The Impact of Parenting a Child with Serious Mental Illness:

Accounting for the Parent’s Genetic Vulnerability to Mental Illness

Submission date: February 4, 2020
Abstract

Parents of adults with serious mental illness (SMI) often are primary caregivers for their affected relative. Prior work has suggested that the toll of caregiving is associated with poorer well-being in family caregivers, particularly parents of affected adults. However, due to methodological limitations, it has not been possible to assess these family caregivers’ own genetic vulnerability to mental and physical health problems, thus the genetic impact of caregiving on well-being may not have been accounted for. With the addition of genetic data to large survey samples, family caregivers’ genetic vulnerability to mental and physical health problems can now be estimated. Parents from the Wisconsin Longitudinal Study who have an adult child with an SMI ($n = 265$) and a comparison group of parents with a child without disabilities ($n = 5,036$) reported their psychological well-being and mental and physical health across four measures. Genetic vulnerability was assessed using polygenic risk scores of neuroticism, bipolar disorder, schizophrenia, and depression. Results indicate that the effect of having a child with an SMI still had significant effects for all four parental health outcomes even after controlling for these measures of genetic vulnerability. This study’s results affirm the negative health impact of parenting a child with SMI, above and beyond genetic vulnerability.

*Keywords*: serious mental illness, aging parents, psychological well-being, physical health, polygenic risk scores
The Impact of Parenting a Child with Serious Mental Illness:
Accounting for the Parent’s Genetic Vulnerability to Mental Illness

Parents of persons with serious mental illness (SMI) often assume a primary caregiving role for their affected relatives because community mental health services are typically fragmented and inadequately resourced to meet the needs of individuals with SMI. Over the past several decades, hundreds of studies have been conducted on the toll of caregiving on the physical and mental health of these family members (e.g., Barker, Greenberg, Seltzer, & Almeida, 2012; Corrigan, Watson, & Miller, 2006; Mulud & McCarthy, 2017; Sartorius, Leff, Lopez-Ibor, Maj, & Okasha, 2005; Saunders, 2003; Taylor, Greenberg, Seltzer, & Floyd, 2008). A major methodological limitation of this body of research has been the inability to take into account the genetic vulnerability of parents to psychiatric problems because until recently, biological samples were not routinely collected in social survey studies. As a result, a criticism of the research on family burden of persons with SMI is that the relationship between caregiving and distress is partly due to the fact that the family caregiver likely also carries a genetic vulnerability to poor mental health outcomes (i.e., shared genetic vulnerability). With the recent addition of genetic data to large-scale social science surveys such as the Wisconsin Longitudinal Study (WLS), it now becomes possible to take into account the genetic vulnerability of these family caregivers through polygenic risk scores (PRS). PRS allow for the aggregation of DNA variants (i.e., single nucleotide polymorphisms, SNPs) associated with traits and disorders to quantify individual genetic liability (The International Schizophrenia Consortium, 2009). The purpose of this brief report was to use this powerful genetic method to investigate whether the research literature on families of persons with SMI may have overestimated the toll of caregiving
on parents by failing to take into account parents’ own genetic vulnerability to mental and associated physical health problems.

Methods

Sample and Procedures

Data were obtained from the WLS, a prospective cohort study of a 1/3 random sample of students who graduated from Wisconsin high schools in 1957, as well as one of their randomly selected siblings (Herd, Carr, & Roan, 2014). Data were collected in 1957, 1964, 1975/77, 1992/94, 2004/06, and 2011.

The present analyses are based on the 2011 wave of data collection in which 8,618 of the longitudinal respondents participated by completing an in-home interview, self-administered questionnaire, or both. The sample for the present analysis was restricted to the 8,341 participants who either completed both the in-home interview and self-administered questionnaire or only the self-administered questionnaire because the primary outcomes variables were measured in the questionnaire. In addition, the analytic sample was further restricted to participants who met the following two criteria: (1) reported having biological children; and (2) provided saliva of sufficient quantity and quality to allow for the assaying the genetic variants and computation of PRS. Among these 5,848 participants, 265 reported having a biological adult child with an SMI (i.e., schizophrenia, bipolar disorder, major depressive disorder), 37 had a non-biological child with SMI (e.g., adopted, step- or foster child), and 510 reporting have an adult child with a developmental disability, unknown diagnosis, or other mental health problem with insufficient reporting on level of impairment, precluding classification of the diagnosis as an SMI (see SAMHSA, 1993), and 5,036 reported that none of their children had a disability. The current analysis is based on the 265 parents who had a
biological adult child with a diagnosis of a SMI and the 5,036 parents of children without disabilities. Among the 265 adult children with an SMI, 46 had been diagnosed with schizophrenia, 174 with bipolar disorder, and 45 with a major depressive disorder that required hospitalization or resulted in substantial functional impairment.

Measures

The psychological and physical health characteristics of parents were assessed across four self-reported scales measuring psychological well-being, mental health, physical health, and broadband self-rated health.

Psychological well-being was assessed using a 31-item version of the Psychological Well-being Scale (Ryff, 1989). Items probe across six dimensions of psychological well-being (i.e., self-acceptance, positive relations with others, purpose in life, personal growth, environmental mastery, and autonomy). Questions include “To what extent do you agree that in general, you feel confident and positive about yourself?” and “To what extent do you agree that it seems that most other people have more friends than you do?” Items were each rated on a scale of 1 (i.e., agree strongly) to 6 (i.e., disagree strongly) and positively-worded items were reverse-coded such that higher scores reflect greater well-being.

Parental mental and physical health status were measured using the 12-Item Short-Form Health Survey (SF-12) to derive a mental health summary score and a physical health summary score (Ware, Kosinski, & Keller, 1996). This questionnaire asks about individuals’ health on a typical day and probes for interference of health symptoms on daily activities, such as: “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?” Higher scores on the SF-12 indicate better mental and
physical health functioning. Physical and mental summary scores are standardized to have a mean of 50 and standard deviation of 10 in the general population (Ware et al., 1996).

Finally, participants were asked to rate their current health using a single item (i.e., “How would you rate your health at the present time?”) with a five-point scale (1 = very poor to 5 = excellent).

Parental age, gender, education, marital status, and employment status were included as covariates to account for potential effects on the outcome variables. Age and education were measured in years; gender (1=female; 0=male), marital status (1=married; 0=not married) and employment status (1=working; 0=not working) were coded dichotomously. Since 98% of the sample self-reported being white, reflecting the Wisconsin population in 1957, race was not included as a covariate.

Saliva samples were collected from participants with Oragene collection kits via a mail-back procedure from 2007-8 and during home visits during Wave 5 data collection in 2011. Genotyping on 713,017 SNPs was completed at the Center for Inherited Disease Research (CIDR) at Johns Hopkins University using the Illumina HumanOmniExpress array. Genotype data was imputed against a reference from the Haplotype Reference Consortium. A quality control procedure was utilized. Samples were removed if surveyed and genetic sex or relatedness did not match. SNPs were removed if more than two alleles were present and if the genotype missingness rate was greater than .05. SNPs with a minor allele frequency of less than .01, significant deviation of the Hardy-Weinberg equilibrium (p < 1e^{-6}), or imputation quality score of less than .8 were removed as well. A total of 7,251,583 autosomal SNPs were retained. Greater detail on the genetic data in WLS have been described previously (see Hu et al., 2019).
We included four measures in an effort to capture the respondent’s genetic risk for having a child with an SMI. First a PRS for neuroticism was entered into the analysis because of the extensive literature indicating that neuroticism is a risk for general psychopathology (Kotov, Gamez, Schmidt, & Watson, 2010; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Li, Hilton, Lu, Hong, Greenberg, & Mailick, 2019; Tackett et al., 2013). We used the Social Science Genetic Association Consortium meta-analytic GWAS ($n = 170,911$; Okbay et al., 2016) as the discovery sample to calculate PRS for neuroticism for each individual in our sample. This GWAS included participants from the UK Biobank and the Genetics of Personality Consortium. Across cohorts, neuroticism was assessed using the Eysenck Personality Inventory, NEO Personality Inventory, or International Personality Item Pool Inventory. These measures of neuroticism were harmonized and a single neuroticism variable was used for the GWAS.

In addition, we included additional PRS for schizophrenia, bipolar disorder, and depression. We included these three additional PRS to better control for the possibility that parents of children with these diagnoses themselves carry a genetic risk for that same disorder. For major depressive disorder we used the PGC-2018 GWAS ($n = 59,851$ cases, $113,154$ controls; Wray et al., 2018) as the discovery sample, excluding the 23andME cohort. Across the cohorts, cases were either required to meet DSM-IV, ICD-9, or ICD-10 criteria for major depressive disorder according to structured diagnostic interviews, or case status was determined according to electronic medical records or self-report of symptoms or treatment. With regards to schizophrenia, we used the GWAS published by Pardiñas et al., 2018 with $40,675$ cases and $64,643$ controls, which built upon the previously published Psychiatric Genomics Consortium GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Cases were required to meet diagnostic criteria for schizophrenia or schizoaffective disorder according
to clinical and/or research consensus diagnosis. Finally, the bipolar disorder PRS was calculated using the PGC-2018 GWAS, with 20,352 cases and 31,358 controls (Stahl et al., 2019). Cases were required to meet diagnostic criteria for bipolar disorder according to the DSM-IV, ICD-9, or ICD-10. Structured diagnostic instruments, medical records, and clinician-administered checklists were used to determine case status.

For the calculation of all PRS, we removed SNPs in strong linkage disequilibrium (LD) using the clumping approach implemented in PLINK (Purcell et al., 2007). Using individuals with European ancestry from the 1000 Genome Project Phase III data as the reference, we clumped the GWAS associations by a window size of 1Mb and a pairwise $r^2$ threshold of 0.1. We used PRSice-2 (Choi & O’Reilly, 2019) to calculate PRS on WLS samples without applying any p-value thresholding. The PRS were standardized to a mean of 0 and a variance of 1 for all analyses.

**Data Analysis**

T-tests, chi-square tests, and bivariate correlations are reported to examine group level differences and the associations among background characteristics, the four indicators of genetic risk, and the outcome variables. Linear multiple regression was conducted in IBM SPSS Statistics Version 25 (IBM Corp, Armonk, N.Y., USA) to investigate whether the effect of having a child with SMI remained significant after taking into account background characteristics and indicators of genetic risk.

**Results**

As shown in Table 1, although parents of an adult child with SMI did not differ from the comparison group with respect to age ($t(5299) = .71, p = .477$), and employment status ($\chi^2(1, N = 5,297) = 0.14, p = .71$, they completed a greater number of years of education ($t(5299) = 1.98,$
were more likely to be female ($\chi^2 (1, N = 5,301) = 14.45, p < .001$), and were less likely to be married ($\chi^2 (1, N = 5,297) = 24.94, p < .001$). Parents of adult children with an SMI had higher PRS for schizophrenia than parents in the comparison group ($t(5290) = 2.08, p = .043$). They also had higher PRS for bipolar disorder ($t(5290) = 2.13 p = .034$) and PRS for depression ($t(5299) = 2.37, p = .018$). There were no differences between the two parent groups on the PRS for neuroticism. Finally, parents of a child with SMI additionally reported both poorer psychological, mental, and physical health than parents in the comparison group.

With respect to the bivariate correlations between the four outcomes variables and the four indicators capturing the respondent’s genetic risk for having a child with an SMI, the PRS for neuroticism was significantly correlated with each of the outcome variables, such that a higher genetic liability for neuroticism was associated with lower levels of psychological well-being ($r = -0.06, p < .001$), poorer SF-12 mental health ($r = -.04, p = .012$), poorer SF-12 physical health ($r = -.05, p < .001$), and poorer self-rated health ($r = -.04, p = .002$). The PRS for schizophrenia was significantly associated with poorer mental health as measured by the SF-12 ($r = -.04, p = .007$) and higher PRS for depression was associated with poorer psychological well-being ($r = -.04, p = .004$), mental health ($r = -.04, p = .007$), and self-rated health ($r = -.04, p = .004$). Finally, all outcomes were significantly positively correlated with one another (ranging from $r = .14$ to $r = .48, p’s < .001$) with the exception of the SF-12 mental and physical health scores ($r = -.09, p < .001$).

Linear Regression Models

We conducted a preliminary analysis in order to present the most parsimonious reduced model. In the preliminary analysis, the PRS for bipolar disorder and depression had no significant effect on any of the outcome measures and dropping them from the models did not
change the overall pattern of findings. All of the other predictors had a significant effect on at least one outcome measure. Therefore, the PRS for bipolar disorder and major depressive disorder were dropped from the regression model and the reduced model is reported. In addition, we conducted a hierarchical regression to determine if the magnitude of the effect of having an adult child with SMI changed upon entering the four PRS. The five parent-level covariates and group membership (i.e., whether the parent reported having an adult child with an SMI or not) were entered on the first step. The PRS for neuroticism, schizophrenia, bipolar disorder, and depression were entered on the second step. Since the coefficient for having an adult child with SMI did not significantly change between the two steps, we report the final model.

As shown in Table 2, across all four measures, parents who reported having a child with an SMI had worse outcomes (i.e., lower levels of well-being, poorer mental and physical health as rated by the SF-12, and poorer self-rated health) after controlling for parental age, education, sex, and marital and work status and the two indicators of genetic risk. The PRS for neuroticism was also associated with poorer health across all four outcomes and the PRS for schizophrenia was associated with poorer mental health as measured by the SF-12.

With respect to the covariates, older parents reported better psychological well-being ($t(5108) = 2.65, p = .008$), and mental health ($t(4755) = 4.82, p < .001$), but poorer physical health as measured by the SF-12 ($t(4755) = -2.77, p = .006$). Women reported higher levels of psychological well-being ($t(5108) = 5.84, p < .001$) and self-rated their physical health ($t(5166) = 6.52, p < .001$) as better than men, but reported more physical health problems as measured by the SF-12 ($t(4755) = -2.92, p = .004$). Respondents with higher levels of education and who were currently working had better psychological well-being ($t(5108) = 14.56, p < .001$ for education; $t(5108) = 3.26, p = .001$ for employment status) and physical health as measured by
the SF-12 ($t(4755) = 8.01, p < .001$ for education; $t(4755) = 5.79, p < .001$ for employment status), and rated their overall health as better ($t(5166) = 14.59, p < .001$ for education; $t(5166) = 6.71, p < .001$ for employment status) compared to those with less education and those who were not working. Finally, those who were currently married reported higher levels of psychological well-being ($t(5108) = 4.50, p < .001$), mental health ($t(4755) = 6.41, p < .001$) and physical health ($t(4755) = 2.68, p = .007$), and rated their overall health ($t(5166) = 4.09, p < .001$) as better than those who were not currently married.

Discussion

The purpose of this study was to address a major limitation of the current research literature on the toll of caregiving on the lives of parents of children with SMI, namely the failure to take into account the parent’s own genetic vulnerability to experiencing poor mental health and correlated physical health problems. In this study, we attempted to take into account this genetic vulnerability by controlling for parental PRS for neuroticism, schizophrenia, bipolar disorder, and depression. After controlling for these genetic risk indicators, the effect of having a child with SMI on all of the outcome variables remained significant. This study’s results affirm the negative impact of parenting a child with SMI, above and beyond genetic vulnerability.

The findings of this study have important implications for the design of large-scale surveys examining families across the life course. A growing number of national longitudinal surveys are beginning to collect and incorporate genetic indicators into their datasets. Unfortunately, these surveys often have limited diagnostic information on the adult children of the respondents. The incorporation of more complete diagnostic information on the adult children would help stimulate a new generation of research on families of persons with SMI that
not only take into account the parent’s genetic vulnerability but also provides rich opportunities to examine gene-by-environment interactions in understanding the tremendous variability in the family’s response and capacity to cope with an adult child who has an SMI.

Although our study has many strengths, it is not without limitations. First, the racial composition of the WLS (98% white) reflects the composition of the Wisconsin population in the 1950s. Second, because all of the graduate respondents and the vast majority of sibling recruits (93%) completed high school, they were more highly educated than the general population of Wisconsin 18-year-olds in the 1950s, as 25% of 18-year-olds in Wisconsin at that time did not complete high school. Another study limitation is the use of parental reports of an adult child’s diagnosis. It is possible that parents may have underreported the incidence of serious mental illness in their children due to stigma. Additionally, the GWAS discovery samples used to calculate the PRS in this study are likely underpowered, contributing to the relatively small effect sizes (Li et al., 2019). Ongoing efforts to refine PRS to capture mental health phenotypes should yield stronger effects in future studies (Li et al., 2019). Finally, to the best of our knowledge this was the first study to incorporate PRS to study the toll on parents of persons with SMI. The study findings should be interpreted cautiously and warrant replication with independent samples of parents of persons with SMI.

In conclusion, the current study is innovative in incorporating individual level genome-wide information in studying the long-term toll on parents of coping with an adult child with SMI. The findings of this study suggest that the effect of parenting an adult child with SMI on parental well-being remains statistically significant after taking into account indicators of the parent’s genetic risk for experiencing lower levels of well-being. With the growing number of large scale surveys collecting genome-wide information, these data will provide opportunities to
replicate the results reported here and calculate more precise estimates of the degree of bias, if any, existing in our current understanding of the impact of SMI on the family.
References


Substance Abuse and Mental Health Services Administration, Center for Mental Health Services. (1993). Final definitions for: (1) Children with a serious emotional disturbance, and (2) adults with a serious mental illness. *Federal Register, 58*(96), 29422–29425.


[https://doi.org/10.1038/s41588-018-0090-3](https://doi.org/10.1038/s41588-018-0090-3)
FAMILIAL GENETIC VULNERABILITY

Table 1

Background Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Mean (SD)</th>
<th>Parents with a child with an SMI (n = 265)</th>
<th>Comparison Parents (n = 5,036)</th>
<th>Test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.70 (3.94)</td>
<td>70.53 (3.87)</td>
<td>70.70 (3.95)</td>
<td>t = 0.71</td>
</tr>
<tr>
<td>Sex (a)</td>
<td>0.54 (0.50)</td>
<td>0.65 (0.48)</td>
<td>0.53 (0.50)</td>
<td>χ² = 14.45***</td>
</tr>
<tr>
<td>Education (b)</td>
<td>13.78 (2.34)</td>
<td>14.06 (2.41)</td>
<td>13.77 (2.33)</td>
<td>t = 1.98*</td>
</tr>
<tr>
<td>Marital status (c)</td>
<td>0.76 (0.42)</td>
<td>0.64 (0.48)</td>
<td>0.77 (0.42)</td>
<td>χ² = 24.94***</td>
</tr>
<tr>
<td>Work status (d)</td>
<td>0.30 (0.46)</td>
<td>0.29 (0.45)</td>
<td>0.30 (0.46)</td>
<td>χ² = 0.14</td>
</tr>
<tr>
<td>Neuroticism PRS (e)</td>
<td>0.00001 (0.000009)</td>
<td>0.00002 (0.000008)</td>
<td>0.00001 (0.000009)</td>
<td>t = 1.35</td>
</tr>
<tr>
<td>Schizophrenia PRS</td>
<td>-0.00172 (0.000027)</td>
<td>-0.00171 (0.000027)</td>
<td>-0.00172 (0.0000027)</td>
<td>t = 2.08*</td>
</tr>
<tr>
<td>Bipolar PRS</td>
<td>-0.00193 (0.000037)</td>
<td>-0.00193 (0.000039)</td>
<td>-0.00193 (0.000037)</td>
<td>t = 2.13*</td>
</tr>
<tr>
<td>Depression PRS</td>
<td>-0.00002 (0.000009)</td>
<td>-0.00001 (0.000008)</td>
<td>-0.00002 (0.000009)</td>
<td>t = 2.37*</td>
</tr>
<tr>
<td>Psychological Well-being</td>
<td>4.76 (0.61)</td>
<td>4.65 (0.63)</td>
<td>4.77 (0.61)</td>
<td>t = 2.92**</td>
</tr>
<tr>
<td>SF-12 Mental Health</td>
<td>55.52 (6.17)</td>
<td>54.20 (6.86)</td>
<td>55.59 (6.12)</td>
<td>t = 3.38***</td>
</tr>
<tr>
<td>SF-12 Physical Health</td>
<td>49.05 (9.54)</td>
<td>46.48 (10.52)</td>
<td>49.18 (9.15)</td>
<td>t = 4.37***</td>
</tr>
<tr>
<td>Self-Rated Health</td>
<td>3.68 (0.94)</td>
<td>3.45 (0.98)</td>
<td>3.69 (0.93)</td>
<td>t = 3.96***</td>
</tr>
</tbody>
</table>
Note. \(^a\) 1 = female; 0 = male. \(^b\) Number of years of education completed. \(^c\) 1 = currently married; 0 = not currently married (i.e., divorced, widowed, separated). \(^d\) 1 = currently working; 0 = not currently working. \(^e\) all PRS standardized using a z-score. * \(p < .05\), ** \(p < .01\), *** \(p < .001\)
Table 2
Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Psychological Well-being</th>
<th>SF-12 Mental</th>
<th>SF-12 Physical</th>
<th>Self-Rated Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.01 (.002)*</td>
<td>.22 (.02)**</td>
<td>-.10 (.04)**</td>
<td>-.01 (.003)</td>
</tr>
<tr>
<td>Education</td>
<td>.05 (.004)**</td>
<td>.01 (.04)</td>
<td>.46 (.06)**</td>
<td>.08 (.01)**</td>
</tr>
<tr>
<td>Sex</td>
<td>.10 (.02)**</td>
<td>-.34 (.19)</td>
<td>-.80 (.28)**</td>
<td>.17 (.03)**</td>
</tr>
<tr>
<td>Marital Status</td>
<td>.09 (.02)**</td>
<td>1.39 (.22)**</td>
<td>.86 (.32)**</td>
<td>.13 (.03)**</td>
</tr>
<tr>
<td>Employment Status</td>
<td>.06 (.02)**</td>
<td>-.05 (.20)</td>
<td>1.74 (.30)**</td>
<td>.19 (.03)**</td>
</tr>
<tr>
<td>Have a child with an SMI</td>
<td>-.13 (.04)**</td>
<td>-1.08 (.41)**</td>
<td>-2.60 (.61)**</td>
<td>-.26 (.06)**</td>
</tr>
<tr>
<td>PRS for Neuroticism</td>
<td>-.03 (.01)**</td>
<td>-.21 (.09)*</td>
<td>-.48 (.13)**</td>
<td>-.03 (.01)**</td>
</tr>
<tr>
<td>PRS for Schizophrenia</td>
<td>.01 (.01)</td>
<td>-.23 (.09)*</td>
<td>.15 (.13)</td>
<td>.00 (.01)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.05***</td>
<td>.02***</td>
<td>.04***</td>
<td>.06***</td>
</tr>
<tr>
<td>$R^2$ adjusted</td>
<td>.05***</td>
<td>.02***</td>
<td>.04***</td>
<td>.06***</td>
</tr>
</tbody>
</table>

Note. * $p < .05$, ** $p < .01$, *** $p < .001$