking and increased risk for depression, theoretically this could lead to adding depression to the list of risks associated with cigarette use in public health campaigns.

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### **Declaration of Interests**

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