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Early childhood psychosocial family risks and cumulative dopaminergic sensitizing score: Links to behavior problems in U.S. 9-year-olds

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Author Statement

1) Dr. Sari Mullola: Main contributor and first author to the present study; substantial contributions to the design of the work; acquisition, analysis, and interpretation of data for the work; writing and drafting the work and revising it critically for important intellectual content; person in charge of all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

2) Dr. Jeanne Brooks-Gunn: Main contributor to the current study; main foreign mentor advisor (Columbia University, NYC, USA); substantial contributions to the design of the work; acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important scientific content; final approval of the version to be published. Dr. Jeanne Brooks-Gunn and Dr. Marko Elovainio contributed equally to this work and are therefore equal second authors.

3) Dr. Marko Elovainio: Main contributor to the current study; main national mentor and advisor (University of Helsinki, Finland); substantial contributor to the conception and design of the data collection and work; acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important scientific content; consent to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published. Dr. Marko Elovainio and Dr. Jeanne Brooks-Gunn contributed equally to this work and are therefore equal second authors.

4) Dr. Christian Hakulinen: Main contributor to the present study; providing guidance regarding statistical analyses, critical review of the manuscript throughout the process; substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual scientific content; final approval of the version to be published.

5) Dr. Lisa M. Schneper: Main contributor to the present study; drafting the work and revising it critically for important intellectual content; consent to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published.

6) Daniel A. Notterman: Main contributor to the present study; drafting the work and revising it critically for important intellectual content, main foreign advisor (Princeton University, NJ, USA) particularly regarding the genetic part of the research; final approval of the version to be published.

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Conflict of Interest

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Abstract

Background: We examined, (a) whether in early childhood exposure to risky family environment in different domains (socioeconomic, mental, parenting practices, health behavior, and child-related risks) and accumulatively across various domains (cumulative risk) is associated with child's problem behavior at age 9, and (b) whether the association is more pronounced in children carrying cumulative dopaminergic sensitizing genotype or living in low-income families.

Methods: Participants were 2,860 9-year old children (48% females; 48% Black) and their mothers from the 'Fragile Families and Child Wellbeing Study', a probability birth cohort from large U.S. cities. Mothers responded to questions on child's problem behavior (CBCL). Children responded to questions about their vandalism and substance use.

Results: Cumulative family risk was associated with higher internalizing and externalizing behavior and higher vandalism and substance use. All domain-specific risk clusters were associated with higher internalizing behavior and, with the exception of child-related risk, with higher externalizing behavior. Mental health risks, risky parenting practices, and risky health behavior were associated with higher vandalism. Risky parenting practices were associated with higher substance use. The associations were robust to adjustment for cumulative dopaminergic sensitizing genotype. No G x E interactions with dopaminergic genotype and family SES were observed.

Limitations: Sample size was relatively small for genetic analysis and polygenic risk scores were not available.

Conclusions: Exposure to cumulative psychosocial family risks from early childhood is associated with early indicators of problem behavior in adolescence.

Keywords

cumulative family risk; domain-specific family risk; problem behavior; antisocial behavior; cumulative dopaminergic sensitizing score

Introduction

Substantial evidence has accrued on the associations between singular family psychosocial risk factors in childhood and problem behavior (e.g., Madigan et al., 2019). Recently, it has been shown that particularly exposure to an accumulation of multiple risks increases the susceptibility to subsequent adverse behavior outcomes (Elovainio et al., 2015; Evans, Li, & Whipple, 2013). An early childhood family environment with multiple risks creates

vulnerabilities and/or interaction with genetically based vulnerabilities that may produce disruptions in three proximal developmental areas associated with child's self-control and self-regulative skills: psychosocial functioning, stress-responsive functioning based on biological regulatory systems, and health-behavior functioning (Allegrini, Evans, de Rooij, Greaves-Lord, & Huizink, 2019). As a consequence, children may exhibit aggressive and antisocial behavior, anxious and depressive behavior and substance use (Weymouth, Fosco, & Feinberg, 2019). This profile of problem behavior shows relatively high phenotypic stability from childhood to adolescence (Haberstick, Schmitz, Young, & Hewitt, 2005; Moffitt, 2005).

Although the timing, depth, and duration of child's exposure to as adverse family environment may differentially affect children's problem behavior (e.g., Heim & Binder, 2012; Thornberry, Ireland, & Smith, 2002) and produce different effects at different life stages (Hecker, Boettcher, Landolt, & Hermenau, 2019), early childhood (e.g., prior to age 3) has been suggested to be especially significant. This is because of its sensitivity to developmental disruptions (Heim & Binder, 2012) and its foundation for subsequent interactions between the child and environment (Laceulle, Veenstra, Vollebergh, & Ormel, 2019). The associations between persistent risks and child's negative outcomes have been similar in early and middle childhood and adolescence (e.g., Augustyn, Thornberry, & Henry, 2019), creating a long-lasting continuum up to adulthood (e.g., Madigan et al., 2019). Only a few longitudinal studies, however, have examined the role of early childhood cumulative family risk in children's problem behavior (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; MacKenzie, Nicklas, Brooks-Gunn, & Waldfogel, 2015) and multiple domains of family risks while taking into account potentially confounding factors (Byrd et al., 2018; MacKenzie et al., 2015; Pittner et al., 2019).

Family environments may also be differentially harmful due to individual variation in genetic variants. According to the Differential Susceptibility Theory (DST) (e.g., Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011), individuals with certain 'sensitive' or 'susceptible' genotypes may display more marked sensitivity than others when exposed to both risk-promoting and development-enhancing environments (i.e., gene by environment interactions) (Allegrini et al., 2019; Mitchell et al., 2013). Genetic susceptibility to the environment emerges in the behavioral indicators of susceptibility, which are grounded in adaptive neurobiological processes moderating the effects of environmental exposures on developmental outcomes across the life span (Ellis et al., 2011). DST is seen as a central mechanism in the regulation of alternative patterns of human development focusing particularly on child-developmental processes (Ellis et al., 2011). Individual differences in these neurobiological functions can contribute directly to development of problem behavior and also indirectly through the way children react to environmental adversity (e.g., increased emotional reactivity to stimuli, lowered sensitivity to reward) (Weeland, Overbeek, de Castro, & Matthys, 2015).

Links between the effects of single dopaminergic genetic variants on children's antisocial problem behavior have been reported (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011; Mitchell et al., 2015) although recent meta-analyses using multiple genetic variants or polygenic scores report small (Pappa et al., 2016; Vassos, Collier, & Fazel, 2013) or no links

(Cao, Cao, & Chen, 2019; Trzaskowski, Dale, & Plomin, 2013). Previous gene–environment interaction research differs in its methodological solutions, such as conceptualization, composition of candidate genes, sample size, and power, which have been extensively addressed elsewhere (Dick, 2018; Dick et al., 2015; Jaffee, Price, & Reyes, 2013; Knafo & Jaffee, 2013). Variants in dopaminergic pathway genes, such as DRD2 (11q23, rs1800497), COMT (Catechol-O-methyltransferase; 22q11.21, rs4680), and DRD4 [−521 C/T single nucleotide polymorphism (SNP) rs1800955]; and 48bp VNTR in the III exon, 11p15.5), have been suggested to be involved in moderating the function of dopaminergic transmission in the limbic brain areas involved in cognition and emotion (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011; Mitchell et al., 2013). They are suggested to contribute to autonomic stress reactivity (Allegrini et al., 2019) and regulate individuals' attentional, emotional, and motivational behavioral responses to environmental threats and rewards (Alexander et al., 2011; Sheikh, Kryski, Kotelnikova, Hayden, & Singh, 2017), as well as parent-child interaction (Bakermans-Kranenburg & van Ijzendoorn, 2011). Low level of efficiency in this neural system may decrease attentional and reward mechanisms (Robbins & Everitt, 1996) which may contribute to antisocial and addictive problem behavior (Mitchell et al., 2015; Pavlov, Chistiakov, & Chekhonin, 2012) together with substance use (Blum et al., 1995) and violent delinquency (Guo, Roettger, & Shih, 2007). However, the aforementioned studies have not taken account of environmental stressors as multiple or cumulative contributors nor have they used cumulative dopaminergic sensitizing genotype.

It has also been suggested (Miller, Chen, & Cole, 2009) that stress effects on negative developmental outcomes are transmitted through epigenetic programming. According to this idea, stressful experiences change the way in which the genes function (epigenetics). The epigenetic changes affect, for instance, the response tendencies of cells of the monocyte/macrophage lineage, which play a key role in initiating and maintaining inflammation in the body. For example, Franklin and co-workers (Franklin et al., 2010) observed a depressive-like phenotype in the offspring of parents who had been subjected to stress in early life (maternal separation), and found that such stress altered the DNA methylation profile in the promoter of several candidate genes in the germline of stressed males. However, evidence from humans is scarce (Lehrner et al., 2014).

In the present study, we examined, using data from the longitudinal Fragile Families and Child Wellbeing Study (FFCWS), (1) whether the exposure to early childhood risky family environment (prenatal and birth to age 3) within different domains (socioeconomic, mental health, risky parenting practices, risky health behavior, and child-related risks) and accumulatively across various domains (cumulative risk index) is associated with child's problem behavior (i.e., internalizing and externalizing behavior, vandalism and substance use) at age 9, (2) whether controlling for dopaminergic sensitizing genotype alters these associations, and (3) whether exposure to different adverse family environments is differently associated with problem behavior among children living in families with different SES (i.e., high vs. low).

We based our study on three models which cover both theoretical and empirical frameworks to approach the issue currently under study: (a) risky families model (Repetti, Taylor, & Seeman, 2002), (b) cumulative risk model (e.g., Elovainio et al., 2015; Evans et al., 2013),

and (c) DST model (e.g., Ellis et al., 2011). Children's problem behavior involving vandalism and substance use at age 9 was chosen as the outcome because it has been associated with adolescence delinquency and drug use (Weymouth et al., 2019), school dropout, and childbearing with low earnings (Thornberry et al., 2002) and with adulthood sociability, which lay the groundwork for long-term and pervasive mental (Elovainio et al., 2015), physical (Hakulinen et al., 2016; Pulkki-Råback et al., 2015; Yang et al., 2016), and economic problems throughout the life span (e.g., Braveman & Barclay, 2009).

We hypothesized that the accumulation of risk scores across different domains present from birth (i.e., prenatal) to age 3, would be associated with higher child's problem behavior at age 9 in terms of all outcomes (e.g., Elovainio et al., 2015; Evans et al., 2013). We also expected that different risk domains would be differentially linked to problem behavior. Specifically, we expected that parental lower SES, and psychoemotional risks, such as higher mental health risks and higher risky parenting practices, would be associated with all outcomes of child's problem behavior (Blair & Raver, 2012; Elovainio et al., 2015; Evans & Kim, 2013; Foster & Brooks-Gunn, 2009). We hypothesized that child's higher cumulative dopaminergic sensitizing genotype [composed of T allele for *DRD2* (Taq1a, 11q23, rs1800497); T allele for *DRD4* (521 SNP rs1800955); 7R exon 3 *VNTR* allele for *DRD4* (48-bp 11p15.5), and the Met allele of the Val^{158} Met polymorphism (rs4680) for *COMT* (catechol-O-methyltransferase, 22q11.21)] (Bakermans-Kranenburg & van Ijzendoorn, 2011; Mitchell et al., 2013; Weeland et al., 2015) and childhood SES (high vs. low) (Barajas-Gonzalez & Brooks-Gunn, 2014; Blair & Raver, 2012; Evans & Kim, 2013) would intensify the association between childhood family risk environment (low SES) and problem behavior (Barajas-Gonzalez & Brooks-Gunn, 2014; Blair & Raver, 2012; Evans & Kim, 2013). More detailed justifications for choosing sensitizing alleles for creating our cumulative dopaminergic sensitizing score are presented in the online supplement Appendix A. The complete details of family risk clusters and their justifications are presented in the online supplement Appendix B.

Methods

Participants

The Fragile Families and Child Wellbeing Study (FFCWS) is a multi-stage, stratified, probability sample of births of 4,898 children in 20 large cities (> 200,000) across the United States between 1998 and 2000. The study design called for a 3:1 oversample of non-marital births, which led to a large number of births to low income, minority parents, although data can be weighted to be representative of births in large U.S. cities in the late 1990's. Data were collected on the mother, father and child at birth and again when the child was approximately 1, 3, 5, 9, and 15 years old (for futher information on the FFCWS study design, sample selection and ethical issues, see https://fragilefamilies.princeton.edu/documentation and Reichman, Teitler, Garfinkel, & McLanahan, 2001). We based our study sample on participants with all information on the genetic data collected in the home when the children were 9 years old resulting in an analytic sample of 2,860 participants. Medical records were extracted from the hospital where the mother gave birth. The core mother survey took place in the hospital at baseline, then by telephone in subsequent waves. The

child survey took place in the home at age 9. Written informed consent was obtained from all mothers, from participants who were 9 years old and from the parents of younger participants. Research plan and data collection procedures were accepted by the ethical review boards of all participating medical institutions. Data collection adhered to WHO standards (WHO, 2011) and the Helsinki Declaration. Treatment of the participants complied with the ethical standards of the American Psychology Association (APA). The present study with secondary data analysis was reviewed and deemed exempt by the institutional review boards of the Princeton University and Columbia University, which are the academic homes to the FFCWS.

Missing data—Although the overall response rate in the FFCWS study is relatively high (the 9-year survey consisting of 76% of the original sample), some information is nevertheless missing from our data (N = 2,860) regarding variables needed for purposes of analyses outside the genetic data [missingness ranging from about 0.3% (ethnicity/race) to 46.0% (risky parenting practices)]. However, it was decided to include risky parenting practices as a significant part of psychosocial risk factors as it refers homes with aggressive, conflictual and cold atmosphere, and with parent-child relationships that are unsupportive and neglectful that have been found to be harmful to offspring's future socio-emotional development (Elovainio et al., 2015; Gershoff & Grogan-Kaylor, 2016). Differences in the values for children's problem behavior between the missing and the non-missing groups in different family risk domains considering raw data are presented in Supplementary Table 2.

We used the multiple imputation method with chained equations in Stata 14.2 (StataCorp, College Station, TX, USA) to correct for possible bias that may be inherent in completed-case data if the individuals in the analytic sample differ systematically from the individuals who dropped out from the study (Rubin & Schenker, 1991; White, Royston, & Wood, 2011). With the exception of genetic data (N = 2,860 for participants for whom all information considering the genetic data was available), which we did not impute, we imputed all other values for participants with missing values in any of the predictor, outcome, or control variables. We generated 50 separate imputed datasets for purposes of analysis and report estimated pooled results averaged across these 50 imputed datasets and standard errors (*SE*) instead of standard deviations (*SD*) (White et al., 2011) for all study variables, resulting in 2,860 participants with full information which form our final analytic sample.

Measures

Childhood problem behavior.—Child's problem behavior was assessed at the 9-year follow-up, where mothers were asked a series of questions about their children's internalizing and externalizing behaviors and children were asked about their own vandalism and alcohol and drug use.

Internalizing behavior.: Mother-rated child's internalizing behavior was assessed with 32 items ($\alpha = 0.87$) drawn from three subscales of the Achenbach Child Behavioral Check List (CBCL) (Achenbach & Rescorla, 2001) focusing on children's anxious-depressed (13 items; $\alpha = 0.78$) and withdrawn-depressed (8 items; $\alpha = 0.91$) behaviors, and somatic complaints

(11 items; α = 0.76). The response options range from 1 (not true) to 3 (very true or often true). The items were added up, creating a scale ranging from 32 to 96.

Externalizing behavior.: Mother-rated child's externalizing behavior was assessed with 35 items (α = 0.91) drawn from two subscales of the CBCL (Achenbach & Rescorla, 2001) focusing on children's aggressive (18 items; α = 0.89) and rule-breaking behaviors (17 items; α = 0.89). The response options range from 1 (not true) to 3 (very true or often true). The items were added up, creating a scale ranging from 35 to 105.

Vandalism.: The 9-year-old children reported their own early vandalism. Dichotomous yes/no items included four questions about whether the child had deliberately set fire to a building or a car, or had tried to do so; thrown rocks or bottles at people or cars; deliberately damaged or destroyed property; and written things or sprayed paint on walls, sidewalks, or cars. Following the previously used procedure with the same FFCWS data (Schneider, Waldfogel, & Brooks-Gunn, 2015), the items were added up, creating a scale ranging from 0 to 4 (α = 0.70).

Substance use.: Children were asked three questions about their own early alcohol and drug use and smoking. Dichotomous yes/no items included questions about whether the child had secretly taken a sip of wine, beer, or other alcohol; smoked marijuana; or smoked a cigarette or used tobacco. Following the previously used procedure with the same FFCWS data (Schneider et al., 2015), the items were added up, creating a scale ranging from 0 to 3 (α = 0.70).

Childhood psychosocial family risk factors.—Five separate family-environmental psychosocial risk clusters were formed based on child's first three years of life: (a) socioeconomic, (b) parental mental health, (c) risky parenting practices, (d) risky parental health behavior, and (e) child-related risks. All the measures used in the childhood family environment were assessed by mother's reports at baseline when the child was born, and/or at child's age one and/or three. The risk domain components (1 = risk; 0 = no risk) were summed up to create five different domain-specific risk cluster indexes recommended and used previously (e.g., Elovainio et al., 2015; Evans et al., 2013) and described in Table 1. The complete details of these measures and their justifications are presented in the online supplement Appendix B. A total of five different family risk domains including 24 binary risk factors were summed up to create a cumulative family environmental risk index during child's first three years.

Cumulative dopaminergic sensitizing score.—A cumulative dopaminergic sensitizing score was created by combining the number of sensitizing alleles from the following four different gene variants involved in the functioning of the dopaminergic system: *DRD2* (rs1800497), *COMT*, *DRD4* (−521 C/T SNP rs180095) and *DRD4* exon 3 *VNTR*. We followed the previously suggested procedures and examined the distributional variation across four dopaminergic gene markers within an individual (e.g., Mitchell et al., 2013). Supplementary Table 3 presents (a) descriptive statistics for genotype and allele frequencies and (b) disequilibrium coefficients for codominant traits of completely known genotypes (N = 2,860) as a result of asymptotic Hardy-Weinberg Equilibrium Test (Cleves,

1999). Genotypes for *DRD2*, *DRD4 (*rs1800955), and *COMT* were determined by a real-time polymerase chain reaction (PCR) using primer systems supplied by U.S. Life Technology and for *DRD4 (VNTR)* by PCR followed by gel capillary electrophoresis.

Control variables at child's birth.—*Sex, mother ethnicity/race*, *mother's childbearing age* (coded as risk if mother's childbearing age ≤ 18 or ≥ 40), *mother place of birth* (coded as risk if mother reported being born outside of the United States), *mother's relationship with child's biological father* at child's birth, *mother's prenatal health care* (coded as risk if mother reported none at all or late starting of prenatal health care)*, mother's gestational pre-eclampsia or eclampsia, mother's gestational diabetes*, and *mother's consideration of abortion during pregnancy* [coded as risk if mother had reported any consideration of abortion at baseline].

Statistical analyses

Ordinary least squares regressions (OLS) and logistic regressions were used. All predictor variables and internalizing and externalizing behaviors as outcome variables were standardized ($M = 0$; $SD = 1$). Univariate associations of childhood cumulative family risk and multivariate associations of different family risk domains (all five family risk domains entered into the model simultaneously) with children's problem behavior at age 9 were examined in three analytical models: (Model 1) without any adjustments for control variables, (Model 2) adjusted for baseline control variables, and (Model 3) adjusted for all control variables and cumulative dopaminergic sensitizing genotype. We tested the univariate and multivariate interaction effects of early childhood family risks and cumulative dopaminergic sensitizing genotype on children's problem behavior at age 9 in two analytical models: (Model 1) without any adjustments for control variables, (Model 2) adjusted for all baseline control variables. The predictors for interaction models were added to the analyses in four blocks: (1) the main effects of cumulative family risk / the main effects of five different family risk domains at the same time, (2) the main effect of cumulative dopaminergic sensitizing genotype, (3) cumulative family risk by dopaminergic sensitizing genotype interaction term / all five family risk domains by dopaminergic genotype interaction terms at the same time, and (4) all nine baseline control variables at the same time.

Finally, we tested the effects of multivariate cluster interactions between childhood family SES and other family risk clusters on children's problem behavior at age 9 after adjusting for all control variables and cumulative dopaminergic sensitizing genotype. This was run to ascertain whether exposure to different adverse family environments was differently associated with problem behavior among children living in families with different SES (i.e., high vs. low). Data analyses were conducted using Stata 14.2 statistical software (StataCorp, College Station, TX, USA).

Supplementary sensitivity analyses.—We also conducted supplementary sensitivity analyses with raw data following the same analytical procedure as with imputed data. This was done to test the robustness of the findings to the cutoff points of childhood family risk

factors and to the patterning of missing data. These univariate and multivariate sensitivity analyses with raw data are shown in Supplementary Tables 8 and 9.

Results

The sample characteristics are shown in Table 2. The analytic study sample included 2,860 9-year-old children (48% female gender) and their biological mothers with a mean age of 25.00 years at child's birth [Standard Error (*SE*) = 0.11; range 14 – 47 years]. The majority of the participants represented Black ethnicity (48%) and native U.S citizens (86%) who lived in a family with single (40%) or cohabiting parent (37%) instead of married parent (23%).

Correlation coefficients between study variables (both imputed data and raw data) are presented in Supplementary Table 5. All family risk domains were weakly or marginally moderately correlated with each other (*r* ranged from 0.19 to 0.35, $p < 0.001$ for all associations) and moderately correlated with cumulative family risk score (*r* ranged from 0.50 to 0.66, $p < 0.001$ for all associations). All family risk domains were correlated with higher internalizing (*r* ranged from 0.09 to 0.15, $p < 0.001$ for all associations) and higher externalizing behavior (*r* ranged from 0.09 to 0.21, $p < 0.001$ for all associations). With the exception of the child-related risk cluster, all other family risk domains were correlated with higher vandalism (*r* ranged from 0.07 to 0.14, $p < 0.001$ for all associations) whereas risky parenting practices was the only family risk domain to correlate with higher substance use ($r = 0.06$, $p < 0.01$). Cumulative family risk index was correlated with higher problem behavior in terms of all outcomes (r ranged from 0.06 to 0.28, $p < 0.001$ for all associations except for substance use $p < 0.05$). Children's higher cumulative dopaminergic sensitizing score was positively associated with early childhood socioeconomic risks ($r = 0.04$, $p < 0.05$). Participants' ethnicity/race and place of birth correlated with higher cumulative dopaminergic sensitizing score ($r = 0.11$ and 0.09, respectively, $p < 0.001$ for both associations) so that participants who were Black, Hispanic and/or of Other ethnicity/race and participants who were born outside the U.S. had higher cumulative dopaminergic sensitizing score than participants representing White ethnicity/race with native U.S. citizenship by reason of being born in the U.S.

Table 3 presents the univariate and multivariate associations of childhood cumulative family risk environment and cumulative dopaminergic sensitizing genotype with internalizing and externalizing problem behavior, with vandalism, and substance use. Cumulative family risk score was associated with higher internalizing (β = 0.08, 95% CI = 0.06 to 0.09) and externalizing behavior (β = 0.09, 95% CI = 0.08 to 0.11) and also as with higher vandalism (OR = 1.11, 95% CI = 1.06 to 1.15) and higher substance use (OR = 1.10, 95% CI = 0.03 to 1.18). Cumulative dopaminergic sensitizing score was not independently associated with any outcomes of child problem behavior at age 9 ($p > 0.05$ for all associations). All risk domains were associated with internalizing behavior. With the exception of child-related risk, all risk domains were associated with higher externalizing behavior. Mental health risks, risky parenting practices and risky parental health behavior were associated with higher vandalism. Children's higher substance use was predicted only by risky parenting practices.

The interaction effects between cumulative family risk and cumulative dopaminergic sensitizing genotype on child's problem behavior were statistically non-significant (Supplementary Table 6). No multivariate cluster interactions between childhood family SES and effects of other family risk environment on children's problem behavior at age 9 were observed (Supplementary table 7).

Discussion

The present study examined whether early childhood family risks within different risk domains and accumulatively across multiple domains are associated with children's problem behavior and whether a cumulative dopaminergic sensitizing score created from multiple gene variants affecting the dopaminergic system might moderate these associations. Cumulative family risk index across different domains was associated with higher problem behavior in terms of all outcomes. Cumulative dopaminergic sensitizing score and family low income did not moderate these associations.

The present findings support previous research (Evans & Kim, 2013; Murray, Farrington, & Sekol, 2012; Repetti et al., 2002) by underscoring the importance of early family environment for the development of child problem behavior. The accumulation of family risk across different domains, in particular, seems to be associated with higher levels of behavior problems. Similar cumulative associations of childhood family risks with antisocial behavior problems in childhood and adolescence (Foster & Brooks-Gunn, 2009) and with adulthood adverse outcomes such as mental (Elovainio et al., 2015; Heim & Binder, 2012; Horan & Widom, 2014) and cardiovascular health problems (Hakulinen et al., 2016; Pulkki-Råback et al., 2015) have been reported. Our finding, however, is significant and novel as it remained robust (a) after controlling for important early confounders [e.g., family structure (Mitchell et al., 2015) and both mother's and child's health-related prenatal factors (Suarez et al., 2018)], (b) after controlling for child's cumulative sensitizing dopaminergic score, which has been suggested to be linked not only to children's antisocial behavior (Moffitt, 2005; Nikolova, Ferrell, Manuck, & Hariri, 2011; Pappa et al., 2016; Vassos et al., 2013), but also to responsiveness to childhood adverse environmental context (Bakermans-Kranenburg & van Ijzendoorn, 2011; Guo et al., 2007; Mitchell et al., 2015), and (c) it also concerned early vandalism and substance use, reported by the 9-year-olds themselves, which may presage problems later on (Horan & Widom, 2014; Moffitt, 2005; Weymouth et al., 2019). Child's exposure to early childhood family risks may cause interruptions to the successful completion of fundamental developmental tasks, and therefore possibly disadvantage children throughout their lives (e.g., Madigan et al., 2019).

Risk clusters also exhibit different patterns of problem behavior, which confirmed our expectations (Blair & Raver, 2012; Evans & Kim, 2013; Foster & Brooks-Gunn, 2009; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). Some family environmental risk domain clusters may be more significant than others for problem behavior (St-Laurent, Dubois-Comtois, Milot, & Cantinotti, 2019). Early childhood SES risks and parental mental health risks, in particular, were most clearly associated with higher levels of internalizing behavior problems, whereas lower income, risky parenting practices, and risky parental health behavior were most clearly associated with externalizing behavior problems. Mental health

risks, risky parenting practices, and parental risky health behavior were the only family risk domains associated with higher rates of vandalism. Risky parenting practices was the only cluster predictive for all outcomes including higher substance use (in fully adjusted non-linear models). Child-related risks (e.g., difficult temperament and low birthweight) had the smallest associations and were predictive only for internalizing behavior. Adverse consequences of lower SES in childhood have recently been reported (e.g., Blair & Raver, 2012; Elovainio et al., 2015; Evans & Kim, 2013; Hakulinen et al., 2016; Heim & Binder, 2012). Our present findings, however, are quite stringent because family SES cluster as well as harsh parenting practices were found to be predictive of children's problem behavior even after those previously used other family risk clusters were simultaneously controlled for.

Early proximal disruptions in child's self-regulative development due to early detrimental family experiences and subsequent interactions with the immediate environment are one mechanism which may explain long-term adverse development (Heim & Binder, 2012; Weeland et al., 2015). Internalizing and externalizing behavior problems as well as vandalism, substance use may partly reflect stress-responsive attempts to compensate for earlier experiences [e.g., exposure to the early detrimental programming of the physiological stress system (Hanson & Chen, 2010; Weeland et al., 2015)], limited opportunities to observe and learn efficient emotional regulation strategies (Heim & Binder, 2012), fewer and weaker coping strategies and internal barriers to risky behavior, detrimental peer influence, and fewer sources of social support (Repetti et al., 2002).

A child's higher cumulative dopaminergic sensitizing score created from multiple dopamine markers did not have a main effect on children's problem behavior and it did not moderate the association between childhood family risk environment and problem behavior at age 9. Although previous research has suggested a plausible linkage between single dopamine markers and children's antisocial behavior (de Almeida, Ferrari, Parmigiani, & Miczek, 2005; Moffitt, 2005; Nikolova et al., 2011; Pappa et al., 2016; Vassos et al., 2013), also in terms of responsiveness to environmental context (Bakermans-Kranenburg & van Ijzendoorn, 2011; Guo et al., 2007; Mitchell et al., 2015), the effects of single dopaminergic genetic variants on children's antisocial problem are likely small (Pappa et al., 2016; Vassos et al., 2013) or non-existent (Cao et al., 2019; Trzaskowski et al., 2013). Using FFCWS data, Mitchell and colleagues (Mitchell et al., 2015) showed that boys with a higher cumulative dopaminergic sensitizing genotype exhibited more antisocial behavior in response to a change in a family environment than boys with less sensitizing genotype. Their study showed the evidence of the dopaminergic DST model (Ellis et al., 2011) for 'both-for-better-and-for-worse' rearing effects on children's G × E susceptibility. The lack of main genetic effects is not seen, however, to be inconsistent with the genetic DST model (Ellis et al., 2011), which postulates a crossover (for better or for worse) model with no main effect of genes. It may actually underline the importance of the psychosocial family environment in determining how genes may shape children's adjustment to the family environment and how the potential role of genetic sensitivity would emerge through childhood psychosocial family risks (Mitchell et al., 2015). It may also be hypothesized that stress related to family environment acts through epigenetic alterations (for example, DNA methylation) and their effects on gene expression. Epigenetic markers may be passed on to future generations and studies have shown that stress experiences of the previous generation can affect epigenetic

changes that persist across 2–3 generations (Cowan, Callaghan, Kan, & Richardson, 2016). However, in this study we were not able to analyze the potential effects of such mechanisms. Given that G × E research examining how the cumulative effect of multiple functional polymorphisms may shape the association between childhood family risks and problem behavior has just begun (Mitchell et al., 2013), future research on polygenetic risk scores is needed to investigate their potential G × E influence on problem behavior in children.

This study has some limitations. First, although our sample size is satisfactory to date for examining the linkage between childhood psychosocial family risks and childhood problem behavior and the moderating role of genetic sensitivity in this association, larger samples are recommended for genome-wide approaches to problem behavior (Pappa et al., 2016). Even small differences in sample size have been found to impact on the statistical power to detect genetic associations in children's problem behavior at the genome-wide significance level (Pappa et al., 2016), a challenge for developmental research (Trzaskowski et al., 2013). In addition, as GWAS data was not available, we could not use polygenetic risk scores (Duncan, Ostacher, & Ballon, 2019). Second, child internalizing and externalizing behavior were reported only by the mothers, which may be a source of reporting bias (Najman et al., 2001) (although the children reported directly on their vandalism and substance use). Finally, externalizing symptoms were examined in global terms only, and this does not allow emphasizing distinct risk pathways to heterogenous forms of antisocial behavior. It is also worth noting that available FFCWS data determined the variables possible to use in the present study. Strengths of the current study compared with the existing literature include a large sample size (N=2,860), the inclusion of possible prenatal confounding factors, the comparing of cumulative family risk to specific risk clusters, and controlling for cumulative dopaminergic sensitizing genotype and other risk factor domains when looking at specific risk domains.

Conclusions

Our results suggest that exposure to psychosocial family risks in early childhood predicts behavior problems at age 9 even after the child's cumulative dopaminergic sensitizing genotype has been controlled for. Our present findings do not indicate that child cumulative dopaminergic sensitizing genotype moderates the association between childhood adverse family environment and problem behavior at age 9. Cumulative family risk from early childhood is associated with early indicators of problem behavior in adolescence, i.e., 9-year-olds' reports of vandalism and substance use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

FFCWS	Fragile Families and Child Wellbeing Study
U.S.	United States
SNP	Single Nucleotide Polymorphism
HWE	Hardy-Weinberg Equilibrium Test
DST	Differential Susceptibility Theory
WAIS-R	Wechsler Adult Intelligence Scale-Revised
CBCL	Achenbach Child Behavioral Check List
CTPSC	Conflict Tactics Scale for Parent and Child
CIDI	Composite International Diagnostic Interview
CIDI-SF	Composite International Diagnostic Interview – Short Form
EAS	Emotionality, Activity, Sociability –Temperament Survey for Children
OLS	Ordinary Least Squares regression
PCR	A real-time Polymerase Chain Reaction
SES	Socioeconomic Status

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Highlights

- Cumulative family risk is associated with internalizing and externalizing behavior
- Cumulative family risk is associated with higher vandalism and substance use
- Mental health, risky parenting and health behavior are associated with vandalism
- Risky parenting practices are associated with higher substance use
- The results reflect the early indicators of problem behavior in adolescence

Table 1.

Childhood family risk categories and their components in a study sample (N=2,860)

Family risk cluster category and its components	Time points when measured			Percentage of valid values			Measure/scale	Risk points
	B	1F	3F	%-A	%-B	%-C		
A. Socioeconomic risk cluster						93		**0–5**
1. Low cognitive ability (IQ)			X	93			WAIS-R; 1SD below the mean toward lower IQ (m)	0–1
2. Low educational attainment	X			100			High school or less than high school (m)	0–1
3. Poverty status	X	X	X	90	2		Under 200% of annual poverty threshold (m)	0–1
4. Economic hardship	X	X	X	89	2		Trouble paying utilities, rent unpaid, borrowed money from friends/family; 1SD above the mean toward higher economic hardship (m)	0–1
5. Low employment status		X	X	90	8		Any unemployment status the week before the child was at age 1 or 3 (m)	0–1
B. Mental health risk cluster						89		**0–5**
1. High mental family history			X	92			Mental health history (anxiety, depression, drug dependence, suicide attempts of respondents' parents); 1SD above the mean toward higher mental family history (m)	0–1
2. Prenatal maternal anxiety or depression	X			98			Parent defined as anxious/nervous or depressed/withdrawn (m)	0–1
3. Parental anxiety or depression		X	X	90	8		CIDI-SF; Parent defined as anxious or depressed (m)	0–1
4. Aggravation in parenting/parenting stress		X	X	78	19		How difficult the parent found being a parent; 1SD above the mean toward higher parental aggravation and stress (m)	0–1
5. Intimate partner violence	X	X	X	20	23		Any reported intimate partner violence during first 3 years (m)	0–1
C. Risky parenting practices cluster						54		**0–4**
1. Low parental warmth [1]			X	54			HOME Inventory; Parental observed warmth toward the child at home visit; 1SD above the mean toward lower warmth (m)	0–1
2. High parental hostility [1]			X	54			HOME Inventory; Parental observed hostility toward the child at home visit; 1SD above the mean toward higher hostility (m)	0–1
3. Parental spanking		X	X	89	9		Parent reported any spanking in the past month (m)	0–1
4. Harsh parenting practices			X	79			CTPSC; Physically and psychologically aggressive parenting behavior; 1SD above the mean toward higher parenting practices (m)	0–1
D. Parental risky health behavior						88		**0–6**
1. Prenatal alcohol, smoke or drugs use	X			99			CIDI; Any prenatal alcohol/drug use/smoking (m)	0–1
2. Parental alcohol dependence		X	X	90	8		CIDI; Parental heavy alcohol dependence at child's age 1 or meeting the full CIDI-SF criteria at age 3 (m)	0–1

Family risk cluster category and its components	Time points when measured			Percentage of valid values			Measure/scale	Risk points
	B	1F	3F	%-A	%-B	%-C		
3. Parental drugs dependence		X	X	93	0		CIDI; Any parental cocaine/crack/speed/LSD/heroin/other hard drug use or smoking marijuana or pot at child's age 1 or meeting the full CIDI-SF drug dependence criteria at child's age 3 (m)	0–1
4. Parental smoking		X		95			Parental smoking in the past month at child's age 1 (m)	0–1
5. Low parental health status	X	X	X	90	2		Any parental self-reported overall health to be lower than excellent or very good (m)	0–1
6. Parent (mother or father) ever in jail	X	X	X	72	22		Any history of paternal and/or maternal incarceration during child's first 3 years (m)	0–1
E. Child-related risk cluster						72		**0–4**
1. Baby's difficult temperament		X		95			EAS; Parent perceived the child to be 1SD above the mean toward higher difficult temperament (m)	0–1
2. Baby low birthweight	X			97			Baby weighed less than 2,500 grams at birth (mr)	0–1
3. Baby's early gestational age	X			78			Baby was defined by pediatrician as preterm or very preterm; gestational age 36 weeks or less (mr)	0–1
4. Baby's low health status		X		94			Parent-rated child's overall health status lower than excellent or very good (m)	0–1
CUMULATIVE FAMILY RISK INDEX						36	A total of five different family risk domains including 24 binary family risk factors	**0–24**

Note. B = baseline variable; 1F = one-year follow up variable; 3F = three-year follow up variable; m = biological mother-reported; mr = derived from medical records

%-A = percentage of 2,860 participants who have valid values in all measured time points.

%-B = percentage of 2,860 participants with valid value at only one time point from two or three measured time points.

%-C = percentage of 2,860 participants with valid values in each item that were required when forming the sum index of the current risk domain cluster.

[1] Observed by interview during home visit.

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Table 2.

Descriptive statistics for control, predictor, moderator, and outcome variables in analytical sample (imputed data; N=2,860)

	IMPUTED DATA				
Variable	**%**	***M***	***SE***	**n**	**Total**
	Demographic / control variables				
Child is female	48.18			1,378	2,860
M race/ethnicity					
Black	48.40			1,384	2,860
White	21.09			603	2,860
Hispanic	27.42			784	2,860
Other	3.09			89	2,860
M immigrant	14.32			410	2,860
M relationship with biological father at baby's birth					
Married	22.91			655	2,860
Cohabiting	37.18			1,063	2,860
Single	39.91			1,142	2,860
M risk childbearing age (<19 or ≥ 40)	10.88			311	2,860
M risk pre-care during pregnancy	19.34			553	2,860
M pre-eclampsia or eclampsia during pregnancy	4.86			139	2,860
M diabetes during pregnancy	4.81			138	2,860
M consideration of abortion during pregnancy	26.99			772	2,860
	Childhood family risk factors (at least one unfavorable risk)				
M Socioeconomic risks (1–5)	91.75	2.95	0.023	2,624	2,860
M Mental health risks (1–5)	73.36	1.71	0.018	2,098	2,860
M Risky parenting practices (1–4)	72.41	1.48	0.015	2,071	2,860
M Risky health behavior (1–6)	83.74	2.08	0.023	2,395	2,860
Child-related risks (1–4)	41.22	1.30	0.018	1,179	2,860
Cumulative family risk (1–24)	98.88	7.35	0.061	2,828	2,860
0–1	3				2,860
2–4	16				2,860
5–7	32				2,860
8–10	30				2,860
11–13	15				2,860
14–16	4				2,860
	Child dopaminergic sensitizing genotype *				
Number of dopaminergic sensitizing alleles (0–8) *					
0–1	9.93			284	2,860
2	22.20			635	2,860
3	30.10			861	2,860

	IMPUTED DATA				
Variable	**%**	***M***	***SE***	**n**	**Total**
4	23.32			667	2,860
5	10.80			309	2,860
6–8	3.64			104	2,860
		Child problem behavior at age 9			
Internalizing behavior (range 32–96)		37.08	0.106		2,860
Externalizing behavior (range 35–105)		41.29	0.130		2,860
Vandalism (range 0–4)		0.25	0.011		2,860
Substance use (range 0–3)		0.05	0.005		2,860
Any vandalism (1–4)	19.15	1.30	0.026	548	2,860
Any substance use (1–3)	4.65	1.10	0.030	133	2,860

Note. M = mother; *M* = mean value; *SE*=Standard Error.

* = genetic data not imputed.

Table 3.

Univariate and multivariate associations of childhood family risk environment and cumulative dopaminergic sensitizing genotype with children's problem behavior at age 9 (N=2,860) *

Childhood family risks	Internalizing behavior [1]				Externalizing behavior [1]				Vandalism (none vs. 1–4) [2]				Substance use (none vs. 1–4) [2]			
Univariate model [3]	**β**	**95% CI**	***p* value**	**ΔR²**	**β**	**95% CI**	***p* value**	**ΔR²**	**OR**	**95% CI**	***p* value**	**ΔR²**	**OR**	**95% CI**	***p* value**	**ΔR²**
Cumulative family risk	**0.08**	**0.06 to 0.09**	**<0.001**		**0.09**	**0.08 to 0.11**	**<0.001**		**1.11**	**1.06 to 1.15**	**<0.001**		**1.10**	**0.03 to 1.18**	**0.006**	
Dopaminergic sensitizing genotype	0.02	-0.02 to 0.06	0.285	0.05	0.00	-0.03 to 0.04	0.809	0.09	0.97	0.88 to 1.07	0.499	0.06	1.06	0.88 to 1.27	0.546	0.01
Multivariate model [4]																
Socioeconomic risks	**0.10**	**0.05 to 0.14**	**<0.001**		**0.10**	**0.06 to 0.14**	**<0.001**		1.04	0.92 to 1.18	0.510		1.07	0.85 to 1.35	0.544	
Mental health risks	**0.11**	**0.07 to 0.15**	**<0.001**		**0.09**	**0.05 to 0.13**	**<0.001**		**1.14**	**1.03 to 1.27**	**0.016**		1.05	0.86 to 1.29	0.637	
Risky parenting practices	**0.07**	**0.02 to 0.13**	**0.008**		**0.13**	**0.07 to 0.18**	**<0.001**		**1.23**	**1.08 to 1.41**	**0.002**		**1.26**	**1.00 to 1.57**	**0.046**	
Risky health behavior	**0.05**	**0.00 to 0.09**	**0.039**		**0.10**	**0.06 to 0.15**	**<0.001**		**1.17**	**1.05 to 1.32**	**0.007**		1.06	0.86 to 1.32	0.570	
Child-related risks	**0.06**	**0.02 to 0.11**	**0.007**		0.04	-0.00 to 0.08	0.075		0.94	0.84 to 1.06	0.305		1.09	0.89 to 1.34	0.410	
Dopaminergic sensitizing genotype	0.02	-0.02 to 0.06	0.279	0.06	0.01	-0.03 to 0.04	0.722	0.09	0.97	0.88 to 1.08	0.598	0.06	1.06	0.89 to 1.27	0.523	0.01

Note.

[1] The results are based on ordinary least squares regression analyses (OLS). β = Standardized regression coefficient (Mean = 0, SD = 1).

[2] The results are based on logistic regression analyses. OR = odds ratio. 95% CI = 95% confidence interval for Exp(β) for internalizing and externalizing behavior and for Exp (OR) for vandalism and substance use. Statistically significant results are presented in bold face. ΔR^2= adjusted R-squared for the whole model.

[3] Cumulative family risk adjusted for all control variables (gender, mother's ethnicity, mother childbearing age, mother's prenatal healthcare, mother's relationship with baby's biological father at baby's birth, mother's place of birth, mother's prenatal pre-eclampsia or eclampsia, mother's prenatal diabetes and mother discussed abortion during pregnancy) and cumulative dopaminergic sensitizing genotype entered into the model at the same time.

[4] Multivariate risk (all risk domains entered into the model at the same time) adjusted for all control variables and cumulative dopaminergic sensitizing genotype entered into the model at the same time.

* With the exception of cumulative dopaminergic sensitizing genotype variable, all predictors and outcomes are imputed.