Chapter 7
Exploring boundaries for the genetic consequences of assortative mating for psychiatric traits

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Chapter 7

ABSTRACT

Importance: Considerable partner-resemblances have been found for a wide range of psychiatric disorders, meaning that partners of affected individuals have an increased risk to be affected compared to partners of unaffected individual. If there is a genetic basis to this resemblance, 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 the prevalence and heritability in the offspring generation were modeled for disorders with varying heritabilities, population prevalences (lifetime risks) and magnitudes of partner-resemblance. This facilitates interpretation for a wide range of psychiatric disorders, such as autism, schizophrenia and depression. The genetic consequences are most pronounced when partner-resemblance is attributable to phenotypic assortment (partner-resemblance 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 we show that assortative mating is unlikely to balance the impact of reduced fecundity of psychiatric patients in the long term. Our modeling suggests that the heritabilities of psychiatric disorders are unlikely to increase by more than 5% from one generation of assortative mating (maximally 13% over 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 one generation of assortative mating (up to 2.4-fold in the long-term), depending on several assumptions.

Conclusion and Relevance: The considerable partner-resemblances found for psychiatric disorders deserve more detailed interpretation than has been provided thus far. While emphasizing the limitations of modeling, we conclude that 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.
INTRODUCTION
Assortative mating is the correlation with respect to a phenotype between the biological parents of children, and has been well described for many traits, for example, height.\textsuperscript{1,2} In this journal, Nordsletten et al published a comprehensive study indicating a clear pattern of nonrandom (assortative) mating within and across eleven major psychiatric disorders.\textsuperscript{3} This study was based on data from Swedish population registers including over 700,000 unique case individuals that were matched with controls in a ratio 1:5 to estimate the tetrachoric correlation between partners with respect to psychiatric diagnosis, and the odds ratio (OR) to be affected as partner of an affected individual compared to being affected as 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 Table 1 of this paper). In the accompanying editorial, Plomin et al discussed that the findings from Nordsletten et al might help to explain why psychiatric disorders are typically highly heritable while associated with reduced fecundity.\textsuperscript{4} Nevertheless, although the partner resemblances were pronounced, neither Nordsletten nor Plomin provided quantitative boundaries of the genetic consequences, leaving interpretation of the impact 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 consequences are not intuitive. Here, we apply genetic models to explore the upper boundaries of the consequences for psychiatric traits of one and of multiple generation of assortative mating, while explicitly acknowledging the inevitable model assumptions.

CAUSES OF PARTNER RESEMBLANCE
The consequences of partner similarity depend on its cause,\textsuperscript{5–9} 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 the liability of risk scale as discussed below), which will have genetic consequences as described in detail below.\textsuperscript{10} Second and more likely, assortative mating can take place for another trait associated to the psychiatric disorder (e.g. personality), which is referred to as secondary assortment\textsuperscript{11} and impacts the trait in future generations via the genetic correlation between both traits. A third cause of partner
resemblance is social homogamy; a tendency to mate with those living in the same environmental conditions with similar environmental psychiatric risk factors, which has no direct genetic consequences.\textsuperscript{10,12–14} Fourth, yet another cause for partner resemblance is found in marital interaction,\textsuperscript{15} the tendency for partners to become more similar during their life together (e.g. partners of OCD patients are likely to adjust their checking habits),\textsuperscript{16} 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.\textsuperscript{13}

\textbf{TETRACHORIC CORRELATION AND THE LIABILITY THRESHOLD MODEL}

The tetrachoric correlation\textsuperscript{17} presented by Nordsletten et al.\textsuperscript{3} is the most convenient measure to explore the consequences of assortative mating, because it represents the partner-correlation on the underlying liability scale.\textsuperscript{18} Notably, they matched five controls to every case (proportion of cases 0.167),\textsuperscript{3} the proportion of which is considerably larger than the anticipated population-estimated lifetime prevalences. As a consequence, the tetrachoric correlations presented are likely overrepresentations of the partner-correlations in the full Swedish population that Nordsletten et al selected subjects from (eMethods). For example, the average partner-correlation of 0.47 found for autism by Nordsletten et al reflects a partner-correlation in the full population approximated at around 0.28 (Table 1). This approximation ranges from 0.24 to 0.31 when considering the estimates in female and male 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).\textsuperscript{19} The estimates of Nordsletten et al adjusted to the full population are largely in line with previous literature (eTable 2).\textsuperscript{5–8,20–29} For modeling, the lifetime disorder population prevalence (K) amongst mating individuals is required, which we approximated from Nordsletten et al (Table 1; with sensitivity modeling in eMethods and eTable 1). These prevalences are relatively small (e.g. 3.6\% for Depression compared to 13\% presented by Sullivan),\textsuperscript{30} which is in line with previous estimates from Swedish national registry data,\textsuperscript{19} and attributable to disorder classification by Nordsletten et al based on diagnoses from admitted individuals from 1973-2001, extended with diagnoses from outpatients settings from 2001 onwards. 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.
Table 1. Approximation of tetrachoric partner-correlations in the full population from case-control estimates presented by Nordsletten et al

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mean from case-control data (ratio 1:5)</th>
<th>Approximation in full population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio for disorder in partner</td>
<td>Population prevalence (K)</td>
</tr>
<tr>
<td></td>
<td>Correlation in case-control</td>
<td>Correlation in population</td>
</tr>
<tr>
<td>Attention-Deficit/Hyperactivity Disorder</td>
<td>7.20</td>
<td>7.2e-03</td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td>10.80</td>
<td>1.5e-03</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>7.30</td>
<td>3.4e-03</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>2.00</td>
<td>7.2e-03</td>
</tr>
<tr>
<td>Depression</td>
<td>1.84</td>
<td>3.6e-02</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>2.64</td>
<td>2.7e-03</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>3.56</td>
<td>1.8e-03</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>3.75</td>
<td>2.8e-03</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>2.42</td>
<td>2.3e-03</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>3.87</td>
<td>3.9e-02</td>
</tr>
<tr>
<td>Anorexia Nervosa</td>
<td>3.10</td>
<td>1.9e-04</td>
</tr>
</tbody>
</table>

Displayed are the study proportion of cases amongst individuals that got a partner (P), the odds ratio to be affected as partner of a control, and the tetrachoric partner-correlation in the case-control sample from Nordsletten et al, while taking the average across male and female. Because of oversampling of cases compared to the population prevalence, these partner-correlations are different from the partner-correlations in the full mating population. From P, odds ratio and case-control correlation presented by Nordsletten et al, we approximated the population prevalence in the mating population (K), as well as the tetrachoric partner-correlation in the mating population (details in eMethods). The approximations of the tetrachoric partner-correlation are not exact, e.g. they range for autism from 0.24 to 0.31 when considering the estimates in female and male respectively, and when taking into account that the prevalence of autism has been estimated at twice the prevalence in female in Sweden (eMethods). Disorder classification of Nordsletten et al that was based on diagnoses from admitted individuals from 1973-2001, 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.
Figure 1. Increase in additive genetic variance ($V_A$) and heritability ($h_i^2$) from one generation of assortative mating. The expected increase in additive genetic variance and heritability from one generation of assortative mating is displayed against the heritability in the parental generation, expressed as the absolute increase (offspring – parental) and relative increase ($100 \times (\text{offspring} - \text{parental})/\text{parental}$), for partner-correlation in liability of 0.1, 0.2, 0.3 and 0.4 respectively. Panel A shows the absolute increase in additive genetic variance, Panel B the relative increase in additive genetic variance, Panel C the absolute increase in heritability, and Panel D the relative increase in heritability. The presented increases depend on assuming the liability threshold model, constant environmental effects in the offspring and parental generation, that the partner resemblance is fully attributable to phenotypic assortment, and that the parental generation is the first to exhibit patterns of assortative mating.
CONSEQUENCES OF ONE GENERATION OF ASSORTATIVE MATING

The consequences of assortative mating depend on the genetic architecture of the disorder, its population prevalence and its heritability.\(^{31}\) To minimize the numbers of assumptions, we will first review the maximum anticipated impact in one generation to later also 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, which depends on the heritability (proportion of variance attributable to genetic factors).\(^{10}\) It is now widely accepted that psychiatric disorders are 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). 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, it can be seen that the additive genetic variance can increase as much as with 16% after one generation of assortative mating with a partner-correlation of 0.4 for a disorder with heritability of 0.8 (Figure 1 Panel B), which represents an absolute increase in additive variance of 0.13 (Figure 1 Panel A). 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 as 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 1 Panels C and D), because the heritability is a ratio of additive genetic variance divided by the additive genetic variance (\(V_A\)) plus the residual variance (\(V_E\)), \(h^2_I = V_A / (V_A + V_E)\), and the increased additive genetic variance features in both the numerator and denominator. As a consequence, the maximum impact of assortative mating on the heritability is found for disorders with heritability between 0.5 and 0.7 (Figure 1 Panels C and D) assuming the residual 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 one generation of assortative mating is expected to be less than 5% of the parental heritability (Figure 1 Panel D).
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) (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 correlations 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. The consequence on population prevalence is thus larger for e.g. autism with relatively high partner-correlation (0.28), high heritability (80%),\(^{30}\) and a low prevalence (~0.15%) that is anticipated to increase by 50% to 0.22%, than for severe depression as classified by Nordsletten et al with a partner correlation of 0.12, heritability of around 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% to 15.1%).

**IMPACT OF MODEL ASSUMPTIONS**

The first key assumption in the models 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 conducted by Nordsletten et al, and although some previous studies did attempt to correct for social homogamy and secondary assortment,\(^5,6,28\) the proportion of partner resemblance that is attributable to phenotypic assortment, secondary assortment, social homogamy, and marital interaction, remains largely unknown. Nevertheless, by assuming phenotypic assortment upper boundaries of the genetic consequences are explored, since 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 (e.g. 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 were
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 above 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 ensures that the upper boundaries are explored because the anticipated consequences are less pronounced in the second, third or consecutive generations of assortative mating.

Figure 2. **Assortative mating: increased population variance leads to increased prevalence.** The distributions of liabilities in the parental and offspring generation are displayed to illustrate how the increased liability variance in offspring increases the proportion of individuals exceeding the disorder-threshold that 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, providing an upper boundary of the consequences of assortative mating for these disorders.
Figure 3. Increase in population prevalence from one generation of assortative mating.
The expected increase in population prevalence (K) from one generation of assortative mating expressed as $100\% \times \left[ K_{\text{offspring}} - K_{\text{parental}} \right]/K_{\text{parental}}$ is displayed against the parental heritability for a parental prevalence of $K_{\text{parental}}=0.001$, 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 generation, that the partner resemblance is fully attributable to phenotypic assortment, and that the parental generation is the first to exhibit patterns of assortative mating.
MULTIPLE GENERATIONS OF ASSORTATIVE MATING

In classical 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.\textsuperscript{36} The correlation between effective loci across the genome, responsible for the increase in additive genetic variance, is bound by a maximum. Notably, the maximum correlation is smaller than one, because i) partner resemblance is smaller than one, ii) heritability is smaller than one, iii) affected individuals can by chance transmit all of their non-risk alleles to their offspring.

Here, we choose to focus on the consequences of one generation of assortative mating, because we believe that it is unlikely that the assumptions of the underlying model would be valid across generations. In the context of psychiatric disorders, it is hard to conceive that the scope for assortative mating afforded today by transport, social services and social media technologies is relevant to previous generations. Nevertheless, for completeness, the consequences of multiple generations of assortative mating and achieving equilibrium were considered in the eMethods. To illustrate, for a disorder, such as autism in Sweden, with a lifetime prevalence of $K = 0.0015$, heritability of $h^2 = 0.8$, 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 its equilibrium of 0.839 in the eighth generation, while the population prevalence would increase from 0.0015 in the founder generation to 0.0022 in the first (i.e. 1.5-fold increase), 0.0028 in the second to the equilibrium of 0.0039 from the ninth generation onwards (i.e. 2.4-fold increase compared to founder population; eTable 4). eFigure 1 displays the increase in additive genetic variance for ten 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 shows that the increase in population prevalence can be more pronounced, as was discussed for the consequences of one generation of assortative mating.

REDUCED FECUNDITY OF PSYCHIATRIC PATIENTS

There has been debate from an evolutionary perspective as to why psychiatric disorders continue to exist despite their reduced fecundity.\textsuperscript{39,40} Because assortative mating increases the population prevalence, considering assortative mating as counter-acting force of natural selection seems relevant. We have,
therefore, derived theory to consider the combined impact of assortative mating and natural selection (eMethods). These models help quantify boundaries but interpretation is limited by many assumptions, so results must be interpreted with caution. In short, while assuming constant mating patterns, constant fecundity, constant environmental effects and constant disorder threshold over generations, while assuming that natural selection and assortment start to act at the same moment in time, and while assuming no other evolutionary forces than selection (e.g., 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,\textsuperscript{19} heritability of 0.8, prevalence of 0.0015 and assortment of 0.28 (eTable 4). First of all, although the consequences of assortment reach equilibrium after around 7 to 10 generations, natural selection acts also in the subsequent 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). Notably, the heritability doesn’t change much from selection, as expected from the polygenic architecture and weak coefficient of selection intensity.\textsuperscript{41} In general, it seems that assortment might counter-act selection for a couple of generations, but not in the longer term considering more subsequent generations. Taken all together, we think other mechanisms are better suited to explain why psychiatric disorders continue to exist despite their reduced fecundity, such as ancestral neutrality (harmful features in current times were not harmful in the past), balancing selection (risk alleles might benefit fitness via impact on e.g. creativity or healthy cautious behavior),\textsuperscript{42} polygenic mutation-selection balance, or psychiatric disorders as fitness trade-off at the extreme end of variation.\textsuperscript{39,40}

**MODEL LIMITATIONS**

There are a number of additional model assumptions than those listed above. First, the liability threshold model was assumed as this is the most convenient parameterization of polygenic disease risk and is recognized as equivalent to other disease models;\textsuperscript{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 (see eMethods, eTable 5, eFigure 3 and eFigure 4). Third, we note
that models are based on lifetime prevalences, and we assume that the case-controls status in Nordsletten et al 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 is justified as assortative mating only acts on additive and not on dominance deviations.\textsuperscript{36} Fifth, the impact of cultural inheritance (of information by communication, imitation, teaching and learning)\textsuperscript{44,45} fell outside the scope of this paper as 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 (e.g. 1.3\% vs 77\% for SCZ and 5-15\% vs 45\% for OCD).\textsuperscript{46,47} It is not possible to draw strong conclusions from modeling, because of these inevitable assumptions. Nevertheless, we believe modeling gives more insight than not modeling, and serves to place upper boundaries of the genetic consequences of assortative mating for psychiatric traits.

**DISCUSSION**

Partner resemblance has been convincingly confirmed by Nordsletten et al for eleven psychiatric disorders in a large-scale study from Sweden\textsuperscript{3} building upon evidence from earlier studies.\textsuperscript{5-8,20-29} Here, we set out to provide quantification of the genetic consequences of partner resemblance for psychiatric traits. When considering 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 generation of e.g. 1.0\% to 1.5\%, while 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.\textsuperscript{48} The estimated consequences are upper boundaries because if the partner-resemblance found by Nordsletten et al were partly attributable to, say, social homogamy,\textsuperscript{10,12-14} the consequences would be considerably less. In addition, other factors also affect the population prevalence, such as reduced fecundity in psychiatric patients. Notably, the presence of assortative mating does not impact genome wide association studies because of the small effects of individual loci.\textsuperscript{49} Estimates of the proportion of variance explained by genome-wide SNPs (SNP-heritability) as assessed with Haseman
Elston regression will be increased more profoundly than the models presented here. These factors taken together imply 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 impact on heritability. A challenge for future research will be to disentangle further partner resemblance owing to phenotypic assortment from partner resemblance as result from secondary assortment, social homogamy, and marital interaction. Future population samples comprising large numbers of partners with both genotype as well as accurate phenotype data may address this challenge by comparing risk alleles in partners to their disease-statuses.

ACKNOWLEDGEMENTS
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REFERENCES
20. van Steijn, D.J., Richards, J.S., Oerlemans, A.M., de Ruiter, S.W., van Aken,
Supplement of Chapter 7. Exploring boundaries for the genetic consequences of assortative mating for psychiatric traits

eMethod 1. Transforming odds ratio (OR) and relative risk (RR) to tetrachoric correlation

The increased disorder risk in partners of affected individuals expressed as OR or RR can be transformed to tetrachoric correlation by first deriving the population prevalences of partner-pairs that can be represented in a Table as

<table>
<thead>
<tr>
<th>Partner 2</th>
<th>Affected</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aff.</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Unaff.</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

The population prevalence in the first partner-group (e.g. males) is $K_1 = a + b$ and in the second partner-group (e.g. females) $K_2 = a + c$ (setting $a + b + c + d = 1$, with $a$, $b$, $c$, $d$ the sample proportions attributed to each partner combinations). To get the values of $a$, $b$, $c$ and $d$ from the $OR = (a/b)/(c/d) = (a/c)/(b/d)$, all of $b$, $c$ and $d$ were expressed in terms of $a$, $OR$, $K_1$, and $K_2$ which were subsequently added together and set to equal 1 resulting in the following squared expression $0 = (OR - 1)a^2 + [(K_1 + K_2)(1 - OR) - 1]a + ORK_1K_2$. One of the two solutions of $a$ of this equation was consistent with the $OR$ and sensible values (between 0 and 1) of $a$, $b$, $c$ and $d$ and was taken forward to get $b$, $c$ and $d$. To get the values of $a$, $b$, $c$ and $d$ from the $RR = [a/(a + b)]/[c/(c + d)]$, $c$ was expressed as $c = [(a/K_1) - a]/RR$ and as $c = K_2 - a$, resulting in $a = RKK_2/[RR - 1 + (1/K_1)]$, from which $b$, $c$ and $d$ followed. Given the values of $a$, $b$, $c$ and $d$ the tetrachoric correlation ($r_{teta}$) was estimated with maximum likelihood as incorporated in the polychor() function from the "polycor" package in the R software. It follows from the above that $r_{teta}$ depends on the disorder prevalences in both partner-groups. The above was validated with simulations (described below), which indicated in addition that $r_{teta}$ could indeed be interpreted as the correlation on the liability scale.

eMethod 2. Tetrachoric correlation and oversampling of cases

The tetrachoric correlation ($r_{teta}$) is estimated from disease-status by assuming an underlying normally distributed latent variable, from which people are deemed affected when they exceed a certain threshold. When estimated on the full population or in a case-control sample with a proportion of cases (P) equal to
the population prevalence (K), these underlying liabilities can be thought of in terms of the liability threshold model. When $r_{tetra}$ is, however, estimated in a case-control sample with oversampling of cases ($P>K$), a different correlation estimate will be found. This can be understood intuitively, because a latent variable normally distributed in the full population will no longer be normally distributed in the case-control sample: thus, a different latent variable will be fitted. For example, when a disorder with prevalence of $K_1 = K_2 = 0.01$ and partner correlation in liability of 0.3 would be studied in a case-control setting with 20% cases ($K_1 = 0.2$ & $K_2$ increased to 0.019 by ascertaining partner 1), a tetrachoric correlation of 0.43 would be found.

Nordsletten et al have presented $r_{tetra}$ based on oversampling of cases by matching five controls to every case ($P=1/6$). However, Nordsletten et al have also presented the OR, which is robust against oversampling of cases. We used three methods to approximate $r_{tetra}$ in terms of the full population (eTable 1). In the first method, we searched literature, particularly publications based on the Swedish registry data, for estimates of the population prevalences K (which were not presented by Nordsletten et al). With this K ($K_2$ in the notation of the previous section), P ($K_1$ in the notation of the previous section), and the OR from Nordsletten et al, we first estimated the case-control $r_{tetra}$ that was used to double-check against the case-control $r_{tetra}$ presented by Nordsletten et al. Second, we replaced P with K found in literature to approximate the $r_{tetra}$ in terms of the full population. In the second method, we corrected the population prevalence K based on the proportion of cases and controls that had a partner in the sample of Nordsletten et al (their Table 1 and Table 2). The double-check from method 2 was less accurate than from method 1, which is hypothesized to be attributable to the large variance in the proportion of individuals that had a partner from cases and in particular also controls (varying from 16% to 80%). In method 3, the population prevalence was theoretically derived by setting $K_1$ to the P from Nordsletten, OR as the OR from Nordsletten, and the $r_{tetra}$ as from Nordsletten. Subsequently, the software R was used to find numerically the $K_2$ in the full population that best fitted OR, $K_1$ and $r_{tetra}$ taking into account the increase in $K_2$ from ascertainment in partner 1. eTable 1 displays the results from the three methods; inaccuracies in the double-check with the case-control $r_{tetra}$ for method 1 and method 2 are hypothesized to be mainly attributable to (1) possible differences in the K from literature and K in the sample from Nordsletten, (2) taking the prevalence of all individuals in the population rather than of those who got a partner, and (3) taking the average of male and female while these prevalences differ for some disorders. The advantage of method 3 is
that it circumvents (1) and (2), but not (3). Nevertheless, all together we feel that the three methods are more or less in concordance in approximating $r_{tetra}$ in terms of the full population. From these approximations, it seems that the case-control $r_{tetra}$ from Nordsletten may overestimate the $r_{tetra}$ in terms of the full population. The population prevalences in method 1 and method 2 were taken from Power et al for SCZ, BIP, ASD, ANP, SUB, MDD, Li et al for GAD, AGO and SOC, and Rück et al for OCD, the prevalence estimated of which were based on the same disorder classification of Nordsletten et al. The classification of Nordsletten et al were based on diagnoses from admitted individuals from 1973-2001, extended with diagnoses from outpatients settings from 2001 onwards, which is reflected in relative low prevalences for disorders that do not require admission regularly, e.g. for major depressive disorder 3.4% versus around 13% in general population. For ADHD, we could not find a prevalence based on the classification of Nordsletten, and used the prevalence of 4.6% from Pinto et al (from a twin registry not requiring admission for diagnosis) leading to a large discrepancy between case-control $r_{tetra}$ from Method 1 (0.52) and the case-control $r_{tetra}$ from Nordsletten (0.45).

The impact of different disorder prevalence in male and female is illustrated for autism. Estimates of the male-female ratio vary from 1.33 to 16.0, but have been estimated at 2.0 in the Swedish population. Method 3 above can be changed to allow for sex-difference by setting $K_{male} = 2 \times K_{female}$. In this way, for parameters provided by Nordsletten et al for ascertainment of male cases (OR=11.3; ascertained correlation 0.48), we approximate a tetrachoric correlation in the full population of 0.31. For the female parameters (OR=10.1; ascertained correlation 0.45), we approximate a tetrachoric correlation in the full population of 0.24. Interpreting this difference is difficult as many factors may contribute such as (1) the unknown exact prevalence-difference between males and females, (2) the sampling variance of male and female cases in the study from Nordsletten et al, and (3) different fecundity in males and females. Hence, interpretation as a real difference requires replication in an independent sample. We note that the approximated tetrachoric correlation based on the average of male and female presented in Table 1 (0.28) is indeed between 0.24 and 0.31.

**eMethod 3. Findings of partner resemblance of psychiatric disorders**

eTable 2 lists papers that have assessed assortative mating for psychiatric traits as found with an explorative search on PubMed ("assortative mating" AND (psychiatry OR depression OR schizophrenia OR anxiety OR ocd OR adhd OR autism OR bipolar)) and selected to comprise at least around hundred partner
pairs and publication date after 1990, and excluding the recently published Nordsletten estimates (displayed in eTable 1). These papers show a large heterogeneity with respect to the partner resemblance found, instruments used, sample origin, and measure of resemblance presented. For example, for ASD three of the listed studies applied the Social Responsiveness Scale (SRS) to find consistent evidence for a partner correlation of 0.25-0.5,\textsuperscript{15-17} whereas the two studies applying the Autism Spectrum Quotient (AQ) found no such evidence.\textsuperscript{9,18}

For general anxiety disorder, two samples were studied in the same paper with the same method, but lead to opposing findings with correlation estimates of 0.21 and -0.01 respectively.\textsuperscript{12} Despite the apparent heterogeneity, there is a trend for a positive partner resemblance found in the larger studies, although we cannot exclude publication bias. The meta-analyses of Mathews et al showed an increased risk for MDD and BIP in the partners of affected individuals with odds ratios of 2.46 and 3.42 respectively,\textsuperscript{19} which can be transposed a tetrachoric correlation between 0.25-0.3 (assuming $K$ between 0.1 and 0.2) and 0.14-0.20 (assuming $K$ between 0.0024 and 0.012) respectively. This is in line with an earlier review by Merikangas also concluding that numerous studies up to 1982 had consistently reported partner resemblance for psychiatric illness.\textsuperscript{23} The findings from a large Dutch population sample\textsuperscript{10,11} reported partner resemblance for attention-deficit/hyperactivity disorder, anxiety symptoms, obsessive compulsive disorder (OCD) and depressive symptoms with correlations estimated as 0.11, 0.17, 0.15, and 0.13 respectively. Most notably, some studies used Swedish population registries comprising over 100,000 partner pairs to find a correlation of 0.13 for OCD,\textsuperscript{13} 0.21 for social anxiety disorder,\textsuperscript{14} and an increased risk for partners of individuals with SCZ with an relative risk of 8.61.\textsuperscript{20} transposed to a tetrachoric correlation of 0.3 based on a prevalence of 0.004 presented by the authors.\textsuperscript{20} These Swedish estimates are in line with the adjusted Swedish estimates from Nordsletten et al of 0.10 for OCD, 0.16 for social anxiety, and 0.26 for schizophrenia (eTable 1).

\textbf{eMethod 4. Modeling the theoretical expectation of the combined impact of assortative mating and natural selection}

The impact of partner resemblance (here assumed attributable to spouse-correlation in disorder liability) on the additive genetic variance $\sigma_g^2$ is shown in Equation 8.20 of Bulmer,\textsuperscript{24} from generation $t$ to generation $t + 1$ with a partner-correlation in liability of $\rho_l$

$$
\sigma_g^2(t + 1) = 0.5\sigma_g^2(t)\{1 + \rho_l h_f^2(t)\} + 0.5\sigma_g^2(t = 0)
$$
which can be extended to include the consequences of selection with Equations 16.22 from Walsh and Lynch. However, Walsh and Lynch only provide an equation for full selection of controls (i.e. none of the affected individuals have offspring), whereas psychiatric patients have a reduced fecundity not equal to zero. Therefore, changes in population prevalence and variation, due to the combined impact of assortative mating and natural selection, were derived as follows. Consider a disorder with population lifetime prevalence before selection and assortative mating at time $t=0$, of $K(t=0) = K(0) = K_{\text{base}}$, which corresponds to a disease threshold on the underlying normally distributed liability scale of $T = \phi^{-1}(1 - K_{\text{base}})$, where $\phi$ is the standard normal cumulative distribution function. Consider a heritability in the base population of $h_i^2(0) = h_{i,\text{base}}^2$, and assume assortative mating on the liability scale with a spouse phenotypic liability-correlation of $\rho_{li}$, and a fecundity ratio of cases compared to controls of $FR = nr\text{ offspring affected}/nr\text{ offspring non-affected}$ starting at generation $t = 0$. In addition, assume that $\rho_{li}$, $FR$, $T$ and the environmental effects $e$ are constant for all generations. Given the mean liability $\mu_i(t)$, variance of liability $\sigma_i^2(t)$ and variance of genetic effect $\sigma_g^2(t)$ in any generation $t$, we will derive the genetic properties and population prevalence in generation $t+1$. We assume selection precedes assortment. Properties of any generation after selection are indicated with an *.

1. **Variances, covariances and means in generation $t$ before selection**

The proportion of cases is given by $K(t) = P(z > T|z\sim N(\mu_i(t), \sigma_i^2(t)))$. Scaling the liability scale to a variance of 1 and mean of 0, the mean liability of cases follow as $i = z/K(t)$, where $z$ is the height of the standard normal distribution at threshold $T_{\text{scaled}}$ with $K(t) = P(z > T_{\text{scaled}}|z\sim N(0,1))$. Hence, $\mu_{i,\text{case}}(t) = \mu_i(t) + i_{\text{scaled}}\sqrt{\sigma_i^2(t)}$, and $\mu_{g,\text{case}}(t) = \mu_i(t) + i_{\text{scaled}}\sqrt{\sigma_i^2(t)}\sigma_g^2(t)/\sigma_i^2(t)$ (the environmental mean is 0). The liability variance in cases follows as $\sigma_{i,\text{case}}^2(t) = \sigma_i^2(t) - k$, where $k$ represents the reduction in variance due to selection: $i_{\text{scaled}}(i_{\text{scaled}} - T_{\text{scaled}})\sigma_i^2(t)$ (Bulmer effect and scaling). The genetic variance follows as $\sigma_{g,\text{case}}^2(t) = \sigma_g^2(t) - k\sigma_g^4(t)/\sigma_i^4(t)$ (Tallis’ extension of the Bulmer effects) noting that the slope of regressing the liability on the genetic effects in the full population equals $\sigma_{g,\text{i}}(t)/\sigma_i^2(t) = [\sigma_{g,\text{g}}(t) + \sigma_{g,\text{e}}(t)]/\sigma_i^2(t) = \sigma_g^2(t)/\sigma_i^2(t)$. The covariance between $g$ and $l$ in cases equals $\sigma_{g,\text{i,\text{case}}}(t) = \sigma_{g,\text{i}}(t) - k\sigma_{g,\text{e}}(t)/\sigma_i^2(t)$. The properties in controls follow analogously with $K_{\text{control}}(t) = 1 - K(t)$.
2. Variances, covariances and means in generation t after selection

The proportion of cases after selection equals \( K^*(t) = \frac{(FR \cdot K(t))}{(FR \cdot K(t) + K_{control}(t))} \), the mean liability values \( \mu_{l^*}(t) = K^*(t)\mu_{l|case}(t) + (1 - K^*(t))\mu_{l|control}(t) \), and the mean genetic values \( \mu_{g^*}(t) = K^*(t)\mu_{g|case}(t) + (1 - K^*(t))\mu_{g|control}(t) \). The variance in liability follows as \( \sigma_{l*}^2 = K^*(t)\mu_{l|case}(t) + (1 - K^*(t))\mu_{l|control}(t) - \{K^*(t)\mu_{l|case}(t)(1 - K^*(t))\mu_{l|control}(t)\}^2 \), where \( \mu_{l|case}(t) = \sigma_{l|case}^2(t) + \mu_{l|case}(t) \). The variance in genetic effects after selection \( \sigma_{g*}^2 \) follows analogously to \( \sigma_{l*}^2 \).

3. Assortative mating: genetic spouse-correlation in generation t

Assortative mating is assumed to act on the liability with a spouse-correlation of \( \rho_{l^*} \), but the genetic consequences depend on the spouse-correlation in genetic effects, \( \rho_{g^*} \), which equals \( \rho_{l^*} \) times the proportion of liability explained by the genetic effects (R-squared of the regression of \( l^* \) on \( g^* \), \( r_{l^*-g^*}^2 \)). The covariance between \( l^* \) and \( g^* \) after selection equals \( \sigma_{g^*,l^*}(t) = K^*(t)\mu_{g|case}(t) + (1 - K^*(t))\mu_{g|control}(t) \) with \( \mu_{g|case}(t) = \sigma_{g|case}^2(t) + \mu_{g|case}(t) \) and \( \mu_{g|control}(t) = \sigma_{g|control}(t) + \mu_{g|control}(t) \). Consequently, the slope equals \( \beta_{l^*-g^*} = \sigma_{g^*,l^*}(t)/\sigma_{g^*}^2 \), the R-Squared \( r_{l^*-g^*}^2 = \beta_{l^*-g^*}^2 \cdot \sigma_{g^*}^2 / \sigma_{l^*}^2 \), and \( \rho_{g^*} = \rho_{l^*} \cdot r_{l^*-g^*}^2 \).

4. Properties in offspring (generation t+1)

The means in the offspring equal \( \mu_{l}(t + 1) = \mu_{g}(t + 1) = \mu_{g^*}(t) \), noting that the mean of environmental effects equals 0, the variance in genetic effects \( \sigma_{g}^2(t + 1) = \frac{1}{2} \sigma_{g}^2 + \frac{1}{2} \rho_{g^*} + \sigma_{seg}^2 \), and variance in liability \( \sigma_{l}^2(t + 1) = \sigma_{l}^2(t + 1) + \sigma_{e}^2 = \sigma_{g}^2(t + 1) + 1 - h_{l,base}^2 \). The meiotic segregating variance \( \sigma_{seg}^2 \) represents Mendelian variation and equals \( \frac{1}{2} \sigma_{g}^2 = \frac{1}{2} h_{l,base}^2 \) (see page 126-127 of Bulmer).\(^{24}\)

5. Validation of theory

When FR=0, our results are the same as those obtained with Equation 16.22 from Walsh and Lynch,\(^{25}\) and when FR=1, our results the same as those obtained with Equation 7.18 from Lynch and Walsh.\(^{27}\) Furthermore, we performed simulation for \( FR = 0.5 \), indicating that the above theory yields correct results (eTable 3). We simulated 10 generations starting with 1024 (\(2^{10}\)) founder samples each consisting of \(10^6\) individuals. An individual from generation 0 was simulated by
l = g + e, with g randomly drawn from $N(0, h_{l, base}^2)$, e from $N(0, 1 - h_{l, base}^2)$, from which disease status followed as $Y = 1$ for $l > T_{disease} = \phi^{-1}(1 - K_{base})$ and 0 otherwise. To simulate generation $t + 1$, the fathers and mothers were obtained from separate samples from generation $t$ to prevent inbreeding (thus reducing the number of samples from 1024 in generation 0 to 1 sample in generation 10). A proportion of $1 - FR$ of the affected individuals were excluded, all other individuals got exactly one offspring. The remaining mothers were matched to the remaining fathers by ranking them according to a vector $v = \rho_l l_{fathers} + w$, with w a vector randomly drawn from $N(0, \sigma_{l,fathers}^2 - \rho_l^{-2})$, thereby assuring that $\text{cor}(l_{fathers}^*, l_{mothers}^*) = \rho_l$. The genetic effects in the offspring generation $t + 1$ were defined by

$$g_{t+1} = \frac{1}{2} g_{fathers}^* + \frac{1}{2} g_{mothers}^* + \text{seg},$$

with seg representing meiotic segregation variation distributed as $N(0, \frac{1}{2} h_{l, base}^2)$.

Environmental effects e were randomly drawn from $N(0, 1 - h_{l, base}^2)$ to yield

$l = g + e$ and subsequently $Y$ for generation $t + 1$.

**eMethod 5. Simulating the consequences of assortative mating for a single genetic locus**

From theory, the impact of assortative mating on a genetic locus explaining 1% of variance (or less) is negligible. For example, for a spouse-correlation in liability of 0.3, the spouse-correlation at a locus explaining 1% of variance is approximated as

$$\text{correlation}_{\text{locus}} = h_{l,locus}^2 \times \text{correlation}_{\text{phenotype}} = 0.01 \times 0.3 = 0.003.$$  

None of the individual loci in psychiatry explain more than 1% of variance. As discussed by Witte et al, even the large effect CNVs in schizophrenia explain less than 1% of phenotypic variance, because these CNVs are very rare. In other words, the chance to be affected with a CNV is considerable, but the chance to have a CNV when affected is small. Hence, when two affected individuals mate, they are unlikely to both carry the same CNV, and even more unlikely to both transmit the same CNV to their offspring. As a consequence, the number of homozygotes is not expected to increase from assortative mating.

The anticipated negligible impact of assortative mating on single genetic loci was confirmed with a simulation study. Therefore, assortative mating was simulated as described above (without natural selection, i.e. FR=1). Here, the genetic values $g$ were simulated from individual loci. Fifty independent loci were simulated, all with MAF=0.5, twenty-five with an effect of 0.0991, and 25 with an effect of -0.0991 (thereby ensuring that all loci explained 1% of variance in liability, resulting in a heritability in the founder samples of $h_{l,base}^2 = 0.5$). An individual was simulated by randomly assigning the number of risk alleles per SNP.
with genotype probabilities of 0.25 (allele count 0, i.e. homozygous for the non-risk allele), 0.5 (allele count 1, i.e. heterozygous), and 0.25 (allele count 2, i.e. homozygous for the risk allele). The genetic liability followed as the product of the standardized allele counts and the effect: 

\[ g_{\text{individual}} = \sum_{\text{SNP}} \frac{\text{allele count}_i - 2 \tilde{\text{MAF}}}{\sqrt{2 \tilde{\text{MAF}}(1 - \tilde{\text{MAF}})}} \times \text{effect}_i = \sum_{\text{SNP}} \frac{\text{allele count}_i - 0.5}{\sqrt{0.5}} \times \pm 0.0991. \]

Partner-pairs were formed with a spouse-correlation in liability of \( \rho_l = 0.3 \) in line with the simulation described above, and offspring were simulated with random segregation per locus (e.g. fathers with respectively 2, 1 or 0 risk alleles gave 1 risk allele to their offspring with probabilities of respectively 100%, 50% and 0%). We simulated 10 generations starting with 1024 \( (2^{10}) \) founder samples each consisting of \( 10^5 \) individuals. Simulating 50 identical loci increased simulation accuracy. For a step-by-step description of simulation of individual loci, we refer to the legend of Table S4 from Peyrot et al.\textsuperscript{30}

From this simulation study, we found that the additive genetic variance increased over generations as expected from theory \( (0.5 \) in base generation; \( \sim 0.537 \) in generation 1; \( \sim 0.597 \) in generation 10), which was attributable to a build up of correlation between effective loci. The number of homozygotes increased from 0.25 in the base generation to 0.2504 in generation 1 to stabilize around 0.2505 in generations 2 to 10. This confirms the negligible impact of assortative mating on the genotype frequency of individual loci.

**eMethod 6. Modeling the theoretical expectation when partner resemblance would be attributable to assortative mating on the observed scale (disorder-status)**

In the derivation above we have assumed that partner resemblance is attributable to assortative mating on the liability scale. Here, we assume that partner resemblance is attributable to assortative mating on the observed disorder-scale. Under this assumption, the partner pairs are divided in four categories: father affected - mother unaffected (FAMa), unaffected-affected (FMa), affected-unaffected (FMu), and unaffected-unaffected (FMu), the frequencies \( P(F,M) \) of which follow from the odds ratio to be affected as partner of an affected individual. We assume random mating within these four categories. The offspring of these categories of partner-pairs have genetic variance 

\[ \sigma^2_{g, \text{offspring of } F,M} = \frac{1}{4} \sigma^2_{g,F} + \frac{1}{4} \sigma^2_{g,M} + \sigma^2_{\text{Seg}}, \]

and genetic mean 

\[ \mu_{g, \text{offspring of } F,M} = \frac{1}{2} \mu_{g,F} + \frac{1}{2} \mu_{g,M}. \]

We note that the meiotic segregating variance equals \( \sigma^2_{\text{Seg}} = \frac{1}{2} h^2_{I,\text{base}} \), and is unaffected by selection under the
infinitesimal model.\textsuperscript{31} The genetic mean and genetic variance in affected and unaffected parents were given above. The genetic mean in the offspring generation equals \( \mu_{g,\text{offspring}} = \sum_{x=U; y=U} P(F_x M_y) \mu_{g,\text{offspring of } F_x M_y} = 0 \). The genetic variance in the offspring generation equals \( \sigma^2_{g,\text{offspring}} = \mu^2_g - (\mu_g)^2 = \sum P(F_x M_y) \mu_{g,\text{offspring of } F_x M_y} - \sum P(F_x M_y) (\mu_{g,\text{offspring of } F_x M_y})^2 \), where we note that \( \mu_{g,\text{offspring of } F_x M_y} = \sigma^2_{g,\text{offspring of } F_x M_y} + \mu_{g,\text{offspring of } F_x M_y} \). This derivation for one generation of assortative mating was validated with a straightforward simulation study (eTable 5). eFigure 3 and eFigure 4 compare the consequences of partner resemblance attributable to assortative mating based on the observed scale to partner resemblance attributable to assortative mating based on the liability scale. It can be seen that the consequences are more pronounced for assortative mating based on the liability scale. This indicates that the consequences presented in the main paper provide upper boundaries.
### Table S1. Approximation of tetrachoric correlation in terms of the full population based on findings from Nordsletten et al

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mean from Nordsletten et al</th>
<th>Method 1 (K literature)</th>
<th>Method 2 (K literature -&gt; mated)</th>
<th>Method 3 (K from P, OR, tetra)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>OR</td>
<td>Tetra CC</td>
<td>K</td>
</tr>
<tr>
<td>ADHD</td>
<td>0.167</td>
<td>7.20</td>
<td>0.45</td>
<td>4.6e-02</td>
</tr>
<tr>
<td>ASD</td>
<td>0.167</td>
<td>10.81</td>
<td>0.47</td>
<td>1.2e-03</td>
</tr>
<tr>
<td>SCZ</td>
<td>0.167</td>
<td>7.30</td>
<td>0.42</td>
<td>8e-03</td>
</tr>
<tr>
<td>BIP</td>
<td>0.167</td>
<td>2.00</td>
<td>0.15</td>
<td>6.1e-03</td>
</tr>
<tr>
<td>DEP</td>
<td>0.167</td>
<td>1.84</td>
<td>0.16</td>
<td>3.4e-02</td>
</tr>
<tr>
<td>GAD</td>
<td>0.167</td>
<td>2.64</td>
<td>0.19</td>
<td>1.7e-05</td>
</tr>
<tr>
<td>AGO</td>
<td>0.167</td>
<td>3.56</td>
<td>0.24</td>
<td>2.7e-06</td>
</tr>
<tr>
<td>SOC</td>
<td>0.167</td>
<td>3.75</td>
<td>0.27</td>
<td>4.9e-06</td>
</tr>
<tr>
<td>OCD</td>
<td>0.167</td>
<td>2.42</td>
<td>0.17</td>
<td>2e-02</td>
</tr>
<tr>
<td>SUB</td>
<td>0.167</td>
<td>3.87</td>
<td>0.37</td>
<td>2.4e-02</td>
</tr>
<tr>
<td>ANO</td>
<td>0.167</td>
<td>3.10</td>
<td>0.18</td>
<td>1.4e-03</td>
</tr>
</tbody>
</table>

See methods for description of Method 1, Method 2, and Method 3. Mean from Nordsletten et al refers to the mean of estimates in male and female. For Method 1 and Method 2, the population prevalences (K) were based on Power et al for SCZ, BIP, ASD, ANP, SUB, DEP, Li et al for GAD, AGO and SOC, Rücks et al for OCD,5 and Pinto et al for ADHD. P=study proportion of cases amongst those with partner (always matched 1:5); Tetra CC= tetrachoric correlation from cases control sample with oversampling of cases with P; Tetra pop=tetrachoric correlation approximated in terms of the full population.
Assortative mating
### Table S2. Overview of literature on psychiatric assortative mating

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Correlation</th>
<th>OR</th>
<th>Instrument</th>
<th>Short description of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>0.02</td>
<td></td>
<td>Conners’ Adult ADHD Rating Scales (CAARS)</td>
<td>121 families with at least one ASD offspring</td>
<td>Van Steijn 2012</td>
</tr>
<tr>
<td>ADHD</td>
<td>0.11</td>
<td></td>
<td>Conners’ Adult ADHD Rating Scales (CAARS)</td>
<td>4560 parents from population sample</td>
<td>Boomsma 2010</td>
</tr>
<tr>
<td>ANX</td>
<td>0.17</td>
<td></td>
<td>Spielberger State Trait Anxiety Inventory</td>
<td>881 partner pairs from population sample</td>
<td>Grootheest 2008</td>
</tr>
<tr>
<td>ANX</td>
<td>0.208/-0.014</td>
<td></td>
<td>Struct. Clin. Interview for DSM-III-R (SCID)</td>
<td>Two samples with parents from 1442 twins/ 2163 twins respectively</td>
<td>Maes 1998</td>
</tr>
<tr>
<td>GAD</td>
<td>0.15</td>
<td></td>
<td>Padua inventory</td>
<td>875 partner pairs from population sample</td>
<td>Grootheest 2008</td>
</tr>
<tr>
<td>OCD</td>
<td>0.13</td>
<td>2.61</td>
<td>ICD disease codes</td>
<td>120,697 partner pairs from Swedish population register</td>
<td>Mataix-Cols 2013</td>
</tr>
<tr>
<td>ANX PD</td>
<td>0.219/0.138</td>
<td></td>
<td>Struct. Clin. Interview for DSM-III-R (SCID)</td>
<td>Two samples with parents from 1442 twins/ 2163 twins respectively</td>
<td>Maes 1998</td>
</tr>
<tr>
<td>ANX SAD</td>
<td>0.21</td>
<td>4.01</td>
<td>ICD disease codes</td>
<td>103,875 partner pairs from Swedish population register</td>
<td>Isomura 2015</td>
</tr>
<tr>
<td>ANX</td>
<td>0.05-0.06 (a)</td>
<td>1.2</td>
<td>Schedule for Aff Dis and Schizophrenia (SADS)</td>
<td>255 spouse of cases with substance and/or anxiety disorder (PD/SAD)</td>
<td>Low 2007</td>
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<tr>
<td>ANX</td>
<td>0.04</td>
<td></td>
<td>Fear Questionnaire tagging three phobia domains</td>
<td>708 spouses of twins from the Netherlands aged 25-30</td>
<td>Distel 2007</td>
</tr>
<tr>
<td>ASD</td>
<td>.29</td>
<td></td>
<td>Social Responsiveness Scale (SRS)</td>
<td>Parents from 285 twin pairs from general population</td>
<td>Constantino 2005</td>
</tr>
<tr>
<td>ASD</td>
<td>.26</td>
<td></td>
<td>Social Responsiveness Scale (SRS)</td>
<td>99 partner pairs from clinical ASD sample</td>
<td>Virkud 2009</td>
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Table S2. (continued)

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Table S2 displays an overview of studies that provide estimates of partner resemblance expressed in terms of a correlation estimate (for continuous instruments or tetrachoric correlation for diagnosis), or odds ratio (OR) or relative risk (RR). Some studies provided an OR as well as the tetrachoric correlation, but some presented only an OR/RR that we transformed to a tetrachoric correlation (labeled with (a)) to increase comparability and aid interpretation of the genetic consequences. ADHD= attention-deficit/ hyperactivity disorder; ANX=anxiety symptoms/disorder; GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; SAD=social anxiety disorder; ASD=autism spectrum disorder; BIP=bipolar disorder; MDD=major depressive disorder; SCZ=schizophrenia. Identified by PubMed search ("assortative mating" AND (psychiatry OR depression OR schizophrenia OR anxiety OR ocd OR adhd OR autism OR bipolar)), and selected to comprise at least around hundred partner pairs and publication date after 1990, and excluding the recently published Nordsletten estimates.
Table S3. Assortative mating vs selection: theory and simulation agree

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Table S4. Assortative mating versus selection for a disorder such as autism \( (K=0.0015, h^2=0.8, \text{phenotypic assortment}=0.28, \text{fecundity ratio}=0.35) \)

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Table S5. Assortative mating on the observed scale: theory and simulation agree

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The consequences of partner resemblance attributable to assortative mating on the observed scale where theoretically derived and validated with a simulation study. Simulation was repeated ten times per parameter setting. The means are presented with the standard error of the point estimates between brackets.
Figure S1. Ten generations of assortative mating: increase in additive genetic variance ($V_A$) and heritability ($h^2_t$). The expected increase in additive genetic variance from ten generation of assortative mating is displayed against the heritability in the generation 0, expressed as the absolute increase (tenth generation – generation 0) and relative increase (100*(tenth generation – generation 0)/ generation 0), for partner-correlation in liability of 0.1, 0.2, 0.3 and 0.4 respectively. The presented increase depends on the assumptions discussed in the main manuscript, and that generation 0 is the first to exhibit patterns of assortative mating.
Figure S2. Ten generations of assortative mating: increase in population prevalence. The expected increase in population prevalence (K) from ten generation of assortative mating expressed as 100% * \[
\left[ K_{10th\, generation} - K_{generation\, 0} \right] / K_{generation\, 0}
\] is displayed against the parental heritability for a prevalence in generation 0 of K=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 the assumptions discussed in the main manuscript, and that generation 0 is the first to exhibit patterns of assortative mating.
Figure S3. Heritability increase from one generation of assortative mating on observed scale. The main results are based on the assumption that partner resemblance is attributable to assortative mating based on the liability scale. Here, the consequences are displayed for assortative mating on the observed scale (disease-status) with $r_{tetr} = 0.3$. The increase in heritability is more pronounced when assortative mating is based on the liability scale than on the observed scale. Hence, assuming assortative mating based on the liability helps to provide upper boundaries of the genetic consequences.
Figure S4. Prevalence increase from one generation of assortative mating on observed scale. The main results are based on the assumption that partner resemblance is attributable to assortative mating based on the liability scale. Here, the consequences are displayed for assortative mating on the observed scale (disease-status) with $r_{tetra} = 0.3$. The increase in population prevalence is more pronounced when assortative mating is based on the liability scale than on the observed scale. Hence, assuming assortative mating based on the liability helps to provide upper boundaries of the genetic consequences.
REFERENCES


http://nitro.biosci.arizona.edu/zbook/NewVolume_2/newvol2.html#2B).