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Examining interactions between risk factors for psychosis†

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Background
For complex multifactorial diseases it seems likely that co-exposure to two risk factors will show a greater than additive relationship on disease risk.

Aims
To test whether greater than additive relationships occur between risk factors for psychosis.

Method
A cohort study of 50 053 Swedish conscripts. Data on IQ, cannabis use, psychiatric diagnoses, disturbed behaviour and social relations assessed at age 18 were linked to admissions with any non-affective psychoses over a 27-year follow-up period. Statistical interactions between risk factors were examined under both additive and multiplicative models.

Results
There was some evidence of interaction for eight of the ten combinations of risk factors under additive models, but for only one combination under multiplicative models.

Conclusions
Multiplicative models describe the joint effect of risk factors more adequately than additive ones do. However, the implications of finding interactions as observed here, or for most interactions reported to date, remain very limited.

Declaration of interest
None.

It has been strongly argued that scientific gains from studying gene–environment or environment–environment interactions are likely to occur relatively rarely, and to come at a substantial cost.[1–3] To study how exposure to two risk factors in combination affects disease risk we compare data with predictions from statistical models. These predictions can be modelled on either additive or multiplicative scales. If a study is adequately powered, one can always find evidence of statistical interaction by looking at the same data under both additive and multiplicative models.[1,3,4] With the exception of qualitative or cross-over interactions, where the direction of association between an exposure and disease is reversed in the presence of another exposure, statistical interaction is therefore model dependent and does not have any clear biological meaning.[1]

Under the sufficient-component cause model of disease it can be shown that risk factors co-participating as causal components in any one causal model will show departure from additivity.[4] For complex multifactorial disorders, where risk factors are usually neither necessary nor sufficient to bring about disease, we would rarely expect to have true additivity between risk factors as it is very unlikely that two risk factors are never both involved in at least one causal model of disease.[4] In this study we describe the patterns of risk for joint exposure to different combinations of risk factors for psychosis and examine whether these patterns are more consistent with additive or multiplicative relationships. Our *a priori* expectation under the sufficient-component cause model of disease discussed above was that the risk of psychosis where there was joint exposure to risk factors would be greater than that expected under an additive model for all risk-factor combinations studied. We discuss the extent to which our results, and those from other studies of interaction, are likely to benefit our understanding of disease aetiology or prevention.

†See editorial, pp. 170–171, this issue.

Method

Participants

The data used in this study were from a longitudinal study of 50 087 men who were conscripted during 1 year (1969–1970) for compulsory military training in Sweden. Over 98% of the men were aged 18–20 at the time of conscription. At that time, only 2–3% of men were exempt from conscription, usually because of severe disability or illness. All of the men completed two non-anonymous, self-reported questionnaires at the time of conscription. The first was regarding social background, upbringing conditions, friendships, relationships, attitudes, adjustment at school and work. The other concerned the use of alcohol, tobacco and other drugs. Each man also had a structured interview with a trained psychologist, who then assessed him for a series of psychological measures on the basis of data from the questionnaire and the interview. They were also given a test of intellectual ability. The psychologist's ratings were regularly checked for interrater reliability. Whenever a psychiatric disorder was reported by the conscript or suspected by the interviewing psychologist, he was referred to a psychiatrist. Psychiatric diagnoses were coded according to the Swedish version of the ICD–8.[5] Permission to use the data for research purposes was granted by the research ethics committee of the Karolinska Institute.

Measures

Outcome

To maximise power we examined clinical diagnoses (according to the Nordic version of ICD–8, ICD–9 from 1987)[6] of all non-affective psychoses as our outcome. This included schizophrenia/schizoaffective disorder (ICD–8/9 295.00–295.99), and other non-affective psychoses (paranoid states, other psychoses, substance-induced psychoses (ICD–8: 297.0–9, 298.2–3, 298.9, 291.2–3; ICD–9: 297.0–9, 298.2–4, 298.8–9, 291.3, 291.5, 292.1)). Participants who received these clinical diagnoses were identified

by linkage with the Swedish National Patient Register from 1970 to 1996. This register recorded about 70% of all psychiatric admissions in 1970, rising to 83% in 1973. Coverage was 97% from 1974 to 1983, 80–95% from 1984 to 1986, and has been virtually complete since 1987. The incomplete registration during some periods is unlikely to have affected the results. Satisfactory validity of schizophrenia diagnoses in Sweden has been previously reported.[7]

Exposures

We identified risk factors that were previously reported as being associated with schizophrenia or other psychoses in this cohort.[8–13] We then selected those that were not strongly correlated with each other (correlations <0.6), and showed the strongest associations with either schizophrenia or other non-affective psychoses (unadjusted odds ratios of $\geqslant 2$). This was an arbitrary cut-off chosen so that we would achieve a balance between having a sufficient number of exposures to examine for interactions, while effect sizes would be of a magnitude that would allow us to have adequate statistical power to study interactions under an additive model. This resulted in the selection of five risk factors, each of which was dichotomised for the purpose of this study to simplify the interpretation and presentation of the interaction results. These risk factors were:

(a) low IQ test score (lowest 33% *v.* rest);

(b) poor social adjustment (lowest 30% on composite variable (range 0–10) derived from questions enquiring about friendships, girlfriends and sensitivity to others *v.* rest);

(c) disturbed behaviour in childhood (highest 20% on composite variable (range 0–9) derived from questions enquiring about misconduct at school, truancy, running away from home and police contact *v.* rest);

(d) cannabis use (ever used *v.* never used);

(e) non-psychotic psychiatric diagnosis at conscription (any *v.* none).

Statistical analysis

Thirty-four participants with a psychotic disorder at conscription were excluded from the analyses. We studied statistical interaction under both additive and multiplicative models using risk differences and risk ratios respectively. Under an additive model, the null hypothesis is that risks for each exposure combine additively ($\text{Risk}_{\text{A and B}} = \text{Risk}_{\text{A only}} + \text{Risk}_{\text{B only}} - \text{Risk}_{\text{Neither A nor B}}$). If risk when exposed to both A and B is greater, or less than additive, there will be statistical interaction under an additive model. Under a multiplicative model, the null hypothesis is that risks for each exposure combine multiplicatively ($\text{Risk ratio}_{\text{A and B}} = \text{Risk ratio}_{\text{A only}} \times \text{Risk ratio}_{\text{B only}}$). If risk when exposed to both A and B is greater, or less than multiplicative, there will be statistical interaction under a multiplicative model (see online supplement for more details).

Tests were implemented in STATA for Windows version 10 using the 'binreg' commands. Interaction *P*-values presented are from Wald tests. For the purposes of this study we have ignored the effects of confounding, as our interest is not in the main effects of any of the risk factors examined, but only in the interactions between them (although data is not presented, adjusting for family history, parental occupation, urbanicity and parental divorce altered the main effects of most of the exposures but had almost no effect on the interaction results presented below). As a sensitivity analysis we also repeated the tests for interaction after using different cut-off thresholds for creating dichotomous variables, and using ordinal measures rather than binary categories of exposure wherever possible.

Results

Out of the 50 053 male participants, there were 630 (1.3%, 95% CI 1.2–1.4%) who had developed schizophrenia or non-affective psychoses by 1996. Frequencies of exposure to each of the five risk factors examined and their associations with schizophrenia and other non-affective psychoses are summarised in Table 1. The tables of non-affective psychosis risk in relation to all possible two-way combinations of these risk factors are in online Tables DS1a–j. Tests of interaction under both additive and multiplicative models for each of these combinations are summarised in Table 2.

When we examined the data under additive models, there was moderate to strong evidence to reject the null hypothesis of an additive relationship for six of the ten combinations, and weaker evidence to reject this hypothesis for two other combinations. The statistical interaction here indicates that the pattern of risk from joint exposure to risk factors showed departure from an

Table 1 Frequency of exposures in relation to presence or absence of any non-affective psychosis, and crude odds ratio (OR) and 95% confidence intervals (95% CI) for association between exposures and non-affective psychosis outcomes

	Non-psychotic, *n*	Non-affective psychosis, *n*	Total, *n* (%)	OR (95% CI) for schizophrenia	OR (95% CI) for other non-affective psychoses	OR (95% CI) for any non-affective psychoses
Cannabis use						
Absent	41 468	460	41 938 (88.6)	1	1	1
Present	5263	122	5133 (11.4)	2.36 (1.81–3.08)	1.76 (1.34–2.31)	2.09 (1.71–2.56)
Lower IQ						
Absent	33 026	294	33 320 (66.7)	1	1	1
Present	16 312	335	16 647 (33.3)	2.63 (2.11–3.26)	2.25 (1.84–2.76)	2.31 (1.97–2.70)
Poorer social relationships						
Absent	33 907	349	34 256 (70.7)	1	1	1
Present	13 959	249	14 208 (29.3)	2.40 (1.92–2.99)	1.39 (1.12–1.73)	1.73 (1.47–2.04)
Disturbed behaviour						
Absent	38 331	381	38 712 (82.0)	1	1	1
Present	8341	186	8527 (18.0)	2.15 (1.69–2.74)	2.16 (1.72–2.71)	2.24 (1.88–2.68)
Other diagnosis						
Absent	43 282	446	43 728 (89.0)	1	1	1
Present	5201	181	5382 (11.0)	4.15 (3.29–5.22)	2.79 (2.21–3.52)	3.38 (2.83–4.02)

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Table 2 Summary of relative risks (RR) for all two-way combinations of risk factors for non-affective psychosis, with tests for interaction under both additive and multiplicative models

		Relative risk observed			A present, B present			Interaction *P* and direction[a]				
Risk factor A	Risk factor B	A absent, B absent	A present, B absent	A absent, B present	Expected under additive	Expected under multiplicative	Observed RR (95% CI)	Under additive model		Under multiplicative model		Relationship most supported
Cannabis use	Low IQ	1	2.1	2.2	3.3	4.6	5.4 (4.1–7.2)	0.006	(+)	0.400	(+)	Multiplicative
Cannabis use	Poor social relationships	1	2.0	1.7	2.7	3.4	4.1 (3.1–5.6)	0.023	(+)	0.322	(+)	Multiplicative
Cannabis use	Disturbed behaviour	1	1.3	1.7	2.0	2.3	3.6 (2.8–4.5)	0.002	(+)	0.048	(+)	>Multiplicative
Cannabis use	Other diagnosis	1	1.6	3.1	3.7	4.8	4.9 (3.8–6.4)	0.077	(+)	0.913	(+)	Multiplicative
Low IQ	Poor social relationships	1	2.3	1.8	3.1	4.0	4.0 (3.2–5.1)	0.019	(+)	0.905	(+)	Multiplicative
Low IQ	Disturbed behaviour	1	2.1	1.9	3.0	3.9	4.5 (3.6–5.6)	0.002	(+)	0.407	(+)	Multiplicative
Low IQ	Other diagnosis	1	1.9	2.5	3.4	4.9	6.3 (5.1–7.8)	<0.001	(+)	0.155	(+)	Multiplicative
Poor social relationships	Disturbed behaviour	1	1.8	2.4	3.2	4.2	3.7 (2.8–4.9)	0.227	(+)	0.631	(−)	Additive/ multiplicative
Poor social relationships	Other diagnosis	1	1.5	3.2	3.7	4.7	4.8 (3.8–6.1)	0.068	(+)	0.904	(+)	Multiplicative
Disturbed behaviour	Other diagnosis	1	1.9	3.3	4.2	6.1	4.7 (3.7–6.0)	0.365	(+)	0.206	(−)	Additive/ multiplicative

a. (+), positive interaction coefficient; (−), negative interaction coefficient.

additive relationship. For all of these, results were consistent with our *a priori* hypothesis of a greater than additive relationship between risk factors for psychosis.

The association between poor social adjustment and schizophrenia was not consistent with that between this exposure and the risk of other non-affective psychoses (Table 1). For risk factor combinations that included poor social adjustment, the evidence to reject the null hypothesis of an additive relationship was substantially stronger when examining schizophrenia rather than any non-affective psychoses as our outcome. For example, although there was only weak evidence to reject the null hypothesis of an additive relationship between poor social adjustment and other diagnosis at conscription when examining any non-affective psychosis as our outcome (Table 2), there was strong evidence to reject such a relationship for schizophrenia (interaction $P=0.003$), with the direction of interaction again consistent with our *a priori* hypothesis of a greater than additive relationship.

When we examined the data under multiplicative models, we found some evidence to reject the null hypothesis of a multiplicative relationship for one of the ten pair-wise combinations of risk factors. This relationship, between cannabis use and disturbed behaviour during childhood, was greater than multiplicative. For one of the pairs (disturbed behaviour and other diagnosis at conscription), there was insufficient evidence to reject the null hypothesis under either an additive or a multiplicative model, although confidence intervals for the combined exposure effect do not include the expected effect for a multiplicative relationship, indicating that this relationship is likely to be less than multiplicative.

In the sensitivity analyses, using ordinal rather than dichotomous measures of exposures resulted in stronger evidence against an additive relationship for almost all combinations examined. Furthermore, where we used different cut-off thresholds for creating dichotomous variables, results were very similar to those presented in Table 2. However, changing the cut-off for disturbed behaviour by +1 (highest 10% on composite variable) or −1 (highest 35%) resulted in stronger evidence of interaction under an additive model for co-exposure with poor social adjustment ($P=0.070$ and $P=0.045$ respectively) and with other diagnosis at conscription ($P=0.172$ and $P=0.058$ respectively), but weaker evidence of interactions under multiplicative models.

Discussion

The risk of developing any non-affective psychosis where any two risk factors were both present was almost always more than an additive effect, in keeping with our *a priori* expectations. There was some evidence of statistical interaction under an additive model for eight of the ten possible combinations of risk factors, with some support for interaction under an additive model for the other two combinations in the sensitivity analyses. We observed evidence of a greater than multiplicative relationship between cannabis use and disturbed behaviour, although the relationship between disturbed behaviour and other diagnosis at conscription was probably inconsistent with a multiplicative relationship, but still consistent with a greater than additive one. The sensitivity analyses indicated that the choice of cut-offs used in the analyses was unlikely to have altered our conclusions, except that we may have underestimated the evidence of a greater than additive relationship between disturbed behaviour and both poor social adjustment and diagnosis at conscription.

Modelling co-exposure to risk factors

When studying main effects, the choice of statistical model used is usually determined by the nature of the outcome data, for example using linear regression (additive model) for continuous outcome data, or logistic regression (multiplicative model) for binary data. The null hypothesis for studying main effects is that the effect of the exposure is equal to the null value. Rejecting the

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null hypothesis has a clear and potentially important meaning.[1] When studying the interaction between two variables however, the null hypothesis is that the combined effect of two risk factors follows an additive, or multiplicative relationship, depending on the statistical model used. Rejecting the null hypothesis tells us only that the model does not adequately describe the relationship between these two factors. Our findings of interaction under additive but not multiplicative models indicates that multiplicative statistical models are likely to provide a better fit than additive ones for modelling the joint relationship of exposures on disease risk. The commonly held assumption within epidemiology is that risk factors, in general, combine together multiplicatively (or at least more than additively) to influence risk of disease. This assumption is based on theoretical considerations about underlying causal models as well as empirical data from multiple areas of medicine, and our data supports this belief.

Implications for understanding aetiology

These results are consistent with what we might expect when we think about sufficient-component cause models of disease, as it seems unlikely that the risk factors examined would not ever co-participate in the same causal model of disease in some people within this sample.[4] The evidence of interaction under additive models that we observed for almost all the interactions examined tells us only that, within each two-way combination of risk factors, there are some people who developed a non-affective psychosis who would not have developed this disease if either one or other risk factor had been absent. These results tell us nothing about underlying pathogenesis (or indeed psychological or social mechanisms) underlying the aetiology of psychosis above and beyond the results from main effects only.[2]

Understanding the way biological substrates 'interact' at a cellular or molecular level is clearly important for understanding aetiology. However, the study of statistical interactions in epidemiological studies does not inform us about this process. For example, although there may be evidence that cannabis affects risk of psychosis through effects on dopaminergic transmission, evidence of an additive interaction between cannabis and low IQ would not mean that the effect of IQ on psychosis risk is also mediated through dopaminergic mechanisms. Similarly, interaction under a multiplicative model, as we observed for example between cannabis use and disturbed behaviour, tells us nothing about underlying pathology above and beyond the results from main effects only. Statistical interaction, as demonstrated by our findings, is model-dependent and therefore does not have any clear biological meaning.[1]

The only exception to this is where qualitative or cross-over interactions occur, where one exposure has opposite effects on disease risk according to the presence or absence of another exposure. For example, it has been reported that in the presence of high paternal antisocial personality traits, the risk of child conduct problems increases the more time the father lives with the child, but with an opposite effect if paternal antisocial personality traits are low, such that the risk of child conduct problems decreases the more time the father lives with the child.[14,15] However, such relationships have only rarely been described in epidemiology. We would not expect higher IQ to completely reverse the possible effect of cannabis, i.e. that cannabis would protect against schizophrenia in those with high IQ. Similarly, where a genetic variant influences the amount or activity of a protein, we would not expect this to completely reverse the influence of another risk factor on disease risk.

Implications for targeted interventions

One could argue that these results, of a greater than additive relationship between most risk factors examined, increases our ability to identify high-risk groups for interventions. Where such greater than additive relationships exist, targeting interventions at those exposed to both risk factors will always lead to the largest reduction in the number of individuals with disease.[3] For example, more cases of psychosis would be prevented if an intervention to reduce cannabis use was implemented in those who also have lower IQ as opposed to those with higher IQ (assuming these associations are causal).

However, although this is true it seems rather unnecessary to test for additive interaction between these risk factors before reaching such a conclusion. As risk factors for multifactorial complex diseases are usually neither necessary nor sufficient to bring about disease, the relationship from co-exposure to these is unlikely to be truly additive at an epidemiological level as it is very unlikely that risk factors never co-participate in any causal models of disease.[4] It would seem to be a relatively safe assumption therefore that the greatest reduction in disease for a targeted intervention will be by prioritising those with co-exposure to multiple risk factors. In fact, a multiplicative (i.e. greater than additive) relationship between risk factors is often assumed within epidemiology, and indeed the programme of interventions aimed at reducing cardiovascular disease by specific targeting of high-risk groups is based on the assumption of multiplicative models of combined effects on risk.[16] Where very strong interactions occur, the case for selective interventions may be strengthened, but it is where qualitative interactions occur that clearly have the most important implications for targeting high-risk groups. In the main, however, evidence of statistical interaction has very limited implications for targeting interventions.

Other implications

Furthermore, although perhaps not directly relevant with respect to the exposures examined in this study, neither studies of interaction under additive or under multiplicative models are likely to benefit identification of novel risk factors for disease, except in rare circumstances.[3,17] Indeed, despite decades of study, there are few examples in epidemiology of the types of interaction that have the potential to enhance our ability to identify novel risk factors for disease, or to increase our understanding of disease pathology.[1,3]

Note that although we find strong evidence of additive interaction for most combinations of risk factors we examined, the implications of these results are extremely limited as such findings contribute little, if anything, to our understanding of underlying aetiological mechanisms or to potential targeting of interventions. Within the context of attempted replications, a need for studying interactions is often expressed without specifying under which model an interaction is hypothesised, or what pattern of interaction is being hypothesised. However, even where specific models are hypothesised, the belief that finding evidence of interaction under either additive or multiplicative models will enhance our understanding of psychiatric disease is likely to be misplaced.

Although gains from studies of interaction are feasible, the sorts of interactions that will bring about these gains, for example those that show a qualitative pattern of interaction, are likely to occur only rarely. It is important that studies of interaction are conducted with a clear understanding of the concept of statistical interaction, and that results, and particularly the implications of these, are interpreted appropriately.

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