Another illustrative example is the fact that authors themselves disagree on the ultimate aim of transdiagnostic research. Some of them claim that transdiagnostic research is a fundamental pathway to clinical utility for improving psychiatric classification and diagnosis[7], while others argue that the transdiagnostic approach does not primarily target the improvement of psychiatric classification and diagnosis, but rather tests a general theory of psychopathology[8]. A further example is the fact that, until the publication of this systematic review[1], the empirical limitations and reporting quality of transdiagnostic research remained unaddressed: appraising and acknowledging the specific limitations of a certain domain of knowledge is equally, if not more, important as celebrating its successes.

It may well be that some versions of a transdiagnostic approach are going to be necessary to improve psychiatric classification and care[7]. What is certain is that, until studies continue to loosely and incoherently self-proclaim transdiagnostic without acknowledging any diagnostic information, it is unlikely that transdiagnostic research will bear any real-world meaning for clinicians, patients, and medical practice. Similarly, poor reporting on the number and type of (trans)diagnostic spectra prevents the appraisal, refinement, and eventual integration of categorical and dimensional approaches in psychiatric classification.

The systematic review acknowledged that transdiagnostic categorical approaches that respect dimensionality are possible in organic medicine as well as in psychiatry[1], but this requires transparent reporting of the results. For example, the largest transdiagnostic study published to date demonstrated that it is possible to report the diagnostic information for almost all ICD-10 mental disorders[9]. Furthermore, while it is possible that transdiagnostic interventions may display superior efficiency, cost-effectiveness, accessibility, and patient-reported satisfaction compared to specific-diagnostic interventions[8], demonstrating this would require robust comparative analyses specifically conducted to test the non-inferiority or superiority of the transdiagnostic approach. These analyses are infrequent in the current literature[1].

The systematic review leveraged these caveats to put forward six empirical transdiagnostic research recommendations: TRANSD[1]. The TRANSD recommendations are pragmatic and focus on improving the quality of appraising and reporting transdiagnostic constructs. Importantly, they do not provide any *a priori* restrictive definition of the transdiagnostic schemata; as such, they can be applied to different topics and stimulate critical research in the field.

The first recommendation is to have a transparent definition of the gold standard (ICD, DSM, other), including specific diagnostic types, official codes, primary vs. secondary diagnoses, and diagnostic assessment interviews. Second, the primary outcome of the study, the study design, and the definition of the transdiagnostic construct should be reported in the abstract and main text. Third, the conceptual framework of the transdiagnostic approach – across-diagnoses (comparing different ICD/DSM categorical diagnoses against each other), beyond-diagnoses (employing ICD/DSM diagnostic information to go beyond it, testing new diagnostic constructs such as biotypes), other (with an explanation of the conceptual framework) – should be appraised. Fourth, the diagnostic categories, diagnostic spectra, and non-clinical samples in which the transdiagnostic construct is being tested and then validated should be indicated. Fifth, the degree of improvement of the transdiagnostic approach should be shown against the specific diagnostic approach through specific comparative analyses. Sixth, the generalizability of the transdiagnostic construct should be demonstrated through external validation studies.

It is hoped that these recommendations will improve the transparency and consistency of the next generation of transdiagnostic research, overcoming the current limitations of knowledge and benefitting psychiatric care.

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Mental illness among relatives of successful academics: implications for psychopathology-creativity research

The relationship between creativity and psychopathology is a long standing topic of research[1]. Creativity is defined as the ability to produce something novel, original, useful and valued, for instance in the domains of art, science or technology. It is being debated if the nature of creativity is general or domain-specific[1]. The assumed relationship between creativity and psychopathology is depicted as an inverted U curve, i.e. vulnerability to or low levels of psychopathology are believed to be associated with creativity, which declines with increased psychopathology[1].

Kyaga et al[2] coupled register information on psychiatric diagnosis with census information on self-reported occupational status. They found that individuals with bipolar disorder and

healthy siblings of people with schizophrenia or bipolar disorder were overrepresented among the scientific and artistic professions. Power et al[3], in a population study in Iceland, found that higher polygenic risk scores for schizophrenia and bipolar disorder were associated with artistic society membership or creative profession, which could not be accounted for by increased relatedness between creative individuals and those with psychoses.

Typically, we consider someone to be creative *post hoc*, on the basis of his/her recognized achievements. However, the contemporary measures of creativity typically rely on psychometric tests[1] or self-reported occupational status[2,3]. Such approaches have limited validity because they may, in fact, measure either a hypothetical disposition or personal aspiration.

We therefore applied a novel approach to the issue by studying the frequency of mental illness among the relatives of successful academics, i.e., people employed in tenured positions at universities. We assumed that such population would reflect a quasi-objective creative achievement compared to the background population.

We designed a study with elements from matched cohort studies and case-control studies. We received the personal identification numbers of all scientific employees in tenured positions at three Danish universities: Copenhagen, Aarhus and Southern Denmark. They were in total 11,803 individuals (referred to as "academics"). These academics were matched 1:6 on age, gender and municipality of residence with randomly selected controls from the background population. Through the Danish Civil Register, we identified first- and second-degree relatives of academics and controls. We divided this population into five subgroups: children, parents, grandparents, siblings and nephews/nieces. Grandchildren were excluded due to low age.

From the Psychiatric Central Research Register, we obtained information on psychiatric diagnoses in academics, controls and their relatives, and grouped these diagnoses following the ICD-10 hierarchy: schizophrenia, non-affective psychosis, bipolar disorder, melancholia, any other mental disorder, or no psychiatric diagnosis.

In comparing the relatives of academics and controls, we adjusted for age and gender. Furthermore, we adjusted for intelligence level, as this has been shown to be a significant epidemiological risk factor for schizophrenia[4] and therefore represents a confounder. We used the educational level (obtained from Statistics Denmark) as a proxy for intelligence.

The five subgroups of relatives were analyzed in a logistic model, with "relation to academic or control" as the dependent variable and the six diagnostic outcomes as the independent variable, adjusted for education, gender and age. The academics and controls were analyzed separately without covarying for educational level.

All data were anonymized, and the authors had no access to any data that could identify individuals. The study was approved by the Danish National Committee on Health Research Ethics and by the administrations of the Universities.

The total population comprised 588,532 individuals: 11,805 academics; 70,818 controls; 69,325 relatives of academics and 436,584 relatives of controls. The odds ratio (OR) for the academics to be diagnosed with any mental disorder was significantly ($p<0.05$) lower than for the controls (OR: 0.44, 95% CI: 0.40-0.49). This also applied to both bipolar disorder (OR: 0.43, 95% CI: 0.27-0.70) and schizophrenia (OR: 0.17, 95% CI: 0.11-0.26).

There was a significantly increased risk for schizophrenia among siblings (OR: 1.92, 95% CI: 1.62-2.27), children (OR: 1.85, 95% CI: 1.38-2.48) and nephews/nieces (OR: 1.50, 95% CI: 1.15-1.96) of the academics. For bipolar disorder, the OR was significantly increased among the academics' parents (OR: 1.38, 95% CI: 1.10-1.74), grandparents (OR: 1.43, 95% CI: 1.03-1.98) and nephews/nieces (OR: 1.62, 95% CI: 1.04-2.50), while significance was borderline ($p=0.05$) for the academics' siblings. The risk for schizophrenia was significantly increased in academics' maternal, but not paternal, half-siblings. The risk for any other mental disorder was significantly lower among the academics' children (OR: 0.75, 95% CI: 0.69-0.82) and nephews/nieces (OR: 0.72, 95% CI: 0.67-0.78).

This study shows that, while successful academics as a group are less prone to mental disorders than the background population, there are increased rates of schizophrenia and bipolar illness among their biological relatives. Other mental disorders, on the other hand, are less frequent among the relatives of academics. Because of our *a priori* hypothesis, we believe that this study supports the idea of a link between creativity and vulnerability to mental illness. We acknowledge, however, that the association between academic status and increased rates of schizophrenia and bipolar disorder in the relatives may be caused by multiple other factors.

The hypothesized relationship between creativity in successful academics and the increased risk for schizophrenia and bipolar disorder in their relatives seems to be mediated by a vulnerability that is not manifested as overt mental disorder in the academics, consistent with the inverted U curve model.

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