of inherent limitations, detailed in our publication, cautious interpretation of the findings is suggested.

In this context, use of estrogen-based therapies for prevention or treatment of postmenopausal depression in the general population, on the basis of our findings, was clearly not recommended. This option is precluded owing to known adverse effects of currently available hormone therapy regimens and uncertainties regarding appropriate combination of estrogens and progestogens in postmenopausal women with intact uterus. However, owing to its potential clinical implication, we considered of interest and accordingly highlighted, the 2-fold increased depression risk of women with premature ovarian insufficiency (menopause at <40 years). These women represent only 1% of the female population but comprise a high-risk group for additional postmenopausal diseases; therefore, they deserve to be appropriately followed up for early recognition and evaluation of depressive symptoms. Hormone therapy has been recommended for treatment of estrogen deficiency symptoms in this group,[5] albeit its effect on preventing depression should be explored following our findings. All in all, our meta-analysis points to novel research questions regarding the effect of the cumulative lifetime sex hormone exposure on nervous system and mental health and the sustained neuroprotective and antidepressive properties of estrogens or progesterone.

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Childhood Trauma as a Neglected Factor in Psychotic Experiences and Cognitive Functioning

To the Editor Mollon and colleagues[1] present data from a population-based study evaluating neuropsychological functioning in adults with subclinical psychotic experiences. As rightly noted by the authors,[1] previous studies did not adjust for key sociodemographic confounders. Therefore, Mollon et al[1] evaluated ethnicity, occupation, cannabis use, and common mental disorders, and all were found to correlate significantly with both psychotic experiences and cognitive performance. Adjusting for these factors notably reduced differences in cognitive functioning between individuals with psychotic experiences and those without. Yet, we believe that one important confounder was not corrected for in the Mollon et al[1] study.

Here, we would like to highlight childhood trauma as another important factor in the association between neuropsychological functioning and the experience of psychotic symptoms, which is often neglected in the literature. Trauma exposure early in life increases the risk for psychosis and is also associated with cognitive dysfunction,[2] especially of functions subserved by the frontal lobe, as this brain region has a gradual natural maturation course. A recent study,[3] including a similar sample of nonclinical adults with and without psychotic features (n = 202), indeed showed that childhood trauma fully explained the association between psychotic experiences and reduced executive functioning as well as lower working memory performance.

The results by Mollon et al[1] and similar studies clearly demonstrate the complexity of the association between neuropsychological functioning and psychotic experiences. To our knowledge, the role of environmental risk factors in the development of cognitive dysfunction has not been adequately investigated. This can lead to confounding of results and could perhaps account for some of the inconsistent findings reported in previous studies. Childhood trauma and sociodemographic factors may constitute a common underlying vulnerability for both psychotic experiences and cognitive deficits. Alternatively, cognitive dysfunction may be the means by which environmental influences, such as childhood trauma and an unfavorable sociodemographic milieu, increase the risk for developing psychotic experiences later in life.

Now that cognitive dysfunctioning is increasingly recognized as a core vulnerability factor for psychosis, we need to carefully examine the effects of relevant covariates, as also noted in the editorial by Gur[4] that accompanied the Mollon et al[1] article. Future large longitudinal studies are needed to understand the temporal sequence and complex interplay between different genetic and environmental factors. In addition to sociodemographic factors, childhood trauma is a crucial factor that should not be omitted in studies investigating the association between cognitive dysfunction and psychotic experiences.

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In Reply We agree with Begemann and colleagues on the importance of considering relevant environmental factors in studies investigating the association between psychotic experiences and cognition. An association between childhood trauma and risk for later psychosis has been documented.[1] Indeed, we found strong evidence in the South East London Community Health (SELCoH) Study for higher rates of psychotic experiences in those who were physically or sexually abused during childhood.[2] While it remains unclear whether the association between childhood trauma and risk for psychosis is a causal one, plausible psychological and biological mechanisms have been proposed[1] and future work, particularly using longitudinal designs, may shed further light on this important question.

Conversely, the association between childhood trauma and cognitive function, especially in association with psychotic experiences, remains largely unexplored. The work by Begemann and colleagues[3] suggests that childhood trauma may partially explain the association between hallucinatory experiences and measures of executive function and working memory, but also that childhood trauma is of no explanatory value in terms of the verbal and general knowledge deficits associated with psychotic features. Similarly, the work by Aas and colleagues[4] suggests that childhood trauma is associated with deficits in general, but not specific, cognitive domains.

Indeed, in our sample, we found only negligible, statistically nonsignificant correlations between childhood trauma and cognition. Specifically, childhood physical abuse showed a positive correlation of 0.05 with IQ, while childhood sexual abuse showed a negative correlation of −0.03. Correlations with measures of general knowledge, working memory, memory, and processing speed followed a similar pattern. Thus, while we found a strong association between childhood trauma and psychotic experiences in the SELCoH sample, we did not find evidence of an association between childhood trauma and cognition. Consequently, adjusting for childhood trauma in our statistical models had no effect on the association between psychotic experiences and cognition, either across domains or age groups. Moreover, we deliberated the complexity of adjusting for childhood trauma in a study investigating psychotic experiences and cognition across adulthood and decided that, in the SELCoH sample at least, adjusting for childhood trauma would not be informative. The reason being that, with the age of participants ranging from 16 to 90 years, trauma occurring in childhood would be unlikely to have the same effect on psychotic experiences and cognition in early vs late adulthood.

Finally, as noted in our article[5] and in the accompanying editorial by Gur,[6] while we modeled sociodemographic factors, cannabis use, and common mental disorders as confounders, they could also be mediators. Begemann and colleagues highlight how the same ambiguity arises with childhood trauma. Large longitudinal data sets are needed to examine interactions between multiple risk factors, which likely give rise to multifactorial traits such as cognition and psychosis. Childhood trauma is one such risk factor that should certainly be considered in these studies. However, the role childhood trauma and other risk factors play, either as covariates, confounders, or mediators, also warrants careful consideration.

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How Similar Are the Disorders Included Under the Umbrella of Obsessive-Compulsive Disorder and Related Disorders?

To the Editor In *JAMA Psychiatry*, Grant and colleagues[1] demonstrated the efficacy of *N*-acetylcysteine (NAC) in the treatment of excoriation disorder (ED). The same group had previously reported the benefits of NAC for adults with trichotillomania (TTM).[2] In both studies, NAC was used in monotherapy in otherwise treatment-free patients. In the *DSM-5*, ED and TTM were included under the umbrella of obsessive-compulsive disorder (OCD) and related disorders because of similarities regarding phenotypic expression and common putative neurobiological underpinnings between these disorders and OCD. When used for treatment-resistant OCD, NAC was not more effective than placebo as a selective serotonin reuptake inhibitor (SSRI) augmentation strategy.[3]

In striking contrast with what we know about OCD, SSRIs have not been proved to be superior to placebo in TTM treatment.[2] As for ED, the evidence regarding the efficacy of SSRIs is still scarce.[1] So far, there are no US Food and Drug Administration–approved treatments for ED and TTM. The divergent results of the trials testing either SSRIs or NAC for ED/TTM and OCD suggest that treatments may not be used interchangeably between OCD and related disorders. Despite the possible methodological issues related to the design of specific trials, do such heterogeneous results regarding treatment response relate to heterogeneous neurobiology between OCD and related disorders?

Pathological grooming behaviors in animals are widely used in the literature as a common animal model of ED/TTM and OCD. However, findings derived from animal studies do not always confirm the association between grooming behavior and OCD. For example, no differences were observed in the results of the marble-burying test of rats with different levels of grooming behavior.[4]

In addition, results from genetic studies also suggest that the neurobiology of pathological grooming may not be necessarily related to OCD. It had been demonstrated that *Sapap3* knockout mice groomed themselves excessively. However, using family-based association analyses, Bienvenu et al[5] found that variation within the human equivalent of the *Sapap3* gene appeared associated with ED/TTM, but not with OCD.

The conflicting results regarding the efficacy of NAC for ED/TTM and OCD, in addition to the findings of translational studies, suggest that the neural basis of repetitive behaviors observed in patients with these disorders might not be the same. So far, similarities between ED/TTM and OCD do not seem to go beyond the characterization by repetitive behaviors and some degree of familial aggregation.

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In Reply Costa and colleagues raise important issues regarding how grooming disorders (GDs) should be optimally treated and classified.

N-acetylcysteine (NAC) showed superiority over placebo as monotherapy in excoriation disorder,[1] similar to findings in trichotillomania. However, NAC's findings in obsessive-compulsive disorder (OCD) are mixed. Two clinical trials reported significant benefits of NAC augmentation over placebo for OCD,[2,3] while a third study did not show benefits over placebo.[4] As Costa and colleagues suggest, differential pharmacological response across disorders is an important factor when considering diagnostic classification. This is also complicated by differences in study designs, as results may vary when using NAC as augmentation to a selective serotonin reuptake inhibitor rather than a primary intervention.

A common link between GD and OCD is an appealing notion based on overt symptoms: these conditions are characterized by repetitive acts that are difficult to suppress. There is evidence for familial and comorbid overlap as well, but whether this overlap is stronger than between GD and other disorders (eg, alcoholism or attention-deficit/hyperactivity disorder) is less clear. Neuropsychological deficits in OCD span a broader range of domains than those identified in GD. Even without these differences, the neurobiological underpinnings may differ between disorders. Also, cognitive dysfunction is heterogeneous even within a given disorder: while patient groups may manifest general cognitive deficits relative to control groups, these problems may not always persist when assessed on an individual basis. The logical question then is whether cognitive, imaging, or other markers could be used to individualize treatment based on unique clinical features, possibly transdiagnostically.