Editorial

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EDITORIAL

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Editorial: Sex-Specific Developmental Trajectories of Psychopathology: The Case of Substance Misuse

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Childhood psychopathology can cause an array of adverse outcomes later in later life, including substance use disorders (SUDs). Perhaps because substance abuse is thought to be on the externalizing continuum, the prospective association between childhood externalizing disorders and SUDs is more frequently studied than the association with internalizing disorder. Indeed, research on attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder (CD) quite consistently demonstrate that these disorders are associated with increased SUDs risk in later life.[1] However, although it is often thought that only externalizing disorders in childhood increase the risk of SUDs in later life, there is evidence, albeit more fragmented, for a similar association between internalizing disorders in childhood and later substance use.[1] Because internalizing and externalizing disorders are often comorbid, it is vital to investigate their joint effect on the developmental trajectory toward SUDs. So far, this trajectory has mainly been studied from an externalizing perspective, but Virtanen *et al.*[2] studied this prospective association with internalizing disorders as the start point, while considering the possibility of biological sex-specific patterns.

Virtanen *et al.*[2] aimed to investigate the prospective association between internalizing disorders and substance misuse in 2 large Swedish registry-based samples while taking familial factors and externalizing comorbidities into account. The population sample (n = 1,768,515) contained all individuals born in Sweden from 1984 through 2000. This large and impressive sample had information on *International Statistical Classification of Diseases (ICD), 9th and 10th Revisions* anxiety and depression (ie, internalizing) disorders, as well as ADHD and CD (externalizing disorders) before age 13. A subsample of this population-based sample represented all twins born since 1992, with additional parent-reported information about anxiety and mood disorders. Twins are of specific interest, because they can shed light on familial compared with environmental factors. In both samples, registry-based substance misuse, based on registry *ICD-9* and *ICD-10* diagnosis or alcohol/drug-related criminal conviction based on registry data or the Crime Registry after age 13 served as the end point.

In both samples, internalizing disorders prospectively conveyed a risk for substance misuse. The authors state that this association can be explained by familial factors in both samples, indicating that SUDs and internalizing disorders share etiological factors such as genetic liability and environmental influences. When correcting for externalizing problems, the risk for substance misuse attenuates in boys, but not in girls. Intriguingly, these results seem to suggest that the internalizing developmental trajectory to substance misuse is more prominent in girls whereas the externalizing pathway to substance misuse is more prominent in boys.

Suggestions of differential internalizing compared with externalizing developmental pathways to substance misuse are not novel in itself. However, previous research has mainly focused on different underlying mechanisms more than sex-specific pathways. For example, it has been previously suggested that substance misuse was linked to impulsivity and novelty seeking in externalizing disorders,[3] whereas in internalizing disorders the hope to alleviate symptoms (coping)[4] causes substance use. Interestingly, a large American epidemiological study[5] investigating sex-specific concurrent associations in adults found that both internalizing and externalizing disorders showed higher associations with alcohol dependence in women than in men. Moreover, women with internalizing and externalizing disorders had an earlier onset and more rapid progression to alcohol use disorder,[5] suggesting that not only the frequency, but also the trajectory of SUDs is sex specific. In contrast, Virtanen *et al.*'s results[2] might suggest that the externalizing pathway to SUDs is male specific. However, it could be that this is due to the age (<13) at which psychopathology was measured.

Virtanen *et al.*[2] found equal proportions of boys and girls meeting criteria for internalizing disorders below the

age of 13, whereas it is generally found that girls are about twice as likely to suffer from lifetime depression.[6] This increased prevalence in females has been linked to not only psychological, but also to biological factors, because the prevalence of depression in women increases in life phases characterized by large hormonal changes, such as puberty.[7] The major reproductive milestones in the lives of women, ie, puberty, menstruation, childbirth, and menopause, and their effects on mental health along with comorbidity patterns over the lifetime are often been overlooked. Especially in substance misuse, this is of great importance, because the fluctuation of hormonal levels in women can modulate the reward system.[8] With these findings of female-specific internalizing developmental trajectories to substance misuse, Virtanen *et al.*[2] add to research into sex-specific trajectories of mental health care, a research area that is still very much in its infancy.

Women have been underrepresented in scientific research for many decades.[9] For example, research on medication is often limited by the use of predominantly male subjects, although results are often extrapolated to women[9] without taking the "noise" caused by hormonal fluctuations into account. However, for half of the population, this "noise" is part of daily life and therefore, sex differences, and their possible causes, deserve a bigger part in scientific research, particularly as more and more evidence is accumulating about sex-specific patterns of psychopathology. Novel methods such as growth mixture modeling can help to unravel differential expression of risk for substance use in men and women over different life phases. Moreover, to "feed" these models, well designed longitudinal cohort studies that include multiple time points, preferably at distinct points during the reproductive life phase, are necessary. While registry-based samples have their limitations, they provide many incredible opportunities to unravel sex-specific pathways to substance misuse, and these samples could be used for more in-depth exploration of these effects. Therefore, the work by Virtanen *et al.*,[2] by showing distinct pathways of substance misuse in boys and girls, is a major first step in the right direction.

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