offset the influence of the (much stronger) negative selection effects in those with schizophrenia, and that therefore overall, there is no reproductive advantage conferred by common variant liability. Neither our new analyses nor those of Lawn and colleagues challenge that conclusion. We believe alternative explanations are required for the persistence of common alleles that increase susceptibility to schizophrenia. Based on work we have published elsewhere (2), we suggest this may occur through the effects of purifying (negative) selection on genetic diversity at particular loci, which in turn allows mildly deleterious alleles to drift to higher frequencies than otherwise expected.

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Smoking and Cognitive Performance: The Chicken and Egg Problem

TO THE EDITOR: In the November 2018 issue of the *Journal*, Vermeulen et al. (1) presented an interesting comparison of cognitive performance in smokers and nonsmokers (nonsmokers did better), and in smokers with psychosis who did and did not manage to stop smoking (quitters had a better score in one subtest at follow-up). However, the authors' conclusion that smoking cessation may improve processing speed, and the accompanying editorial (2) that goes much further and asserts that the study shows that smoking has adverse effects on, and that stopping smoking leads to a rapid recovery of, cognitive performance, may be an overinterpretation of the findings.

Adolescents with lower education and socioeconomic status are more likely to become smokers (3, 4), and it is possible that the lower cognitive performance in smokers in this sample was not caused by smoking, but preceded it. Regarding the finding that patients who achieved smoking abstinence had faster processing speed at follow-up, it is likely that patients who are in good remission are more likely to stop smoking than those who are not, and that it is the remission, rather than smoking cessation, that is accompanied by cognitive improvement (especially as it is usually also accompanied by reduced medication that the yes/no medication variable that was controlled for may not capture). This interpretation is supported by the fact that such improvements were not seen in the other cohorts in this study.

Rather than concluding that smoking impairs and that stopping smoking improves cognitive performance, a possibility needs to be considered that the results simply confirm that people who find smoking rewarding differ from those who do not and that patients in good remission are more likely to stop smoking than those whose health status and medication levels have not changed.

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The Unhealthy Chicken or the Unhealthy Egg: Quitting Smoking Matters: Response to Hajek et al.

TO THE EDITOR: In their letter, Hajek et al. suggest (residual) confounding and reverse causation as possible alternative explanations for the observed associations between (changes in) smoking and (changes in) cognition in our article (1). We agree that this could be possible, and we already mentioned this in the limitation section of the article. However, we think that these alternative explanations are not very plausible. First, we used statistical models with an extensive set of

covariates (including years of education) to control for confounding factors. We also corrected for symptom remission by including positive, negative, and general symptoms as covariates in all models. We would like to note that there is a growing body of observational studies in the general population suggesting that smokers generally show an increased decline in cognitive abilities in later life compared with ex-smokers or nonsmokers (2–4). Second, regarding reverse causation, studies about cognitive functioning being predictive for successful smoking cessation have been inconsistent (5). One method that can be used to demonstrate how variables influence one another over time is cross-lagged panel analysis. We tried this strategy to investigate the relationship between cognitive functioning and smoking status or cigarettes smoked per day after 3 and 6 years. However, the models showed poor fit measures, implicating unreliable results probably due to a lack of statistical power. To the best of our knowledge, long-term trials with smoking patients with psychosis who were randomly assigned to smoking cessation or continued smoking are lacking because of the considerable ethical implications. An emerging method that aims to overcome residual confounding and reverse causation is Mendelian randomization. This approach builds on genetic variation as a natural experiment and uses genetic variants as instrumental variables to investigate the effects of modifiable risk factors for disease (6). The plausibility of the findings of Mendelian randomization (7) and multivariable Mendelian randomization (8) depends on several key assumptions. Multivariable Mendelian randomization could be used to investigate the lifetime effects of cognition or education on the odds of smoking, and vice versa, while including liability to schizophrenia as a confounding effect. For example, a study using multivariable Mendelian randomization suggested that educational attainment, but not cognitive ability, has an effect on smoking behavior (unpublished 2018 study of E. Sanderson et al.). Of note, the fact that Mendelian randomization typically investigates long-term effects over the life course makes it difficult to investigate transient effects of (changes in) smoking on cognition (9).

Hajek et al. state that our results might not imply that smoking impairs cognitive functioning and that the findings simply confirm that people who find smoking rewarding differ from those who do not. We argue that our results indicate at least that smoking or starting to smoke is not associated with improvement of long-term cognitive functioning. A lack of long-term benefit does not support an important aspect of self-medication (i.e., smoking as treatment for cognitive impairment). Clinicians frequently cite smoking as self-medication as a reason for not treating patients for a nicotine addiction (10). There is an urgent need to further investigate other reasons patients smoke (e.g., shared vulnerability, misattribution, or adverse coping strategies) (11). Previous research has shown that patients with psychosis can safely quit smoking with medication or nicotine-replacement therapy and by learning healthier coping strategies (12). This is important because the potential gain of smoking cessation for general medical and financial health, and most likely psychological and cognitive health, is large (13). This is the case for patients with psychosis in particular because they smoke more often and more heavily (14). Whether it is the chicken or the egg, smoking is unhealthy, and patients should be supported to quit this potentially fatal behavior.

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