JAMA Psychiatry | Special Communication

Exploring Boundaries for the Genetic Consequences of Assortative Mating for Psychiatric Traits

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IMPORTANCE Considerable partner resemblances have been found for a wide range of psychiatric disorders, meaning that partners of affected individuals have an increased risk of being affected compared with partners of unaffected individuals. If this resemblance is reflected in genetic similarity between partners, genetic risk is anticipated to accumulate in offspring, but these potential consequences have not been quantified and have been left implicit.

OBSERVATIONS The anticipated consequences of partner resemblance on prevalence and heritability of psychiatric traits in the offspring generation were modeled for disorders with varying heritabilities, population prevalence (lifetime risk), and magnitudes of partner resemblance. These models facilitate interpretation for a wide range of psychiatric disorders, such as autism, schizophrenia, and depression. The genetic consequences of partner resemblance are most pronounced when attributable to phenotypic assortment (driven by the psychiatric trait). Phenotypic assortment results in increased genetic variance in the offspring generation, which may result in increased heritability and population prevalence. These consequences add generation after generation to a limit, but assortative mating is unlikely to balance the impact of reduced fecundity of patients with psychiatric disorders in the long term. This modeling suggests that the heritabilities of psychiatric disorders are unlikely to increase by more than 5% from 1 generation of assortative mating (maximally 13% across multiple generations). The population prevalence will increase most for less common disorders with high heritability; for example, the prevalence of autism might increase by 1.5-fold after 1 generation of assortative mating (≥2.4-fold in the long term) depending on several assumptions.

CONCLUSIONS AND RELEVANCE The considerable partner resemblances found for psychiatric disorders deserve more detailed interpretation than has been provided thus far. Although the limitations of modeling are emphasized, the anticipated consequences are at most modest for the heritability but may be considerable for the population prevalence of rare disorders with a high heritability.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2016.2566
Published online October 12, 2016.

Supplemental content

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Assortative mating is the correlation with respect to a phenotype between the biological parents of children and has been well described for many traits (eg, height).[1,2] Nordsletten et al[3] recently published a comprehensive study indicating a clear pattern of nonrandom (assortative) mating within and across 11 major psychiatric disorders. This study was based on data from Swedish population registers that included more than 700 000 unique cases matched with control individuals in a ratio of 1:5. The tetrachoric correlation was estimated between partners with respect to psychiatric diagnosis and the odds ratio (OR) for being affected as the partner of an affected individual compared with being affected as the partner of an unaffected individual. The strongest partner resemblance was found for autism, with a partner correlation of approximately 0.47 (the other estimates are summarized in the **Table**). In an accompanying editorial, Plomin et al[5] suggested that the findings from Nordsletten et al[3] might help to explain why psychiatric disorders are typically highly heritable while associated with reduced fecundity.[5] Nevertheless, although the partner resemblances were pronounced, neither Nordsletten et al[3] nor Plomin et al[5] provided quantitative boundaries of the genetic consequences, leaving interpretation of the effect of assortative mating on the prevalence and heritability of psychiatric disorders implicit. For example, although increased heritability is readily understood as a potential consequence of assortative mating, the expected magnitude of this increase and quantification of the consequences are not intuitive. Herein, we apply genetic models to explore the upper boundaries of the consequences for psychiatric traits of 1 and multiple generations of assortative mating while explicitly acknowledging the inevitable model assumptions.

Table. Approximation of Tetrachoric Partner Correlations in the Full Population From Case-Control Estimates

Disorder	Mean From Case-Control Data (Ratio 1:5)[a]		Approximation in Full Population	
	OR of Partner Being Affected	Tetrachoric Partner Correlation	Prevalence, *K* Value	Tetrachoric Partner Correlation[b]
Attention-deficit/hyperactivity disorder	7.20	0.45	7.2×10^{-3}	0.31
Autism spectrum disorder	10.80	0.47	1.5×10^{-3}	0.28
Schizophrenia	7.30	0.42	3.4×10^{-3}	0.26
Bipolar disorder	2.00	0.15	7.2×10^{-3}	0.10
Depression	1.84	0.16	3.6×10^{-2}	0.12
Generalized anxiety disorder	2.64	0.19	2.7×10^{-3}	0.11
Agoraphobia	3.56	0.24	1.8×10^{-3}	0.14
Social phobia	3.75	0.27	2.8×10^{-3}	0.16
Obsessive-compulsive disorder	2.42	0.17	2.3×10^{-3}	0.10
Substance abuse	3.87	0.37	3.9×10^{-2}	0.30
Anorexia nervosa	3.10	0.18	1.9×10^{-4}	0.08

Abbreviation: OR, odds ratio.

[a] Data are from Nordsletten et al[3] with the mean values across males and females. Because of oversampling of cases compared with the population prevalence, these partner correlations are different from the partner correlations in the full mating population. The disorder classification of Nordsletten et al was based on diagnoses from admitted individuals from 1973 to 2001, extended with diagnoses from outpatients settings from 2001 onwards, and the prevalences presented can therefore be interpreted as the prevalences of severe disorders that require specialized psychiatric care.

[b] The approximations of the tetrachoric partner correlation are not exact; for example, for autism they range from 0.24 to 0.31 when considering the estimates in females and males, respectively, and when taking into account that the prevalence of autism in males has been estimated at twice the prevalence in females in Sweden (eMethods 1 and 2 in the Supplement).[4]

Causes of Partner Resemblance

The consequences of partner similarity depend on its cause,[6-10] which we consider here in the context of traits relevant to psychiatric disorders. First, partner resemblance can arise when individuals are more likely to partner with someone purely based on resemblance in vulnerability for the psychiatric disorder studied (phenotypic assortative mating; here assumed to be based on a scale of the liability of risk, as discussed below), which will have genetic consequences.[11] Second and more likely, assortative mating can take place for another trait associated with the psychiatric disorder (eg, personality), which is referred to as secondary assortment[12] and affects the trait in future generations via the genetic correlation between both traits. A third cause of partner resemblance is social homogamy, which is a tendency to mate with those living in the same environmental conditions with similar environmental psychiatric risk factors and which has no direct genetic consequences.[11,13-15] A fourth, cause of partner resemblance is found in marital interaction,[16] which is the tendency for partners to become more similar during their life together (eg, partners of patients with obsessive-compulsive disorder are likely to adjust their checking habits),[17] which is unlikely to reflect a partner correlation in genetic effects. An example of social homogamy and/or marital interaction is that partners may drink alcohol or use drugs together.[14]

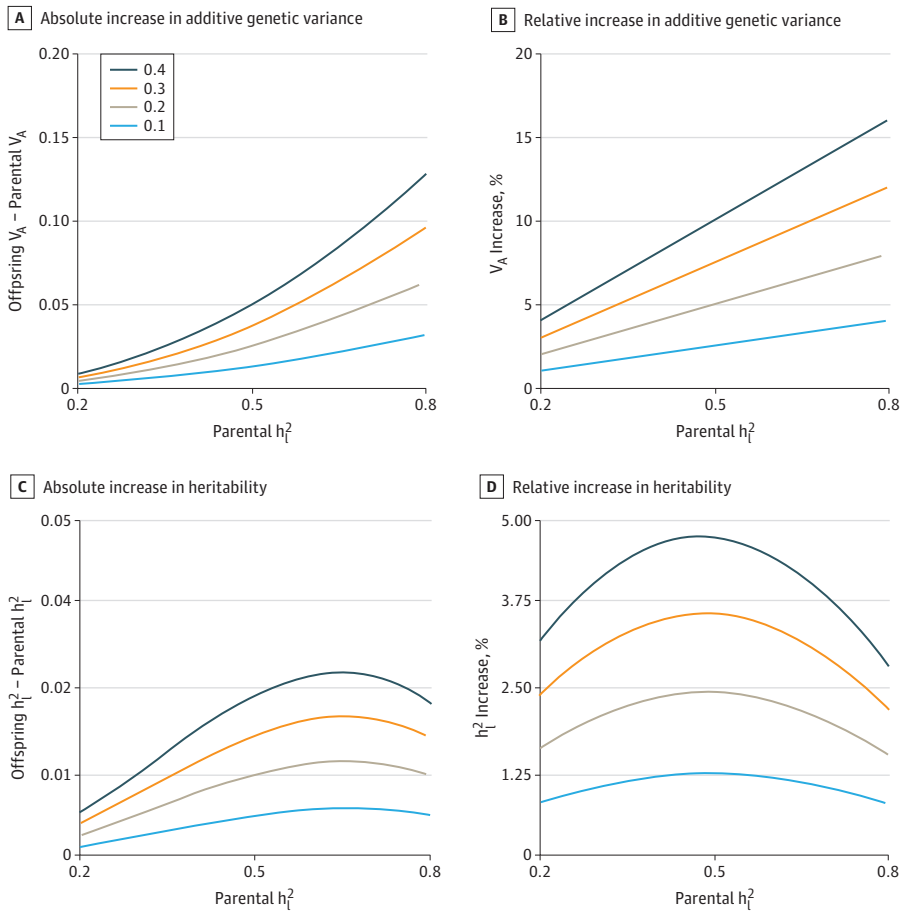
Tetrachoric Correlation and the Liability Threshold Model

The tetrachoric correlation[18] presented by Nordsletten et al[3] is the most convenient measure to explore the consequences of assortative mating, because it represents the partner correlation on the underlying liability scale.[19] Notably, the investigators matched 5 controls to every case (proportion of cases, 0.167),[3] the proportion of which is considerably larger than the anticipated population-estimated lifetime prevalence. As a consequence, the tetrachoric correlations presented are likely overrepresentations of the partner correlations in the full Swedish population from which Nordsletten et al selected individuals (eMethods 1 and 2 and eTable 1 in the Supplement). For example, the mean partner correlation of 0.47 found for autism by Nordsletten et al[3] reflects a partner correlation in the full population approximated at 0.28 (Table). This approximation ranges from 0.24 to 0.31 when considering the estimates in female and male individuals, respectively, and when taking into account that the prevalence of autism in males has been estimated at twice the prevalence in females in Sweden (eMethods 2 in the Supplement).[4] The estimates of Nordsletten et al[3] adjusted to the full population are largely in line with those of the previous literature (eMethods 3 and eTable 2 in the Supplement).[6-9,20-29] For modeling, the lifetime disorder population prevalence (*K* value) among mating individuals is required, which we approximated from Nordsletten et al[3] (Table; with sensitivity modeling in eMethods 1 and 2 and eTable 1 in the Supplement). These prevalences are relatively small (eg, 3.6% for depression compared with 13% presented by Sullivan et al[30]), which is in line with previous estimates from Swedish National Registry data[4] and attributable to disorder classification by Nordsletten et al[3] based on diagnoses from admitted individuals from 1973 to 2001 and extended with diagnoses from outpatient settings from 2001 onward. The disorder prevalences can therefore be interpreted as the prevalences of disorders that require specialized psychiatric care and are used as the estimates of minimum lifetime prevalence of the disorders.

Consequences of 1 Generation of Assortative Mating

The consequences of assortative mating depend on the genetic architecture of the disorder, its population prevalence, and its

Figure 1. Increase in Additive Genetic Variance (V_A) and Heritability (h_l^2) From 1 Generation of Assortative Mating



The expected increase in additive genetic variance and heritability from 1 generation of assortative mating is displayed against the heritability in the parental generation, expressed as the absolute increase (offspring − parental) and relative increase [100 × (offspring − parental)/parental] of additive genetic variance (A and B) and heritability (C and D), for partner correlation in liability of 0.1, 0.2, 0.3, and 0.4 respectively. The presented increases depend on assuming the liability threshold model, constant environmental effects in the offspring and parental generations, partner resemblance fully attributable to phenotypic assortment, and the parental generation as the first to exhibit patterns of assortative mating.

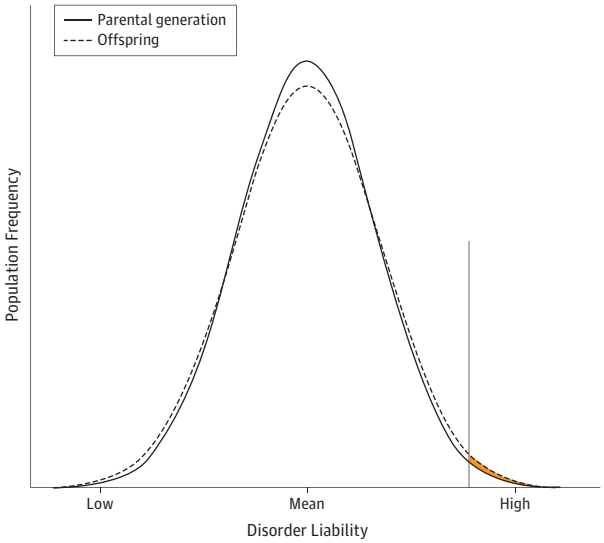
heritability.[31] To minimize the numbers of assumptions, we will first review the maximum anticipated impact in 1 generation to later address the consequences of multiple generations of assortative mating. *Assortative mating* describes phenotypic partner resemblance, but its consequences for the following generation are a result of the partner correlation in genetic values, the magnitude of which depends on the heritability (proportion of variance attributable to genetic factors).[11] Psychiatric disorders are now widely accepted to be highly polygenic and affected by many loci[32-34] that individually explain less than 1% of variance.[35] As a consequence, genotype frequencies of individual loci do not, or only very slightly, change as a result of assortative mating (eMethods 4 in the Supplement). Rather, assortment introduces correlation between effective loci because the many risk alleles of the fathers correlate with the many risk alleles of the mothers.[36,37] This correlation between effective loci increases the additive genetic variance from the parent to the offspring generation, which is the key consequence of assortative mating from which changes in heritability and population prevalence follow.[36,37]

The increased genetic variance introduced by assortative mating results in an increased heritability in the offspring generation.[38] From **Figure 1**, the additive genetic variance can be seen to increase as much as 16% after 1 generation of assortative mating, with a partner correlation of 0.4 for a disorder with heritability of 0.8 (Figure 1B), which represents an absolute increase in additive variance of 0.13 (Figure 1A). This increase in additive genetic variance is less pronounced for disorders with smaller heritability, as discussed above. Notably, the increase does not depend on the disorder prevalence because the partner correlation is expressed on the liability scale. Contrary to the additive genetic variance, the offspring heritability does not monotonically increase with increasing parental heritability (Figure 1C and D) because the heritability is a ratio of additive genetic variance divided by the sum of additive genetic variance (V_A) and residual variance (V_E), as shown in the following equation:

$$h_l^2 = V_A/(V_A + V_E).$$

The increased additive genetic variance features in the numerator and denominator. As a consequence, the maximum effect of assortative mating on the heritability is found for disorders with heritability ranging from 0.5 to 0.7 (Figure 1C and D), assuming the re-

Figure 2. Assortative Mating and Increased Population Variance



The distributions of liabilities in the parental and offspring generations are displayed to illustrate how the increased liability variance in offspring increases the proportion of individuals exceeding the disorder threshold (highlighted in orange) who are thus affected. The increased variance in liability is attributable to the increased variance in additive genetic effects resulting from assortative mating. This example is based on a disorder with a heritability of 0.8, prevalence of 0.01, and partner correlation in liability of 0.4 fully attributable to phenotypic assortment, which may be approximately representative of disorders such as schizophrenia, bipolar disorder, or autism, thus providing an upper boundary of the consequences of assortative mating for these disorders.

sidual variance is the same in the offspring as in the parental generation. For a partner correlation of 0.4, the maximum increase in heritability from 1 generation of assortative mating is expected to be less than 5% of the parental heritability (Figure 1D).

The increased genetic variance introduced by assortative mating generates increased variance of phenotypic liability and heavier tails in the liability distribution, which means an increased proportion of individuals exceeding the disorder threshold, and hence an increase in population disorder prevalence (*K* value) (**Figure 2**). In **Figure 3**, the relative increase in population prevalence is displayed for disorders with prevalences in the parental population of 0.001, 0.01, 0.05, and 0.15 for heritabilities ranging from 0.2 to 0.8 and partner correlation (phenotypic assortment) of 0.4, 0.3, 0.2, and 0.1. The relative increase in population prevalence is largest for rare disorders with large heritability and large partner correlation. For example, autism has a relatively high partner correlation of 0.28, high heritability of 80%,[30] and a low prevalence of approximately 0.15% that is anticipated to increase by 50% to 0.22%, whereas severe depression as classified by Nordsletten et al[3] has a partner correlation of 0.12, heritability of approximately 37%,[30] and a prevalence of 3.4% that is anticipated to increase to 3.5% (or, when assuming similar partner correlation for the broader depression definition, from 15.0%-15.1%).

Impact of Model Assumptions

The first key assumption in the models described above is that partner resemblance is attributable to phenotypic assortment on the liability scale. This assumption is difficult to test in a large-scale population study as that conducted by Nordsletten et al,[3] and, although some previous studies[6,7,28] attempted to correct for social homogamy and secondary assortment, the proportion of partner resemblance that is attributable to phenotypic assortment, secondary assortment, social homogamy, and marital interaction remains largely unknown. Nevertheless, assuming phenotypic assortment defines upper boundaries of the genetic consequences are explored, because social homogamy and marital interaction are expected to represent no changes in additive genetic variance, and secondary assortment is expected to result in less change in genetic variance than phenotypic assortative mating.

The second key assumption is that the residual variance (reflecting environmental, stochastic, and measurement error effects) is equal in the offspring and parental generations, which is difficult to test, but on average acceptable given the range of countering environmental effects between generations (eg, born after rather than before World War II, or financial crisis in offspring vs financial prosperity in parents). However, if the mean of environmental effects is smaller (or larger) in offspring, the prevalence would be lower (or higher) than presented. If the variance of environmental effects was larger in the offspring generation, the offspring heritability would be smaller and the offspring prevalence larger than presented.

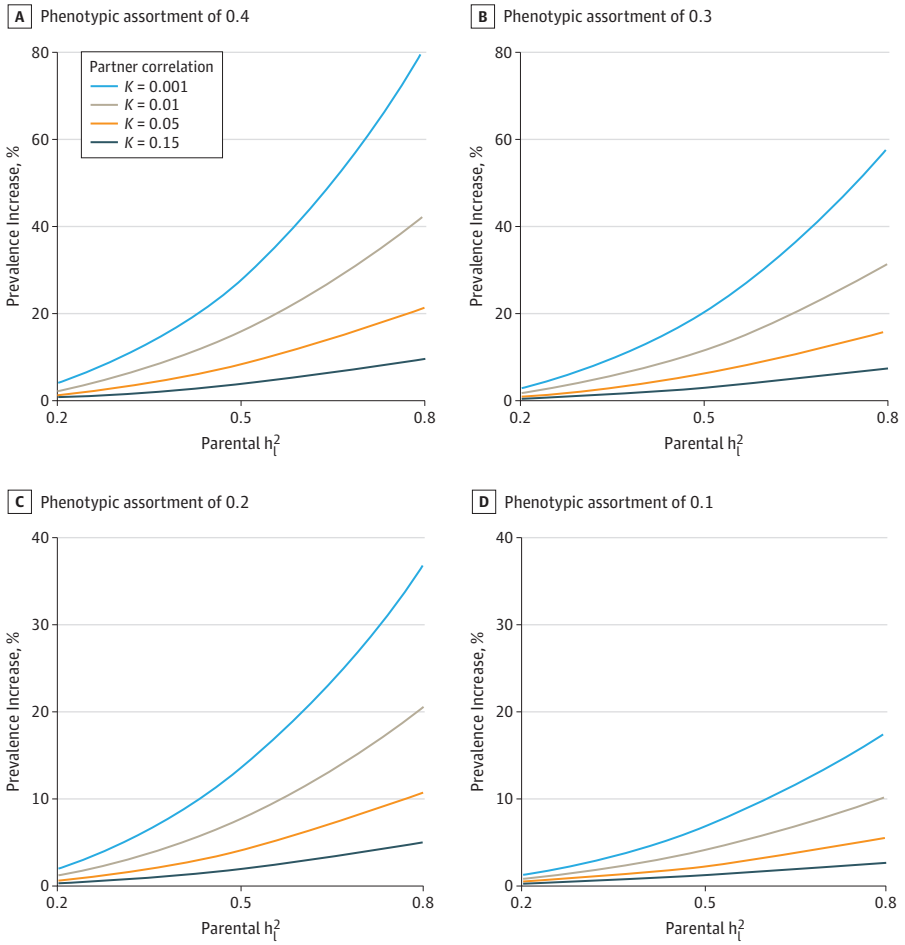
The third key assumption in the models is that the generation considered is the first to exhibit patterns of assortative mating. This assumption is unlikely to hold and difficult to test, but it ensures that the upper boundaries are explored because the anticipated consequences are less pronounced in the second, third, or consecutive generations of assortative mating.

Multiple Generations of Assortative Mating

In classic quantitative genetics theory, the consequences of assortative mating are usually explored in a population at equilibrium, because the anticipated increase in additive genetic variance introduced by assortative mating adds generation after generation to asymptotically stabilize at a maximum.[36] The correlation between effective loci across the genome, which is responsible for the increase in additive genetic variance, is bound by a maximum. Notably, the maximum correlation is smaller than 1 because (1) partner resemblance is smaller than 1, (2) heritability is smaller than 1, and (3) affected individuals can by chance transmit all of their nonrisk alleles to their offspring.

Here, we choose to focus on the consequences of 1 generation of assortative mating because we believe that the assumptions of the underlying model are unlikely to be valid across generations. In the context of psychiatric disorders, the scope for assortative mating afforded today by transport, social services, and social media technologies is difficult to conceive as relevant to previous generations. Nevertheless, for completeness, the consequences of multiple generations of assortative mating and achieving equilibrium were considered in eMethods 5 and eTable 3 in the Supplement. To illustrate for a disorder such as autism in Sweden, with a lifetime prevalence of 0.0015, heritability of 0.8, and partner correlation of 0.28 assumed fully attributable to phenotypic assortment, the heritability would increase from 0.80 in the founder population via 0.816 in the first generation and 0.826 in the second generation to reach

Figure 3. Increase in Population Prevalence After 1 Generation of Assortative Mating



The expected increase in population prevalence (K) from 1 generation of assortative mating expressed as 100% × ($K_{offspring} - K_{parental}$)/$K_{parental}$ is displayed against the parental heritability (h_l^2) for a parental prevalence of $K_{parental}$ = 0.001, 0.01, 0.05, and 0.15 and partner correlation of 0.4, 0.3, 0.2, and 0.1, respectively. The presented increase depends on assuming the liability threshold model, constant environmental effects in the offspring and parental generations, partner resemblance fully attributable to phenotypic assortment, and the parental generation as the first to exhibit patterns of assortative mating.

its equilibrium of 0.839 in the eighth generation, whereas the population prevalence would increase from 0.0015 in the founder generation to 0.0022 in the first (ie, a 1.5-fold increase) and 0.0028 in the second generation to the equilibrium of 0.0039 from the ninth generation onward (ie, a 2.4-fold increase compared with the founder population; eTable 4 in the Supplement). eFigure 1 in the Supplement displays the increase in additive genetic variance for 10 generations of assortative mating and illustrates an upper boundary for heritability increase of 13% that was found for a disorder with heritability of 0.5 in the founder generation and phenotypic assortment of 0.4. eFigure 2 in the Supplement shows that the increase in population prevalence can be more pronounced, as was discussed for the consequences of 1 generation of assortative mating.

Reduced Fecundity of Psychiatric Patients

Debate has proceeded from an evolutionary perspective as to why psychiatric disorders continue to exist despite the reduced fecundity of affected persons.[39,40] Because assortative mating increases the population prevalence, considering assortative mating as a counteracting force of natural selection seems relevant. We have, therefore, derived a theory to consider the combined impact of assortative mating and natural selection (eMethods 5 in the Supplement). These models help to quantify boundaries, but interpretation is limited by many assumptions, so results must be interpreted with caution. In short, while assuming (1) constant mating patterns, constant fecundity, constant environmental effects, and constant disorder threshold over generations; (2) natural selection and assortment starting to act at the same moment in time; and (3) no other evolutionary forces than selection (eg, no new mutations), we modeled reduced fecundity as partial truncation selection and assortment as before. To illustrate the impact of reduced fecundity, a numeric example is provided for disorders such as autism with a fecundity ratio of 0.35,[4] heritability of 0.8, prevalence of 0.0015, and assortment of 0.28 (eTable 4 in the Supplement). First, although the consequences of assortment reach equilibrium after approximately 7 to 10 generations, natural selection acts also in the subse-

quent generations, resulting in a combined impact of assortment and selection with an increased population prevalence in the first couple of generations, followed by a decrease to 0.0013 in generation 100 and 0.0001 in generation 1000 (eTable 4 in the Supplement). Notably, the heritability does not change much from selection, as expected from the polygenic architecture and weak coefficient of selection intensity.[41] In general, assortment might counteract selection for a few generations, but not in the longer term for subsequent generations. Taken together, we believe other mechanisms are better suited to explain why psychiatric disorders continue to exist despite the reduced fecundity, such as ancestral neutrality (harmful features in current times were not harmful in the past), balancing selection (eg, risk alleles might benefit fitness via their effect on creativity or healthy cautious behavior),[42] polygenic mutation-selection balance, or psychiatric disorders as a fitness trade-off at the extreme end of variation.[39,40]

Model Limitations

Several additional model assumptions exist than those listed above. First, the liability threshold model was assumed because this is the most convenient parameterization of polygenic disease risk and is recognized as equivalent to other disease models[43]; although this model cannot be observed, available empirical data provide no reason to reject this model. Second, we assume that phenotypic assortment is based on the liability scale rather than disease status; when partner resemblance would be attributable to phenotypic assortment based on disease status, the consequences would have been much less pronounced (eMethods 6, eTable 5, and eFigures 3 and 4 in the Supplement). Third, we note that models are based on lifetime prevalences, and we assume that the case-control status in the study by Nordsletten et al[3] approximates lifetime status. Fourth, the disorders were implicitly assumed to be only affected by additive genetic effects and not by dominance deviations from additivity, but this assumption is justified because assortative mating only acts on additive and not on dominance deviations.[36] Fifth, the impact of cultural inheritance (of information by communication, imitation, teaching, and learning)[44,45] fell outside the scope of this study because we aimed to explore boundaries for the genetic consequences of assortative mating. However, cultural inheritance is modeled as common environment in twin models, and we note that common environment explains considerably less variation for psychiatric traits than additive genetic effects (eg, 1.3% vs 77% for schizophrenia and 5%-15% vs 45% for obsessive-compulsive disorder).[46,47] We cannot draw strong conclusions from modeling because of these inevitable assumptions. Nevertheless, we believe modeling gives more insight than not modeling and places upper boundaries to the genetic consequences of assortative mating for psychiatric traits.

Discussion

Partner resemblance has been convincingly confirmed by Nordsletten et al[3] for 11 psychiatric disorders in a large-scale study from Sweden building on evidence from earlier studies.[6-9,20-29] Here, we set out to provide quantification of the genetic consequences of partner resemblance for psychiatric traits. When we consider all factors consistent with empirical data, we find that assortative mating likely plays a substantial role in psychiatric genetics with considerable anticipated consequences on the population prevalence of rare disorders with high heritability and, to a lesser extent, on the heritability. In reality, the prevalence increase from parental to offspring generations of 1.0% to 1.5%, for example, although highly important, may be hard to detect in empirical data or to attribute to assortative mating given the standard errors around these estimates. Nevertheless, increased rates of disorders have been suggested when both parents are affected.[48] The estimated consequences are upper boundaries because if the partner resemblance found by Nordsletten et al[3] was partly attributable to, for example, social homogamy,[11,13-15] the consequences would be considerably less. In addition, other factors also affect the population prevalence, such as reduced fecundity in patients with psychiatric disorders. Notably, the presence of assortative mating does not affect genome-wide association studies because of the small effects of individual loci.[49] Estimates of the proportion of variance explained by genome-wide single-nucleotide polymorphisms (single-nucleotide polymorphism heritability) will be increased in line with the models in this report that are attributable to the correlation between effective single-nucleotide polymorphisms.[49]

Conclusions

These factors together suggest that current trends in assortative mating might lead to a considerable increase in the prevalence of rare disorders with high heritability, but assortative mating will at most have a modest effect on heritability. A challenge for future research will be to disentangle further partner resemblance owing to phenotypic assortment from partner resemblance as a result of secondary assortment, social homogamy, and marital interaction. Future population samples consisting of large numbers of partners with genotype and phenotype data may address this challenge by comparing risk alleles in partners with their disease status.

ARTICLE INFORMATION

Accepted for Publication: August 21, 2016.

Published Online: October 12, 2016. doi:10.1001/jamapsychiatry.2016.2566

Conflict of Interest Disclosures: Dr Penninx reported receiving research funding from Jansen Research. No other disclosures were reported.

Funding/Support: This study was supported by travel grant 2001228 from EMGO Institute for Health and Care Research (Dr Peyrot), the Center for Medical Systems Biology (NWO Genomics), and by grants 1050218 and 1078901 and fellowship 1087889 from the National Health and Medical Research Council (Dr Wray).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Ashley E. Nordsletten, PhD, James J. Crowley, PhD, and David Mataix-Cols, PhD (Department of Clinical Neuroscience, Karolinska Institutet), and John J. McGrath, PhD (Queensland Brain Institute, University of Queensland), provided useful feedback, for which they were not compensated.

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