Depression and smoking

In their study of a birth cohort \((n = 1265)\) in Christchurch, New Zealand, Boden et al.\(^1\) found that cigarette smoking increased the risk of depression. The cohort was ‘studied’ at birth, 4 months, 1 year, then annually to age 16 years, and at age 18, 21 and 25 years. At the last three assessments, the study participants were interviewed and data on depression and smoking were collected. The Composite International Diagnostic Interview (CIDI) was used to ascertain the symptoms of major depression and data on the number of cigarettes smoked and the symptoms of nicotine dependence were recorded. The authors used a variety of regression analyses to determine the causal relationship between depression and smoking, adjusted for covariates.

No matter how sophisticated the analyses are, the results of the study reflect the quality of data. The data for this study were incomplete and flawed. The data on depression and smoking were for three 12-month periods and three 1-month periods prior to the interviews. Consequently, the data on the prevalence of depression before age 17 and from age 18 to 20 and age 21 to 24 were missing. Except for three 1-month periods between age 18 and 25, all data on smoking and nicotine dependence were also missing. It is possible that some teenagers experienced depression and smoked cigarettes before age 17. It is also possible that the study participants started and quit smoking or recovered from depression between age 18 and 20, and between age 21 and 24, periods for which data were not collected. In effect, the data collected at age 18, 21 and 25 were almost cross-sectional, which cannot provide evidence for the direction of the association. If a study participant reported smoking at the age-18 interview and gave history of depression prevalent in the year prior to age 21, the authors would conclude that smoking caused depression because, according to their data, smoking preceded depression. But the authors did not know that this participant had quit smoking before the onset of depression at age 19 because they did not obtain the data for the 2 years prior to age 20. In fact, this participant’s depression had been caused by smoking cessation, not by smoking.

As Munafò & Araya remarked in their editorial,\(^2\) the CIDI uses symptoms to determine the diagnosis of depression, not its severity. The number of cigarettes smoked is an appropriate measure of exposure to tobacco smoke, not the number of symptoms of nicotine dependence. Consequently, an association between the number of symptoms of depression and those of nicotine dependence is meaningless.

Given that tobacco smoke has anti-anxiety and antidepressant properties,\(^3\) and that attempted or successful smoking cessation results in depression regardless of prophylactic nicotine replacement or antidepressant therapy,\(^4,5\) smoking cannot cause depression. If smoking causes depression, smoking cessation would relieve depression. The authors neglected to describe data on smokers developing depression when they quit smoking and data on antidepressant therapy during the observation period. Any study that does not use data on depression following reduction in or cessation, even transient, of tobacco smoking and data on pharmacotherapy cannot reliably determine the direction of the cause–effect relationship between smoking and depression.


Authors’ reply: Dr Sheikh notes that ‘It is possible that some teenagers experienced depression and smoked cigarettes before age 17’. In response we would point out that the purpose of the study was not to measure or compare the onset or first cause of either depression or cigarette smoking, but rather to examine the dynamic interplay between cigarette smoking and symptoms of depression during early adulthood, and the extent to which either cigarette smoking or depression played a causal role in the maintenance of this association across time.

He also asserts that ‘the data collected... were almost cross-sectional’. This is not true. The data were discrete longitudinal data, in which both smoking and depression were assessed over several time periods. The separation of these assessments by unobserved periods was not sufficient to render the data cross-sectional.

It is also not strictly true to suggest that data observed at the same time periods could not be used to model causality. Given the availability of data observed at multiple points in time, it proves possible to fit structural equation models of the time-dynamic associations between two variables (such as cigarette smoking and depression) across time, comparing the relative fit of models that posit: (a) a reciprocal causal effect between smoking and depression; (b) a unidirectional causal effect from smoking to depression; and (c) a unidirectional causal effect from depression to smoking. Our data clearly show that the most parsimonious model is one in which there is a unidirectional causal effect from smoking to depression. This same approach has been used to examine the causal associations between numerous variables using the Christchurch Health and Development Study (CHDHS) data.\(^1,2\)

Dr Sheikh argues that measures other than nicotine dependence might have led to differing results. We have in fact conducted several additional analyses using a range of measures of both cigarette smoking and depression, including: measures of smoking frequency; measures of the number of cigarettes smoked; and whether participants met criteria for DSM–IV nicotine dependence and major depression. In all cases the analyses were consistent with those reported in the original study; measures of smoking and measures of depression demonstrated significant \((P < 0.05)\) associations using fixed-effects regression models; and the results of structural equation modelling showed
that the best-fitting model was one in which cigarette smoking (or nicotine dependence) predicted depression. In the original study, they reported on analyses of nicotine dependence symptoms and symptoms of depression in order to maintain a focus on measures germane to psychiatry, in view of the scope of this Journal.

Finally, Dr Sheikh argues that depression must be caused by nicotine withdrawal rather than smoking. However, Benowitz\(^4\) has shown that active smokers go through several withdrawal phases during each day, and that these withdrawal phases are one of the factors that causes self-administration of nicotine. Therefore, it could also be argued that depressive symptomatology may be increased among active smokers because of this continual cycle of withdrawal and satiety.


**Evolution and non-clinical psychotic symptoms**

In their recent editorial, Kelleher et al\(^1\) emphasised the importance of evolutionary theory for explaining the persistence of psychotic symptoms, depression and anxiety in humans. The authors did not mention the difference between proximate and ultimate explanations, in other words between ‘how’ and ‘why’ explanations, and this could make their argument for using evolutionary theory in psychiatric research more specific. In the development of treatments one needs an explanation at the proximate level, whereas the ultimate level can be necessary for generating hypotheses.

In evolutionary-based research the challenge is to find not which behaviour is beneficial now, but which behaviour has been advantageous for the procreation of ancestors in the past. This is the ultimate-level explanation. We know very little about our human ancestors and hypotheses can easily become ‘just-so’ stories with limited predictive value. Therefore rigorous testing at the how level is required.\(^1\) Furthermore, there are complicating factors such as cliff-edged fitness,\(^4\) whereby a limited number of factors such as cliff-edged fitness,\(^4\) whereby a limited number of traits is beneficial but too many are detrimental.

The possible theories for psychosis or schizophrenia mentioned by Kelleher et al vary enormously. It might have something to do with language development, complex social cognition, hypervigilance or with something completely different. However, all these theories need to be further developed to generate hypotheses at the how level, for example how language/hypervigilance/social cognition skills differ in humans with genes associated with schizophrenia or in family members of people with schizophrenia. The aim is to explain psychotic disorders at the proximate level, because that is needed to find the best possible treatment.


I found the editorial by Kelleher et al\(^1\) both stimulating and thought provoking. However, it is important to bear in mind that a given characteristic must either promote or hinder an individual’s chances of survival and procreation if it is going to have an impact on natural selection. Even if the presence of a
certain trait – such as hypervigilance for possible dangers, as argued in the editorial – in a few members of a social group is potentially beneficial for the group, this would not affect the ability of each one of those hypervigilant individuals to spread their genes. At an individual level, it would be difficult to argue that hypervigilance would increase the overall chances of survival and procreation of a particular human. This individual would be cautious, but also seriously handicapped by an inability to trust others in the social group. Certain aspects of a human phenotype, such as psychotic symptoms, are not advantageous, but they have not been eradicated by evolution simply because they do not have a sufficient impact on survival before reproductive age. An evolutionary approach would not find any advantages in having bad teeth or weak coronary arteries, but the fact that these widespread human characteristics manifest themselves only after the individual has already had the chance to reproduce explains why it is that they are still – unfortunately – very much with us.


Authors’ reply: We thank readers for their interest in our editorial.1 The main purposes of the editorial were threefold: (i) to highlight the relatively recent identification and characterisation of a non-clinical psychosis population (for review see Kelleher & Cannon2); (ii) to point out that there might be important overlap in the genetics of the clinical and non-clinical psychosis phenotypes; and (iii) to discuss the potential value of this population for empirically testing evolutionary theories of psychosis.

Dr Euba points out that hypervigilance may lead to an individual being ‘handicapped by an inability to trust others in the social group’ and as a result being less likely to procreate. However, hypervigilance is not in itself a disadvantage. In fact, the more vigilant an animal, the more likely it is to identify threats such as predators and to protect both itself and its progeny, allowing the propagation of associated genes. Increasing levels of vigilance, however, would promote survival of the organism and its progeny only to a point. As this trait becomes ever more pronounced, it would eventually lead to the dysfunction identified by Euba – paranoia. Nesse referred to this as cliff-edged fitness,3 whereby traits may increase fitness up to a critical threshold, but beyond this point, fitness drops precipitously (the cliff edge here being the transition from hypervigilance into paranoia). Thus, while in its extreme form – paranoia – hypervigilance will be negatively selected owing to negative fitness consequences, a ‘subthreshold’ level of this trait would be positively selected.

We agree with Trefurth that it is possible that non-clinical psychotic symptoms may be neither advantageous nor disadvantageous and that associated genes may have been passed on alongside other fitness-enhancing phenotypes. Our argument, however, is that if, as has been suggested by many researchers to date, the genetics of psychosis encode for positive as well as negative traits, then people with the recently characterised non-clinical psychosis phenotype may provide a valuable population in which to conduct empirical research.

Hubbeling makes the very point that we wished to emphasise in our editorial – that the non-clinical psychosis phenotype provides us with a population in which to test hypotheses about the evolutionary benefit of psychosis genes. It is clear why genes that promote certain traits, such as language development, hypervigilance and complex social cognition, would be selected in evolution. The ‘how’ questions, as Hubbeling points out, require attention, for instance how these traits differ in (non-psychotic) persons with psychosis genes compared with persons without (or with fewer) psychosis genes. This type of research is precisely what we wish to encourage by highlighting the validity of the non-clinical psychosis phenotype for empirical investigation. This population provides a potentially valuable means for moving beyond ‘just-so’ stories into the realm of testable hypotheses.


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Corrections

Auditory hallucinations and brain structure in schizophrenia: voxel-based morphometric study. BJP, 196, 412–413. All correlations reported in this paper are negative (i.e. the higher the hallucination scores, the smaller the gray matter values). There were no positive correlations.

Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. BJP, 197, 330–331. Page 330, col. 1, the fifth sentence should read: ‘In a double-blind, 16-week multicentre trial (n = 207), various doses of nalmefene (25, 50, 100 mg/day) showed similar efficacy, but premature discontinuation was common (drop-out rate: 66%).’

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