HHS Public Access

Author manuscript

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2019 June ; 180(4): 249–257. doi:10.1002/ajmg.b.32720.

Parent-offspring transmission of drug abuse and alcohol use disorder: Application of the multiple parenting relationships design

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Abstract

With complete genealogical and cohabitation information, new genetic-epidemiological designs can be developed to clarify causes of parent-offspring transmission. We propose the *Multiple Parenting Relationships (MPR) Design* and apply it to drug abuse (DA) and alcohol use disorder (AUD). Using national Swedish registries, we identified four kinds of informative parents with multiple children with whom they had different genetic and/or rearing relationships. These types had children for whom they provided: (a) genes (G) plus rearing (R), G only and R only; (b) G + R and G only; (c) G only and R only; and (d) G + R and R only. We identified DA and AUD cases from national registries in over 475,000 informative parent-offspring pairs. Controlling for parental resemblance for DA or AUD, all estimates were statistically homogeneous across family types. The weighted average tetrachoric correlation (SE) for DA for G + R, R only and G only relationships were, respectively, +0.21 (0.01), +0.10 (0.02), and +0.16 (0.02). Parallel results for AUD were +0.16 (0.01), +0.04 (0.02), and +0.14 (0.01). Analyses within families with affected parents showed significantly higher disorder risks in offspring with a G + R versus an R only relationship. The MPR design is complementary to other methods, especially adoption and triparental designs, in clarifying the sources of cross-generational transmission. Consistent with

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

results from these other designs applied to the Swedish population, we find that for DA and AUD, parent-offspring resemblance was strongest for G + R relationships, intermediate for G only relationships and weakest but significant for R only relationships.

Keywords

alcohol use disorders; cross-generational transmission; drug abuse; genetic epidemiology; parent-offspring resemblance

1 | INTRODUCTION

Over the last several decades, psychiatric genetic epidemiology has, through the rapid growth in the number and size of twin registries, focused largely on clarifying the contributions of genetic and environmental factors to familial aggregation within generations (Polderman et al., 2015). Understanding the sources of cross-generational transmission has been more challenging with most efforts utilizing the potentially elegant adoption design. Adoptions have become increasingly rare in Western countries. Furthermore, adoption studies typically have several potential methodological limitations including nonrandom placement of adoptees, frequent missing information on biological fathers, and adoptive parents typically screened for mental health (Cadoret, 1986).

Other methods for studying cross-generational transmission—including the examination of offspring of twins or siblings (Jundong et al., 2012; McAdams et al., 2014; Silberg, Maes, & Eaves, 2012) and children of mothers with egg donations (Thapar et al., 2009)—have been increasingly widely implemented in recent years.

With the increasing availability to researchers of complete population registries in Scandinavian countries, further approaches to disentangling the sources of parent-offspring resemblance have become available. While no design is without its biases, ideally the biases involved are different from those of other methods such as the adoption design.

We recently proposed one such design: *the triparental family* (Kendler, Ohlsson, Sundquist, & Sundquist, 2015). These families are identified by selecting offspring with three kinds of parents: (a) a biological parent who reared them; (b) a biological parent with whom they had minimal post-natal contact (a “not-lived-with” parent); and (c) a step-parent. Such a design is appealing because, to a first approximation, these three parents provide their offspring, respectively, “genes + rearing,” “genes only,” and “rearing only.” We will use the abbreviations “G + R”, “G only,” and “R only” for such parent-offspring relationships.

In this article, we propose and implement a distinct but complementary approach which we call the *Multiple Parenting Relationships* (MPRs) design. Unlike the triparental family design which begins with children, the MPR design begins with parents. From the general population sample, we identify parents with multiple children with whom they have different genetic and/or rearing relationships. That is, the parents are either genetically related or unrelated to their child and step-child, respectively, and either rear the child (defined as residing in the same household for ≥5 or ≥10 of the child’s first 15 years) or never live with

or near the child. Four possible kinds of such parents exist in the MPR. The four types have children for whom they provided: (a) G + R, G only, and R only; (b) G + R and G only; (c) G only and R only; and (d) G + R and R only.

We illustrate the latter three parental types in plainer language. The “G + R and G only” parent has at least two biological children one of whom he raised and the other he did not. The “G only and R only” parent would have at least one biological child he did not raise and one step-child whom he did raise. The “G + R and R only” parent has at least one biological child and one step-child both of whom he reared.

Utilizing the MPR design in a nationwide Swedish sample, we then examine the nature of the cross-generational transmission of drug abuse (DA) and alcohol use disorder (AUD) ascertained from official nation-wide registries. These disorders are of particular interest because of prior evidence of complex familial transmission involving both genetic and familial-environmental processes (Cadoret, Troughton, O’Gorman, & Heywood, 1986; Cloninger, Bohman, & Sigvardsson, 1981; Tsuang et al., 1996; Verhulst, Neale, & Kendler, 2015). We studied these disorders using the triparental family (Kendler, Ohlsson, et al., 2015) and found that for both syndromes, parent-offspring resemblance was strongest from the biological rearing parent who provided G + R, intermediate for not-lived-with father who provided only G, and weakest but still significant for step-fathers who provided only R.

As with triparental families, the MPR design permits correlational analyses examining the association between parents and specific kinds of offspring. In addition to being parent rather than child-ascertained, the MPR design differs from the triparental design in two other ways. First, the triparental design includes only one family type while the MPR design includes four different types. The MPR therefore permits a test of equivalence of relationships across family types by examining the heterogeneity of estimates of G + R, R only, and G only in different family constellations. Second, unlike the triparental families, the MPR design supports contrastive analyses where we can examine, within a single-family type, differences in risk across different types of offspring. For example, for a “G + R and R only” parent who has DA, we can compare the risk for DA in their biological child and step-child both of whom he raised. These results produce, by that contrast, an index of the importance of genetic effects on parent-offspring resemblance.

2 | METHODS

We used linked data from multiple Swedish nationwide registries and healthcare data with linking achieved via the unique individual Swedish 10-digit personal ID number assigned at birth or immigration to all Swedish residents. This ID number was replaced by a serial number to preserve confidentiality. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

DA was identified in the Swedish medical registries by ICD codes (ICD8: Drug dependence (304); ICD9: Drug psychoses (292) and Drug dependence (304); ICD10: Mental and behavioral disorders due to psychoactive substance use (F10-F19), except those due to alcohol (F10) or tobacco (F17)); in the Suspicion Register by codes 3070, 5010, 5011, and

5012, that reflect crimes related to DA; and in the Crime Register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offenses (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). DA was identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (in average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (Anatomical Therapeutic Chemical [ATC] Classification System N05C and N05BA) or Opioids (ATC: N02A). DA was treated as dichotomous variable (any registration vs. no registration) with an assumed underlying normal liability distribution.

AUD was identified in the Swedish medical and mortality registries by ICD codes: ICD9: V79B, 305A, 357F, 571A-D, 425F, 535D, 291, 303, 980; ICD 10: E244, G312, G621, G721, I426, K292, K70, K852, K860, O354, T51, F10; in the Crime Register by codes 3005, 3201, which reflect crimes related to alcohol abuse; in the Suspicion Register by codes 0004, 0005 (Only those individuals with at least two alcohol-related crimes or suspicion of crimes from both Crime Register and Suspicion Register were included); in the Prescribed Drug Register by the drugs disulfiram (Anatomical Therapeutic Chemical [ATC] Classification System N07BB01), acamprosate (N07BB03), and naltrexone (N07BB04). AUD was treated as dichotomous variable (any registration vs. no registration) with an assumed underlying normal liability distribution.

2.1 | Sample

The database was created by entering all individuals born in Sweden between 1960 and 1990 who resided in Sweden at age 15. Based on information from the Swedish population registers, we calculated the number of years, from ages 0 to 15, that the individual resided in the same household and the same geographical area as their mother, father, possible step-mother, and possible step-father.

Household was defined as follows: From 1960 to 1985 (every fifth year) we used Household ID from the Population and Housing Census. The Household ID includes all individuals living in the same dwelling. For the years we did not have information, we approximated the Household ID with the information from the year closest in time. From 1986 and onward (every year) we used the Family ID from the Total Population Register. The Family ID is defined by individuals that are related or married and who are registered at the same property (a person can only be part of one family). In addition, adults who are registered at the same property and have common children, but are not married, are registered in the same family. This means that, during the period 1986 and onward, for an offspring living with his/her mother, we only capture the step-father if he is either married with the mother to the offspring and/or having a common child together with the mother of the offspring.

Geographical area was defined based on Small Areas for Market Statistics (SAMS) that are small geographical units defined by Statistics Sweden, the Swedish government-owned statistics bureau. There are approximately 9,200 SAMS throughout Sweden, their average population being around 1,000. From 1960 to 1970 we had no information on SAMS areas, therefore we used parishes as a proxy for SAMS for these years. The parishes serve as districts for the Swedish census and elections and have approximately the same number of

inhabitants as SAMS areas. From 1960 to 1970 we only had information every fifth year and for that reason we approximated the geographical status with the information from the year closest in time.

From this database we selected four types of parents: (a) G + R, G only, and R only: a parent with at least one biological child whom he raised (G + R), at least one biological child whom he did not raise (G) and at least one step-child whom he raised (R); (b) G + R and G only: a parent with at least one biological child whom he raised (G + R), and at least one biological child whom he did not raise (G); (c) G only and R only: a parent with at least one biological child whom he did not raise (G) and at least one step-child whom he raised (R); and (d) G + R and R only: a parent with at least one biological child whom he raised (G + R), and at least one step-child whom he also raised (R). We also required that parent was alive and residing in Sweden in the year 1975.

We used two definitions of parental rearing in our analyses. The first defined parental rearing as residing in the same household for at least 5 years during the ages 0–15 of the child, while in the second we defined it as at least 10 years. In both analyses, the G-only relationship (i.e., biological child whom the parent did not raise) was defined as never living either in the same household or in the same geographical area when the child was 0–15 years of age.

In the first analysis utilizing the MPR design, we examined the tetrachoric correlation between parental DA (AUD) and DA (AUD) in specific kinds of offspring while adjusting for year of birth and sex of the offspring. In the second model, we also included DA (AUD) in the other biological parent(s). In situations where there were two other biological parents (for “R only” children [step-children]) the DA (AUD) in the other biological parent was defined as DA (AUD) in any of the two biological parents. In these models, we could study all three correlations in the “G + R, G only, and R only” sample (i.e., the parent-offspring correlation when a biological parent raised the child, the parent-offspring correlation when a biological parent did not raise the child and the parent-offspring correlation when a step-parent raised the child). In the other three samples, we could study two types of correlations. We used the Mantel–Haenszel meta-analysis method to combine the results from the different samples.

In the next step, we used stratified Cox proportional hazards models to investigate the future risk for DA (AUD) in offspring as a function of the type of relation between parent and offspring (i.e., G + R, G only, or R only). In this model, only parents with DA (AUD) were included. For example, within the “G + R, G only” sample, we obtained one Hazard ratio (HR) that illustrated the increased risk for DA (AUD) among biological children whom the parent (that was registered for DA) raised versus biological children whom they did not raise. Follow-up time in number of years was measured from age 15 of the child until year of first registration for DA, death, emigration or end of follow-up (year 2012), whichever came first. In all models, we investigated the proportionality assumption. When using stratified Cox models in a sample like ours, the HR will, within each stratum (i.e., within each parent), be adjusted for a range of unmeasured shared factors that is complicated to control for in studies using children from different parents. In the first model, we only

included year of birth and sex of the offspring while in the second model we also included DA (AUD) in the other parent. To combine the results from the different samples, we used the Mantel–Haenszel meta-analysis method. All statistical analyses were performed using SAS 9.4 (SAS Institute, 2012) and Mplus software (Muthén & Muthén, 2015).

3 | RESULTS

Key descriptive statistics for the informative families in the MPR design, utilizing our two definitions of rearing, are presented in Table 1. Across both rearing definitions, the most common parental type was G + R and R only, followed by G + R and G only, and G + R, R only, and G only. R only and G only parents were the rarest. All parental types were preponderantly male. With respect to rates of disorders in the parents, AUD was more common across all types than DA while the opposite was seen in the offspring. This pattern likely arises as a result both from increasing rates of DA in Sweden over this time period (Giordano et al., 2013) and an earlier age at registration for DA than AUD in the Swedish population. Compared to the general population, rates of both DA and AUD were elevated in the G + R, R only, and G only, G + R and G only and especially R only and G only parents. However, they were modestly reduced in the G + R and R only parents. Compared to general population figures, rates of both DA and AUD were increased in offspring of all family types and in the parents of all family types except G + R and R only families.

The results of our correlational analyses of parent-offspring resemblance for our three types of relationships (G + R, R only, and G only) across each parental type and then the weighted average across all parental types are presented in Table 2. (Parallel results using HRs are presented in Supporting Information Tables 1 and 2). We present correlations controlling for year of birth and sex of the offspring and then add, as a covariate, the presence or absence of the relevant disorder (DA or AUD) in other biological parents. Six results are noteworthy. First, the parent–child resemblance for the G + R or R relationships did not systematically differ when rearing was defined as a minimum of 10 years of cohabitation during the first 15 years of the child's life versus a minimum of 5 years. Second, no statistical evidence for heterogeneity was seen in estimates of parent-offspring resemblance across any of the parental types for DA or AUD. This is an important validating finding suggesting the strength of the broad sources of parent-offspring resemblance (i.e., genes and rearing effects) is not sensitive to family context. Third, focusing therefore on the weighted averages across both DA and AUD and both definitions of rearing, a consistent relationship is seen in the strength of parent-offspring resemblance across different relationship types. In all analyses, the G + R relationships were the strongest, the G only relationships intermediate and R only relationships the weakest. However, all these correlations were statistically significant, often substantially so. Fourth, across our three kinds of relationships, parent-offspring resemblance was consistently stronger for DA than for AUD. This difference was most marked for rearing only relationships. Fifth, as expected, parent-offspring resemblance for both disorders across all types of relationships was weaker when we controlled for the occurrence of the relevant disorder in the other biological parent(s). The proportional impact on the parent-offspring correlations was greatest for the rearing only relationship. Sixth, across all analyses, the sum of the parent-offspring correlations for the G-only and R-only relationships exceeded that seen for the G + R relationships.

Table 3 presents the sample sizes available for the contrastive relationships in the MPR design which could only be done with parents who are affected with DA or AUD. Tables 4 and 5 present the results of these analyses for DA and AUD, respectively. Sample sizes were often relatively small and analyses therefore of limited power. We focus here on the weighted averages for the analyses controlling for spouse diagnoses which were statistically homogeneous in 11 of the 12 analyses. Within families, parent-offspring resemblance for DA and AUD were both statistically stronger for G + R than for R only relationships with HRs approximating 1.30 for DA and 1.45 for AUD. Surprisingly, for DA, the other contrasts (G + R vs. G only and G only vs. R only) produced nonsignificant HRs with estimates close to unity. For AUD, the G only versus R only contrast, defining rearing at ≥5 years cohabitation, produced a significant HR of 1.26. The other G + R versus G only and G only versus R only contrasts were close to unity and nonsignificant.

4 | DISCUSSION

The initial goal for this report was to introduce the MPR design to assess the sources of parent-offspring transmission. This design has five important strengths. First, informative parent-offspring combinations are relatively common. Examining the birth years 1960–1990 and using our broad and narrow definitions of rearing (5 and 10 years of cohabitation, respectively), utilizing the MPR design we identified, respectively, over 475,000 and 290,000 informative parent-offspring pairs. This compares to 18,115 adoptees found in Sweden over the same period (Loeber & LeBlanc, 1990). Second, the legal and confidentiality issues that typically surround adoptions and which outside of Scandinavia have substantially limited adoption research do not apply to the families studied in this design. Third, the atypicality of adoptive parents is an important methodological limitation of adoption studies (Cadoret, 1986). In Sweden and most other Western countries, adoptive parents are selected for high levels of income and education, and low rates of psychopathology and substance abuse (Bohman, 1970). This reduction in the level and variation of environmental adversity in adoptive homes could produce an underestimation of impact of rearing effects. Contrary to adoptive parents in Sweden, which have levels of AUD and DA lower than the general population (Kendler et al., 2012; Loeber & LeBlanc, 1990), the step-fathers in MPR families have rates of substance misuse more representative of the general population. This could result in more generalizable estimates of the rearing effects than might be obtained from adoption designs. Fourth, like adoption studies, MPR families provide direct assessments of genes only and rearing only parent–child relationships. But, unlike adoption samples, and similar to the triparental family design, the MPR design also provides indirect assessments of genes-only and rearing-only effects. Assuming additivity, an estimate of genes-only and rearing-only effects can be obtained from the MPR design by examining the difference between G + R and, respectively, R only and G only parent-offspring relationships. Finally, unlike both the adoptive and triparental designs, the MPR design permits contrastive relationships between children of the same parent who have a differing kind of relationship to that parent. Although poorly powered for traits that are rare in parents, this is an elegant design because it controls for all parental characteristics across the different parent-offspring relationships.

However, the MPR design has two noteworthy limitations. First, fathers are much more likely than mothers to have multiple kinds of parenting relationships with their children. Therefore, the large preponderance of parents contributing to the MPR design is men. We did examine whether the magnitude of the G + R, R only, and G only relationships differed for DA and AUD in mother-offspring and father-offspring pairs. As seen in Supporting Information Table 3, they did not. Second, all but the G + R and R families could be considered “disrupted” and members have considerably higher rates of externalizing syndromes of DA and AUD than do members of the general population. However, these prevalence differences are modeled appropriately in the calculations of the tetrachoric correlations which take proper account of differences in threshold location.

The second goal of this report was to utilize the MPR design to further clarify the sources of cross-generational transmission for DA and AUD. Congruent with the results from the triparental family design, we found for both AUD and DA that the strongest parent-offspring resemblance was found with the G + R relationship, followed by the G only relationship, with the R only relationship the weakest. It is of interest to compare the results from the MPR design (assuming rearing requires at least 10 years of cohabitation) to those found previously from adoption and triparental designs in Sweden. We present these results in Table 6, using HRs or the very similar statistic odds ratios (ORs) as these statistical approaches were used in our prior publications (Kendler et al., 2012; Kendler, Ohlsson, et al., 2015; Loeber & LeBlanc, 1990). Looking first at genetic effects, for DA, the aggregate HR for the G-only relationship from the MPR design was 2.17 (1.92–2.46). This was similar to that found from biological parents in the adoption design and not-lived-with father from the triparental design, and no evidence for significant heterogeneity was detected. The weighted average across these three samples was 2.27 (2.09–2.47). For AUD, the estimate for G-only relationships from the MPR design was 1.80 (1.66–1.95). This was quite close to that obtained from the triparental design but higher than that seen from our adoption study. We found for this analysis significant between-design heterogeneity with a weight average estimate of 1.75 (1.66–1.85). Turning to environmental parent-offspring transmission, the aggregate HR for the R-only relationship from the MPR design for DA was 1.72 (1.43–2.07) which was relatively close to that estimated from the adoption and triparental designs. No evidence of between design heterogeneity was seen and the weighted average estimate was 1.79 (1.55–2.07). Finally, the R-only relationship with AUD from the MPR design was estimated at 1.24 (1.11; 1.40) and was close to that obtained with the adoptive and triparental designs with a nonsignificant test of heterogeneity. The weighted across-design estimate was 1.27 (1.14–1.41).

Much attention has recently been paid to the “replication crisis” in the psychological sciences (Lilienfeld, 2017). An important distinction has been made between direct or exact replication (an attempt to repeat a study in a manner as close to the original as possible) and conceptual replications which try to test the same theoretical process as a prior study but importantly use at least partially different methods with recent authors suggesting that conceptual replications are ultimately of more value to the field (Crandall & Sherman, 2016; Schmidt, 2009). This is because obtaining the same general results from different methods is a more powerful confirmation of the original findings than getting the same results repeating the exact same study again. We suggest that our effort to examine the nature and causes of

cross-generational transmission in adoption, triparental and, now, MPR designs is an example of conceptual replications. Obtaining similar, albeit not identical, findings from these different methods substantially increases our confidence in the validity of our results.

Our presentation of parent-offspring correlations both ignoring and taking into account the diagnostic status of the other parent deserves comment. If the parental correlation in risk for AUD or DA was entirely the result of assortative mating, then it is probably correct to account for diagnoses in the spouse. Otherwise parent-offspring resemblance would be over-estimated by including the "path" of liability from parent to spouse to child. But if the correlation between spouses results from direct causal effects—that is one spouse's substance abuse increasing risk for abuse in the partner—then accounting for diagnoses in the spouse might downwardly bias parent-offspring resemblance. The truth is probably somewhere in the middle, as evidence suggests that spousal resemblance for DA and AUD in Sweden likely results from both assortative mating and direct causal effects (Kendler, Lönn, Salvatore, Sundquist, & Sundquist, 2018; Kendler, Ohlsson, Sundquist, & Sundquist, 2013).

Our correlational analyses using the MPR design suggested for DA and perhaps for AUD that genetic and rearing effects were not acting additively in their impact on parent-offspring resemblance. Indeed, we saw some evidence of a *negative* gene–environment interaction in that the total effect of genes and environment in G + R parent-offspring pairs was consistently less than what would have been predicted from the G only and R only relationships. This was somewhat surprising and meant that, utilizing tetrachoric correlations, the direct and indirect estimates of genetic and rearing effects from the MPR design do not agree well. For example, examining our weighted correlations assuming our narrow definition of rearing, direct estimates of R and G for DA are, respectively, +0.10 and 0.16. However, the indirect estimates (obtained by subtracting from the correlations for the G + R relationships the correlations, respectively, of the G only and R only relationships) are much lower, estimated at +0.05 and +0.11. We do not currently have a good explanation for this finding as our prior analyses in adoption samples, using a linear probability regression model, showed for DA evidence for a positive gene–environment interaction (Kendler et al., 2012) and for AUD additive effects (Loeber & LeBlanc, 1990). Interaction analyses are sensitive to the scale of measurement (Kendler & Gardner, 2010) and it is possible that our different analytic models, which in the adoption design included other indices of genetic and environmental risk, are contributing to these discrepant results.

We did not find, using our two definitions of rearing, an association between the length of cohabitation between parents and children and the strength of the association in risk for DA and AUD. We have no clear explanation for this finding although it is consistent with unpublished observations from other parent-offspring designs in the Swedish population. Only further research in this and other samples can help us understand better the nature of this relationship.

Finally, a strength of the MPR design is that it can be analyzed in two ways—as overall correlations and as within family contrasts. However, while these two methods replicated well for the most divergent of our relationships (G + R vs. R only), their performance for the

other two contrasts (G + R vs. G only and G only vs. R only) were less consistent with the aggregate correlational analyses showing clear differences. In the eight relevant contrastive analyses (Tables 4 and 5), only one was significant and the other seven were very close to unity. We have no ready explanation for this trend. However, the contrastive relationships, although certainly controlling better for parental characteristics, were much less powerful statistically as only families with affected parents could be included.

5 | LIMITATIONS

These results should be interpreted in the context of six potentially important methodological limitations. First, our results are obtained in Sweden and may or may not extrapolate to other countries. Second, while ascertaining cases of DA and AUD from registries data has important advantages (e.g., independence from subject cooperation and accurate recall and reporting), it also has significant limitations. There are surely individuals who are false negatives for DA and AUD who abuse substances but avoid medical attention or get into legal difficulties. However, the validity of our detection of these syndromes is supported by evidence for strong associations of cases detected from our different registries. The mean OR for case detection of DA across our relevant registries was 52 (Kendler et al., 2012) and for AUD was 33 (Kendler et al., 2015).

Third, we set 10 years as a minimum duration of cohabitation for step-parents and children because the sample sized declined precipitously with longer periods. Therefore, we were not able to match precisely for duration of rearing in the G + R and R-only parents. This could lead to an underestimation of the rearing effect obtained from R-only parents. However, the fact that we see little difference in parent–child resemblance in the R-only parents with a minimum of 5 and 10 years of contact suggest that such a bias is not likely to be large. Fourth, we have, in this article, assumed that the MPR and triparental samples were independent of each other. However, there must be some sample overlap as some of the children from triparental families would be expected to be included in our MPR design. Examining our smaller MPR sample (rearing defined as ≥10 years of cohabitation), 10% of the offspring were also in triparental families. So, the overlap of these two designs in the Swedish population is quite modest.

Fifth, our informative families were not fully representative of all Swedish families with most of our parents having rates of DA and AUD higher than the general population. This is an opposite problem from that seen with adoptive parents in adoption designs who have lower rates of such disorders due to the screening of adoption agencies (Kendler et al., 2012; Loeber & LeBlanc, 1990).

Finally, was it possible that offspring of families with a G-only parent–child relationship often cohabited with biological relatives of this parent, hence producing indirect rearing effects? Given G-only relationship between a parent and a child, 98.0% of the time the children never resided with biological relatives of this G-only (i.e., “not-lived-with”) parent. When they did live with such relatives, the contact was often brief and in 63% of cases occurred after the child was 11 years of age or older.

6 | CONCLUSIONS

With detailed information about genetic relationships and cohabitation histories, it is possible in general populations to select a range of family relationships that are informative about the sources and magnitude of cross-generational transmission outside of formal adoption studies. We proposed a new genetic epidemiological design, termed the MPRs design. The study relies on the identification of parents who have multiple children with whom they have different combinations of genetic and rearing relationships. We showed that sample sizes for this design in Sweden were substantial and much larger than those found for adoptions. We applied this design to AUD and DA showing, consistent with prior studies utilizing adoption and triparental designs, that resemblance for both these disorders was strongest when parents were both genetically related to and reared their children, next strongest when they only had a genetic relationship with them and weakest when they only reared them. Given the nonexperimental nature of all genetic epidemiologic studies in humans, we advocate for conceptual replications in which investigators seek out distinct designs with which to test the validity of their findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding information

National Institutes of Health, Grant/Award Numbers: R01DA030005, R01AA023534

REFERENCES

Bohman M 1970 Adopted children and their families: A follow-up study of adopted children, their background, environment and adjustment, ASIN:B0006C3F18 ed. Proprius, [Solna, Seelig].

Cadoret R (1986). Adoption studies: Historical and methodological critique. Psychiatric Developments, 1, 45–64.

Cadoret RJ, Troughton E, O'Gorman TW, & Heywood E (1986). An adoption study of genetic and environmental factors in drug abuse. Archives of General Psychiatry, 43, 1131–1136. [PubMed: 3778110]

Cloninger CR, Bohman M, & Sigvardsson S (1981). Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Archives of General Psychiatry, 38, 861–868. [PubMed: 7259422]

Crandall CS, & Sherman JW (2016). On the scientific superiority of conceptual replications for scientific progress. Journal of Experimental Social Psychology, 66, 93–99.

Giordano GN, Ohlsson H, Kendler KS, Winkleby MA, Sundquist K, & Sundquist J (2013). Age, period and cohort trends in drug abuse hospitalizations within the total Swedish population (1975–2010). Drug and Alcohol Dependence, 134, 355–361. [PubMed: 24300899]

Jundong J, Kuja-Halkola R, Hultman C, Langstrom N, D'Onofrio BM, & Lichtenstein P (2012). Poor school performance in offspring of patients with schizophrenia: What are the mechanisms? Psychological Medicine, 42, 111–123. [PubMed: 21733288]

Kendler KS, & Gardner CO (2010). Interpretation of interactions: Guide for the perplexed. The British Journal of Psychiatry, 197, 170–171. [PubMed: 20807958]

Kendler KS, Ji J, Edwards AC, Ohlsson H, Sundquist J, & Sundquist K (2015). An extended Swedish National Adoption Study of alcohol use disorders. JAMA Psychiatry, 72, 211–218. [PubMed: 25565339]

Kendler KS, Lönn SL, Salvatore J, Sundquist J, & Sundquist K (2018). The origin of spousal resemblance for alcohol use disorder. JAMA Psychiatry, 75, 280–286. [PubMed: 29417130]

Kendler KS, Ohlsson H, Sundquist J, & Sundquist K (2015). Triparental families: A new genetic-epidemiological design applied to drug abuse, alcohol use disorders, and criminal behavior in a Swedish national sample. The American Journal of Psychiatry, 172, 553–560. [PubMed: 25698436]

Kendler KS, Ohlsson H, Sundquist K, & Sundquist J (2013). Within-family environmental transmission of drug abuse: A Swedish national study. JAMA Psychiatry, 70, 235–242. [PubMed: 23229904]

Kendler KS, Sundquist K, Ohlsson H, Palmer K, Maes H, Winkleby MA, & Sundquist J (2012). Genetic and familial environmental influences on the risk for drug abuse: A national Swedish adoption study. Archives of General Psychiatry, 69, 690–697. [PubMed: 22393206]

Lilienfeld SO (2017). Psychology's replication crisis and the Grant culture: Righting the ship. Perspectives on Psychological Science, 12, 660–664. [PubMed: 28727961]

Loeber R, & LeBlanc M (1990). Toward a developmental criminology In Tonry M & Morris N (Eds.), Crime and justice: A review of research (Vol. 12, pp. 375–473). Chicago, IL: University of Chicago Press.

McAdams TA, Neiderhiser JM, Rijsdijk FV, Narusyte J, Lichtenstein P, & Eley TC (2014). Accounting for genetic and environmental confounds in associations between parent and child characteristics: A systematic review of children-of-twins studies. Psychological Bulletin, 140, 1138–1173. [PubMed: 24749497]

Muthén LK, & Muthén BO (2015). Mplus User's Guide: 1998–2015 (7th ed.). Los Angeles, CA: Muthén & Muthén.

Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van BA, Visscher PM, & Posthuma D (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nature Genetics, 47, 702–709. [PubMed: 25985137]

SAS Institute. (2012). SAS/STAT® Online Documentation, Version 9.4. Cary, NC: SAS Institute.

Schmidt S (2009). Shall we really do it again? The powerful concept of replication is neglected in the social sciences. Review of General Psychology, 13, 90–100.

Silberg JL, Maes H, & Eaves LJ (2012). Unraveling the effect of genes and environment in the transmission of parental antisocial behavior to children's conduct disturbance, depression and hyperactivity. Journal of Child Psychology and Psychiatry, 53, 668–677. [PubMed: 22141405]

Thapar A, Rice F, Hay D, Boivin J, Langley K, van den Bree M, … Harold G (2009). Prenatal smoking might not cause attention-deficit/-hyperactivity disorder: Evidence from a novel design. Biological Psychiatry, 66, 722–727. [PubMed: 19596120]

Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, … Eaves L (1996). Genetic influences on DSM-III-R drug abuse and dependence: A study of 3,372 twin pairs. American Journal of Medical Genetics, 67, 473–477. [PubMed: 8886164]

Verhulst B, Neale MC, & Kendler KS (2015). The heritability of alcohol use disorders: A meta-analysis of twin and adoption studies. Psychological Medicine, 45, 1061–1072. [PubMed: 25171596]

TABLE 1

Descriptive statistics on informative families

Type of parent	Rearing defined as:	*N* parents	*N* offspring	% DA parent	% AUD parent	% male parents	YoB parents (mean)	% DA offspring	% AUD offspring	% Male offspring
G + R, R only and G only	≥ 5 years	8,004	31,956	3.1%	13.4%	96.2%	1947	7.2%	6.0%	51.2%
G + R and G only		52,898	157,835	3.8%	14.1%	83.4%	1945	6.6%	5.7%	51.4%
R only and G only		4,674	11,627	5.2%	17.3%	97.9%	1949	8.7%	6.3%	50.3%
G + R and R only		96,323	278,570	1.5%	7.2%	83.5%	1948	5.7%	4.8%	51.5%
G + R, R only and G only	≥ 10 years	3,806	14,417	2.3%	10.2%	94.5%	1947	6.3%	5.5%	51.4%
G + R and G only		45,980	135,020	2.9%	11.4%	82.5%	1945	6.1%	5.3%	51.7%
R only and G only		1,854	4,303	3.5%	12.6%	96.8%	1949	8.0%	5.9%	50.4%
G + R and R only		50,394	137,011	1.2%	6.1%	85.5%	1947	5.3%	4.6%	51.8%
Relevant comparison groups		%da	%AUD	YoB (mean)						
Offspring generation		3.9%	3.4%	1974						
Parental generation (females)		1.6%	3.2%	1947						
Parental generation (males)		1.8%	8.1%	1945						

TABLE 2

Parent-offspring tetrachoric correlations for drug abuse and alcohol use disorder by relationship type

		G + R offspring	R only offspring	G-only offspring	G + R offspring	R only offspring	G-only offspring	G + R offspring	R only offspring	G-only offspring	G + R off-spring	R only offspring	G-only offspring
Type of parent	**Rearing defined as:**	**Drug abuse tetrachoric correlations (SEs)[a]**			**Drug abuse tetrachoric correlations (SEs)[b]**			**Alcohol use disorder tetrachoric correlations (SEs)[a]**			**Alcohol use disorder tetrachoric correlations (SEs)[b]**		
G + R, R only and G only	≥5 years	0.30(0.03)	0.19 (0.04)	0.22 (0.04)	0.25 (0.03)	0.15 (0.04)	0.18 (0.04)	0.18 (0.03)	0.14 (0.03)	0.17 (0.03)	0.16 (0.03)	0.11 (0.03)	0.15 (0.03)
G + R and G only		0.29 (0.01)		0.22 (0.02)	0.19 (0.01)		0.17 (0.02)	0.21 (0.01)		0.17 (0.01)	0.16 (0.01)		0.14 (0.01)
R only and G only			0.20 (0.04)	0.17 (0.04)		0.11 (0.05)	0.14 (0.05)		0.07 (0.04)	0.16 (0.04)		0.02 (0.04)	0.13 (0.04)
G + R and R only		0.26 (0.01)	0.13 (0.02)		0.21 (0.01)	0.08 (0.02)		0.20 (0.01)	0.07 (0.01)		0.17 (0.01)	0.04 (0.01)	
Weighted average		0.28 (0.01)	0.15 (0.01)	0.21 (0.01)	0.20 (0.01)	0.09 (0.01)	0.16 (0.01)	0.20 (0.01)	0.08 (0.01)	0.17 (0.01)	0.16 (0.00)	0.05 (0.01)	0.14 (0.01)
Test of heterogeneity		0.148	0.156	0.546	0.220	0.188	0.793	0.478	0.088	0.989	0.663	0.052	0.915
G + R, R only and G only	≥10 years	0.34(0.05)	0.17 (0.07)	0.22 (0.07)	0.29 (0.06)	0.14 (0.08)	0.17 (0.07)	0.22 (0.04)	0.09 (0.05)	0.11 (0.05)	0.20 (0.04)	0.07 (0.05)	0.08 (0.05)
G + R and G only		0.28 (0.01)		0.21 (0.02)	0.19 (0.02)		0.16 (0.02)	0.20 (0.01)		0.18 (0.01)	0.15 (0.01)		0.15 (0.01)
R only and G only			0.22 (0.08)	0.12 (0.09)		0.18 (0.09)	0.10 (0.09)		0.06 (0.02)	0.13 (0.06)		0.06 (0.07)	0.09 (0.06)
G + R and R only		0.25 (0.02)	0.14 (0.02)		0.22 (0.02)	0.09 (0.03)		0.20 (0.01)	0.06 (0.02)		0.17 (0.02)	0.04 (0.02)	
Weighted average		0.27 (0.01)	0.15 (0.02)	0.20 (0.02)	0.21 (0.01)	0.10 (0.02)	0.16 (0.02)	0.21 (0.01)	0.06 (0.01)	0.17 (0.01)	0.16 (0.01)	0.04 (0.02)	0.14 (0.01)
Test of heterogeneity		0.311	0.574	0.544	0.178	0.573	0.781	0.892	0.713	0.294	0.223	0.749	0.255

[a] Controlling for year of birth and sex of proband.

[b] Controlling for DA (or AUD) in other parent, year of birth and sex of proband.

TABLE 3

Sample sizes of parents and offspring from informative families containing an affected parent

		Alcohol use disorder					Drug abuse				
	Definition of rearing	***N* parents**	***N* offspring**	**G + R offspring**	**R only offspring**	**G-only offspring**	***N* parents**	***N* offspring**	**G + R offspring**	**R only offspring**	**G-only offspring**
G + R, R only and G only	>5 years	1,069	4,280	1,654	1,352	1,274	246	985	380	312	293
G + R and G only		7,467	21,844	12,911		8,933	2,003	5,742	3,338		2,404
R only and G only		807	2,064		1,029	1,035	242	632		329	303
G + R and R only		6,952	19,964	11,547	8,417		1,409	4,039	2,319	1,720	
G + R, R only and G only	>10 years	387	1,503	600	439	464	86	321	128	94	99
G + R and G only		5,244	15,016	8,875		6,141	1,337	3,769	2,203		1,566
R only and G only		233	539		258	281	64	155		72	83
G + R and R only		3,060	8,266	4,930	3,336		582	1,587	931	656	

TABLE 4

Contrastive within-family analyses for drug abuse

	Rearing defined as:	Contrast	Hazard ratio[a]	Hazard ratio[b]	Weighted average[b]		Test of heterogeneity
G + R, R only and G only	≥5 years	GR VS R	0.93 (0.67; 1.28)	1.01 (0.73; 1.40)	GR VS R	1.26 (1.08; 1.48)	0.124
		G VS R	0.85 (0.59; 1.21)	0.96 (0.66; 1.39)	G VS R	1.04 (0.80; 1.36)	0.545
		GR VS G	1.10 (0.77; 1.57)	1.05 (0.73; 1.51)	GR VS G	1.04 (0.92; 1.18)	0.962
G + R and G only		GR VS G	1.07 (0.94, 1.22)	1.04 (0.91; 1.19)			
R only and G only		G VS R	1.04 (0.73; 1.50)	1.13 (0.78; 1.65)			
G + R and R only		GR VS R	1.15 (0.98; 1.36)	1.35 (1.13, 1.61)			
G + R, R only and G only	≥10 years	GR VS R	1.29 (0.66; 2.49)	1.40 (0.71; 2.75)	GR VS R	1.34 (1.03; 1.74)	0.891
		G VS R	1.03 (0.54; 2.00)	1.17 (0.61; 2.24)	G VS R	0.96 (0.57; 1.62)	0.310
		GR VS G	1.25 (0.67; 2.32)	1.20 (0.65; 2.20)	GR VS G	1.00 (0.85; 1.19)	0.551
G + R and G only		GR VS G	1.02 (0.87; 1.22)	0.99 (0.84; 1.18)			
R only and G only		G VS R	0.48 (0.19; 1.21)	0.66 (0.27, 1.61)			
G + R and R only		GR VS R	1.17 (0.91; 1.51)	1.33 (1.00; 1.77)			

[a]Controlling for YoB and sex of proband.

[b]Controlling for DA in other parent, YoB and sex of proband.

TABLE 5

Contrastive within family analyses for alcohol use disorder

	Rearing defined as:	Contrast	Hazard ratio	Hazard ratio[a]	Weighted average[b]		Test of heterogeneity
G + R, R only and G only	≥5 years	GR VS R	1.15 (0.92, 1.45)	1.29 (1.02; 1.62)	GR VS R	1.42 (1.29; 1.56)	0.361
		G VS R	1.01 (0.79; 1.29)	1.12 (0.87; 1.44)	G VS R	1.26 (1.04; 1.52)	0.165
		GR VS G	1.15 (0.91, 1.43)	1.15 (0.91; 1.44)	GR VS G	1.07 (0.99; 1.16)	0.516
G + R and G only		GR VS G	1.05 (0.97; 1.15)	1.06 (0.97, 1.15)			
R only and G only		G VS R	1.23 (0.93; 1.63)	1.47 (1.10; 1.96)			
G + R and R only		GR VS R	1.12 (1.01, 1.23)	1.45 (1.30; 1.61)			
G + R, R only and G only	≥10 years	GR VS R	1.44 (0.97; 2.14)	1.61 (1.09, 2.39)	GR VS R	1.47 (1.27; 1.71)	0.631
		G VS R	0.83 (0.53; 1.31)	0.92 (0.58; 1.45)	G VS R	1.04 (0.72; 1.49)	0.403
		GR VS G	1.73 (1.13; 2.65)	1.76 (1.15; 2.70)	GR VS G	1.04 (0.94; 1.16)	0.014
G + R and G only		GR VS G	1.02 (0.92; 1.14)	1.01 (0.91; 1.13)			
R only and G only		G VS R	1.00 (0.57, 1.75)	1.27 (0.70; 2.30)			
G + R and R only		GR VS R	1.10 (0.95; 1.28)	1.45 (1.23; 1.70)			

[a] Controlling for YoB and sex of proband.

[b] Controlling for AUD in other parent, YoB and sex of proband.

TABLE 6

A comparison of estimates of parent-offspring resemblance due to genetic and rearing effects from the multiple parenting relationships, adoption, and triparental parents designs

Design	Genetic	Rearing
Drug abuse	HRs or ORs (95% CIs)	HRs or ORs (95% CIs)
Multiple parenting relationships	2.17 (1.92; 2.46)	1.72 (1.43; 2.07)
Adoption	2.09 (1.66; 2.63)	1.55 (0.86; 2.80)
Triparental	2.45 (2.14; 2.79)	1.99 (1.55; 2.56)
Weighted average	2.27 (2.09; 2.47)	1.79 (1.55; 2.07)
Test of heterogeneity (*p* value)	0.314	0.581
Alcohol use disorder		
Multiple parenting relationships	1.80 (1.66; 1.95)	1.24 (1.11; 1.40)
Adoption	1.46 (1.29; 1.66)	1.40 (1.09; 1.80)
Triparental	1.84 (1.69; 2.00)	1.27 (1.12; 2.43)
Weighted average	1.75 (1.66; 1.85)	1.27 (1.14; 1.41)
Test of heterogeneity (*p* value)	0.009	0.695