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Familial Aggregation of Major Depressive Disorder in an African-American Community

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Abstract

Background—African Americans (AAs) with major depressive disorder (MDD) experience more impairment and poorer treatment outcomes relative to whites, yet are underrepresented in family studies of MDD. This is the first study to investigate the familial aggregation of major depression among AAs.

Methods—Participant reports of depression from clinical and family history interviews were used to examine depression rates among 435 first-degree relatives and half-siblings of 63 depressed cases and 222 relatives of 33 non-depressed controls. Binary logistic regression was used to compute odds ratios (ORs) for family history (FH) of MDD and level of trauma exposure (high, low) in cases vs. controls. Poisson regression models with generalized estimating equations were used to assess MDD in relatives of cases vs. relatives of controls.

Results—Cases and controls did not differ in either FH of MDD (OR= 1.2, 95% confidence interval [CI] 0.5-2.9), or prevalence of MDD in relatives (RR = 1.5, 95% CI 0.8-2.5). However, exposure to high trauma was associated with increased risk of MDD (OR=3.0, 95% CI 1.22-7.17) and the combined effect of FH and trauma was greater than expected under an additive model. Similarly, the RR for MDD among relatives of cases with high trauma levels was 2.2 (1.24-4.2), compared to relatives of controls with low trauma.

Conclusion—The effect of family history of MDD appears to be exacerbated among individuals exposed to high trauma. Replication and further research on the chronology and subtypes of trauma and MDD, and their interactions, remain essential in AA populations.

Introduction

Major depressive disorder is disabling and costly, and by 2030 projected to be the largest cause of illness and mortality in the United States (Lépine & Briley, 2011; World Health Organization, 2008). Studies have consistently shown that depression is familial, with a two- to three-fold increased risk among individuals with positive family history (Gershon et al.,

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Declaration of Conflict of Interest

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1982; Tsuang, Winokur, & Crowe, 1980; Weissman, Gershon, et al., 1984), and up to six-fold increased risk among relatives of those with early-onset and/or recurrent depression (Kupfer, Frank, Carpenter, & Neiswanger, 1989; Weissman, Wickramaratne, et al., 1984). Heritability estimates from twin studies suggest on average, moderate genetic influence and substantial unique environmental influences (Kendler & Prescott, 1999; Lyons et al., 1998).

Estimates of familial risks and heritability of depression have been derived from predominantly European-American samples, with minimal inclusion of racial and ethnic minorities (Chiao & Blizinsky, 2013; Murphy, 2016). For racial and ethnic minority groups, differences in environmental pressures and culture may interact with genetic risks to produce outcomes that may differ from those of whites (Chaudhry, Neelam, Duddu, & Husain, 2008; Chiao & Blizinsky, 2013).

African Americans (AAs), an ethnically- and culturally-heterogeneous racial group consisting of Non-Hispanic Blacks born in the US, and representing roughly 12 % of the US population (United States Census Bureau, 2016b), are shown to have lower prevalence of major depression compared to whites. Despite lower rates of depression, AAs have more severe forms of the illness, longer duration, more impairment and poorer treatment outcomes (Kessler et al., 1994; D. R. Williams et al., 2007). Despite the additional burden of depression among AAs, who are the second largest racial group in the US, they typically comprise 5% or less in most family studies of major depression, and to date there are no published family studies of major depression focusing on AA (Murphy, 2016).

Increased mortality among AAs and physical health disparities between AAs and whites have been linked to lower socioeconomic status (SES), higher levels of social stress and racial discrimination among AAs relative to whites (D.R. Williams, Yu, Jackson, & Anderson, 1997). However, the association of SES and stress with mental health outcomes remains more complicated for AAs. Major depression is an established correlate and consequence of lower SES, higher trauma and stress levels (Assari, 2017; Bradley et al., 2008; Hammen, 2005), with moderating factors that may include genetics and other biological and environmental contexts (Caspi et al., 2003; Klengel & Binder, 2013; Wingo et al., 2010; Youssef et al., 2017). Although lower SES and higher stress are reliably associated with greater depression, this association is more complex and yields variable outcomes for AAs compared to whites (Assari, 2017; Assari & Caldwell, 2017). For example a landmark population-based study has shown that higher SES may be associated with greater prevalence of MDD for AA males, thereby highlighting the moderating influences of race and gender on the relationship between SES and MDD (Assari & Caldwell, 2017). Further, certain gene-environment interactions for MDD that have been demonstrated in whites have not been found in AAs (Karg, Burmeister, Shedden, & Sen, 2011; Klengel & Binder, 2013; Lotrich, Pollock, & Ferrell, 2003; Odgerel, Talati, Hamilton, Levinson, & Weissman, 2013).

Trauma exposure is an important consideration in family studies of depression among AA for a variety of reasons. First, post-traumatic stress disorder (PTSD) is the only affective disorder shown across a range of epidemiological studies to have significantly higher prevalence among AAs than whites and other minority groups (Alegría et al., 2013; Asnaani, Richey, Dimaite, Hinton, & Hofmann, 2010; Himle, Baser, Taylor, Campbell, & Jackson,

2009; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). This finding is robust and holds when compared to other disorders that are highly comorbid with major depression, including substance use disorders and anxiety disorders. Second, traumatic events, particularly those with a childhood onset, have reliably predicted major depression later in life (Bradley et al., 2008), and population-based studies have shown that AAs report higher childhood abuse/neglect trauma relative to whites, even when their overall trauma levels are comparable to or lower than that of whites (Alegría et al., 2013; Bradley et al., 2008; Roberts et al., 2011). In addition, there is mounting support for the idea that depression and traumatic events may share similar genetic contributions, which have implications for family history studies of depression (Bradley et al., 2008; Fu et al., 2007; Inslicht et al., 2010; Sartor, Grant, Lynskey, & et al., 2012). Presently, the relationships between traumatic events and depression in AA groups remain ambiguous. Identifying patterns of familial aggregation of depression under different levels of trauma exposure for depression may help to clarify these relationships.

To our knowledge, this is the first family history study of MDD focusing specifically on AA. Here, we compared family histories of depression among AA persons with MDD (cases) and without MDD (controls), and examined the relationship between case/control trauma and family history of depression. We further examined rates of depression among relatives of cases and controls by relationship (parents, offspring, full siblings and half siblings) to, and age and gender of the participants.

Methods and Materials

Study Procedures

Recruitment Sources—The initial point of recruitment was the Harlem Hospital Medical Center and satellite clinics in New York City; data collection was then snowballed to neighborhoods in Washington Heights, South and Central Bronx, Brooklyn and Queens. Recruitment flyers were placed in hospital clinics and community health centers. The participants learned of the study via word-of-mouth from friends or acquaintances who had participated in the study (80%), recruitment flyers (11%), and word-of-mouth from health care or social service workers at the satellite clinics. The recruitment flyers indicated that the study was about depression and would entail two separate interviews; no references were made to family history on the flyers. Volunteers learned of the family history interview on first contact prior to screening. No volunteer at screening refused to participate further after learning about the family history interview.

Eligibility Criteria—To be eligible for this study, participants had to be age 18 or older, English-speaking, and familiar with the psychiatric history of one or more first-degree relatives. To be classified as an MDD case, study participants had to meet DSM-IV criteria for one or more lifetime major depressive episodes, not better accounted for by medical conditions, drugs, or other exclusionary major psychiatric disorders, including any bipolar or psychotic disorder. Non-MDD controls could not have ever met DSM-IV criteria for major depression at any time in their lives. Otherwise, they had the same inclusion-exclusion criteria as MDD cases. Volunteers were not excluded from participating in the study based on race or ethnicity. However, analyses in this paper are restricted to participants who self-

identified as non-Hispanic black or AA. Race/ethnicity options were based on self-report categories formulated according to National Institutes of Health (NIH) guidelines (National Institutes of Health, 2015).

Data Collection Methods: Participants who were initially recruited as index cases or controls are hence referred to as “probands” to distinguish from relatives who are included in our analyses. Data collection consisted of a telephone screening interview, in-person clinical interview and telephone family history interview, all done on separate days. There was a fourth optional component in which up to two first- or second-degree relatives per proband could volunteer to complete a family history interview, reporting on themselves and other first-degree relatives of the probands. The family history interviewer differed from the clinical interviewer and was therefore blind to the case-control status of the proband. The study was approved by the Institutional Review Board of the New York State Psychiatric Institute.

Proband volunteers gave verbal consent to be screened via telephone, and eligible participants gave written informed consent for the clinical interview and family interviews. They also gave written consent to invite relatives to participate as family history informants. Informants were screened and verbally consented via telephone on a separate day, prior to completing the family history interview. All participants received cash incentives for completing both interviews, with pro-rated amounts for partially completed interview(s).

One hundred and sixty-eight volunteers were screened via telephone, of whom 31 were eliminated or dropped out after screening and before study enrollment (Figure 1). A majority of volunteers (60%) resided in the borough of Manhattan; most were from low-income communities. Based on residential zip codes, the Community Distress Index (CDI), Median Income Ratio (MIR), and percent below poverty level for those neighborhoods were obtained from 2015 census estimates (United States Census Bureau, 2016a).

Among the 137 probands who enrolled, signed written consent forms, and participated in the larger family study, 41 were excluded from our analyses because they did not self-report AA ancestry, their interviews were judged to be unreliable, or they did not meet diagnostic criteria (Figure 1). Those excluded from the analyses were more likely to be male than female, and slightly younger (but not significantly so), than the study sample. The study sample did not differ from the excluded group based on years of schooling or neighborhood economic characteristics (Supplementary Table S1).

Measures

Diagnostic clinical interview: To collect clinical information from probands, we used a full structured clinical interview, the Diagnostic Interview for Genetic Studies (DIGS) Version 4.0 (Nurnberger et al., 1994), administered on site, and face-to-face by a doctoral-level, experienced clinical interviewer. Along with other major DSM axis I disorders including post-traumatic stress disorder (PTSD), other anxiety and substance use disorders, probands were assessed on lifetime major depression episodes, according to DSM-IV criteria. Probands were ascertained as “cases” if they met the criteria for one or more major depressive episodes that were not better accounted for by bereavement, organic causes (e.g.,

drugs/alcohol, pregnancy, medical and neurological illness, or medication), or another exclusionary psychiatric disorder (e.g., bipolar disorder or psychotic disorder).

Independent raters who were doctoral level trained clinical researchers with five or more years of experience in administering, scoring, and rating the DIGS instrument, completed best estimate reliability ratings on 94 probands, with a Cohen's Kappa of 0.92 for depression diagnosis. Probands were classified as non-MDD "controls" if they did not at any time meet criteria for major depression, or any of the exclusionary psychiatric diagnoses for cases and controls.

Traumatic events: Traumatic events were assessed by the Life Events Checklist in which respondents were presented with 16 traumatic event categories and asked whether they witnessed or directly experienced an event at any time in their lives (Gray, Litz, Hsu, & Lombardo, 2004). For each individual, the number of items they reported experiencing was summed and then divided by the total to obtain the mean traumatic events score on a continuum ranging from 0 (lowest) to 1 (highest). Participants who reported experiencing or witnessing an event that caused them intense distress were then administered the PTSD Module F adapted from the Structured Clinical Interview for DSM-VI Disorders - Research Version (Michael, Spitzer, Gibbons, & Williams, 2010; Spitzer, Williams, Gibbon, & First, 1992). The items in this module correspond to the DSM-IV symptom criteria for PTSD.

Medical history: Participants were asked about their past and current history of medical conditions from a checklist on the DIGS interview. Lifetime history of medical illnesses were coded as 1 = present or 0 = absent, then summed and averaged to produce a composite medical index score on a continuum from 0 (lowest) to 1 (highest). Participants' body mass index was calculated using their self-reported height and weight.

Family interviews: The Family History Screen (FHS) (Weissman et al., 2000), and Family interview for Genetic Studies (FIGS) (Maxwell, 1992) were used to ask respondents about the psychiatric history of each first-degree relative separately. The FHS screened for presence or absence of the disorders and the FIGS asked about details such as symptoms, number and duration of episodes, treatment and age at onset. For relatives who screened "positive" on the FHS for depression, mania, substance use disorders, or psychotic disorders, detailed information on symptomatology, age of onset, number of episodes, and treatment received was obtained for these disorders from the FIGS. We resolved discrepancies among informants by selecting the more reliable informant, based on our clinical judgement. FHS and FIGS interview data were independently rated and then reconciled by two doctoral-level clinical interviewers, who were blind to proband status through the use of redacted narratives and masked ID numbers.

Statistical Analyses

Descriptive analyses: We conducted descriptive analyses of demographic and clinical variables and family composition, based on case-control status and family history status of probands. We investigated whether any of these factors was associated with both case-control status and family history ($p < .20$). We used independent samples t-tests for

continuous variables, and Chi-square tests (with Bonferroni corrections where necessary), and Fisher's exact tests for categorical and dichotomous variables. All descriptive and inferential tests were two-tailed.

Research designs: We analyzed the data as case-control and reconstructed cohort family designs (Susser & Susser, 1989). In the case control design, the risk factor of interest was dichotomously scored as family history positive (1 relative with MDD), or negative (0 relatives with MDD). The outcome of interest was the dichotomously-scored case or control status in the proband. In the reconstructed cohort design, we compared the prevalence of MDD among relatives of cases versus relatives of controls, defining the risk factor of interest (exposure) as the case/control status of the proband, and the MDD status of each relative as the outcome. We then repeated the analysis after stratifying the cohort of relatives by gender, relationship to the proband, and sibling type (full sibling, maternal half sibling, paternal half sibling).

Analytic Models: Binary logistic regression models were used to examine the effects of family history of depression on proband depression status. We then stratified the analysis according to trauma level reported by the proband (e.g., high trauma vs. low trauma). The median traumatic events score for the sample was dichotomized into "high" and "low" trauma categories, using the median traumatic events score of .33 as the cut-off.

In the reconstructed cohort analysis, we examined the effect of proband case-control status on family depression risks. Relative risks were estimated through Poisson regression models using generalized estimating equations (GEE) to control for within-family dependence with an exchangeable working correlation structure (Homish, Edwards, Eiden, & Leonard, 2010). We specified Poisson distribution with a log link function for estimating the models (Zou, 2004).

Interaction effects—We tested for interaction between family history of depression and proband trauma on an additive scale (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007; Knol & VanderWeele, 2012), by estimating the relative excess risk due to interaction (RERI). In a test for interaction between two exposures, the RERI measures the deviation of the observed odds ratio when both exposures are present (using neither exposure as the referent) from that expected if the effects of the two exposures are additive. The RERI could be less than zero (negative interaction), equal to zero (no interaction), or greater than zero (positive interaction). If the combined effects of family history and proband trauma are greater than expected under an additive model, then we would expect a RERI greater than zero (positive interaction). Another index of interaction on the additive scale, the attributable proportion (AP) (de Mutsert, Jager, Zoccali, & Dekker, 2009), quantifies the prevalence of depression in probands that is attributable to the interaction between family history and trauma level. We would also expect an AP greater than zero if there was positive interaction between trauma exposure and family history.

Sensitivity analyses

(i) **Proband-relative agreement:** We analyzed agreement between proband reports of depression in relatives and self-reports of relatives who provided information on themselves and appeared to be reliable informants. We calculated sensitivity and specificity for proband reports of MDD in relatives, using the relatives' self-reported history of depression as the reference standard.

(ii) **Family history and prevalence among relatives according to MDD subtype:** We examined the reports of family history and rates of MDD among relatives, according to proband MDD subtypes based on the probands' age of onset and single vs. recurrent episodes. We devised six MDD subtypes, using age 30 as the cutoff age for early-onset MDD.

Results

Table 1 compares cases and controls on key demographic, social, and clinical variables. Means and standard deviations are shown for continuous variables, and proportions (%) are shown for categorical variables. The proband sample comprised 56 women and 40 men, ranging in age from 25 to 79 years, with median of 53.4 years. Years of school completed ranged from 8 to 18 with a median of 12. A majority of participants (68%) had graduated from high school or obtained a GED, and 8% had a college degree or higher. The community distress index (CDI) ranged from 16 to 94; the median income ratio (MIR) ranged from 32-190% with a mean of 59%. Percent below poverty line ranged from 8-49%, with an average of 32%. Average estimates for the general US population are 14% below poverty level, 94% MIR, and 40-60 for CDI (United States Census Bureau, 2016a).

Cases had significantly more PTSD and traumatic events, and greater BMI than controls. Relative to controls, there were more women than men among cases ($p = 0.10$). Cases and controls did not differ significantly on mode or region of recruitment, age, years of schooling, or SES indices. The higher rates of substance use and anxiety disorders among cases relative to controls were not significant.

The 63 cases reported a total of 515 relatives (including first-degree relatives and half-siblings), with psychiatric history known for 435 (84%) of them. The 33 controls reported a total of 254 relatives, with psychiatric history known for 222 (87%) of them. Cases and controls did not differ significantly in the proportion of total relatives whose history was known ($\chi^2 = 0.421$, $p = .94$). The 657 relatives with known psychiatric history included 149 parents, 212 full siblings, 179 offspring and 184 half-siblings. Cases reported fewer half-siblings than controls (38% vs 63% $p < 0.001$). About 51% (337) of the relatives were female. No relative was reported as non-binary or transgendered. The parents had median age of 70, siblings and offspring had median ages of 51 and 27, respectively. There were no significant age or gender differences between relatives of cases and controls.

Case-Control Analysis

Effect of family history on proband MDD status—To assess potential confounding in the case-control analysis, we examined whether each of the three variables associated with

proband case-control status, (i.e., BMI, gender, and sibling type), was associated with either family history of MDD or proband trauma exposure. Among these variables, only sibling type (full siblings only, half-siblings only, and both full and half-siblings) was also associated with family history of MDD ($\chi^2 = 4.09$, $p = .03$), and none was significantly associated with proband trauma exposure. Hence, only sibling type was included in the adjusted analyses. A family history of MDD was reported by 32 cases (51%) and 15 controls (45%) (Table 2). This difference was not significant, with an adjusted odds ratio (OR) of 1.1 (0.47-2.76). Probands with a high trauma level were significantly more likely to be depressed than those with a low trauma level (adjusted OR = 2.8, 95% Confidence Interval [CI] = 1.10-7.10)

Combined effect of proband trauma and family history on proband MDD

status—We tested for interaction between family history and proband trauma level by computing the ORs for each combination of the two risk factors, using low trauma with negative family history as the reference group (Table 2). The results show a greater OR of 3.1 for the combined effect of high trauma and positive family history than the expected OR of 0.9 under an additive model for the joint effects of the two variables ($1.5 + 0.4 - 1.0 = 0.9$) (Ottman, 1996). The relative excess risk due to interaction (RERI) (Knol et al., 2007) was estimated as 2.1; 95% CI = (−1.15-5.32), $p = .21$, and the attributable proportion of depression due to the interaction (AP) was 0.68; 95% CI = (0.10-1.31), $p = .034$. The point estimates for RERI and AP were both greater than zero, with the latter being significantly so, suggesting positive interaction between family history and trauma level. Based on the AP, we can attribute 68% of the depression prevalence in individuals with both positive family history and high trauma level to this interaction.

The data in Table 2 also show a significant association between FH and trauma level within cases but not within controls. High trauma cases were over six times more likely than low trauma cases to report a positive family history of MDD: OR = 6.8 (2.05-22.55). In contrast, trauma level was not associated with family history among controls: OR = 1.5 (0.35-6.35).

Reconstructed Cohort Analysis

Familial aggregation of MDD among first-degree relatives—The prevalence of MDD among relatives of cases was 12%, versus 8% among relatives of controls (Table 3: adjusted RR for MDD = 1.4 [0.84-2.47]). In analyses of the relations of proband trauma level on depression in the relatives using relatives of control probands with low trauma as the reference group, the RR for relatives of cases with high trauma was 2.21 (1.16-4.24). Using the same formula as in the case-control analysis, RERI was estimated as 1.1, 95% CI = (−0.22-2.84), and AP as 0.51, 95% CI = (−0.07-1.09), $p = .08$. These estimates, though non-significant, showed interaction trends similar to those in the case-control analysis.

Major Depression according to relationship type, gender, and sibling status

The proportions of relatives reported to have MDD are shown in Table 4, by sex, relationship to proband, and proband case/control status. RRs for MDD were highest in parents and lowest in paternal half-siblings, and were slightly higher among male than

female relatives (1.8 vs. 1.2). A detailed breakdown of the MDD rates by relative sex and relationship to the proband is shown in Supplementary Table S2.

Sensitivity Analyses

Proband-relative agreement—There were 21 instances (19 families) in which a relative reported on by the proband also reported on him/herself. Details of proband age, gender, and relationship of relative to proband are shown in Supplementary Table S3. With the relative's report of MDD in him/herself used as the reference standard, sensitivity of the proband's report was 50% and specificity was 100%, reflecting underreporting by probands of their relatives' history of MDD. Percent agreement was 76% and kappa = 0.51. Supplementary Table S3b shows sensitivity/specificity estimates by relative type and proband gender. Though numbers were very small, sensitivity appeared to be higher for female vs. male probands. Cases and controls both showed underreporting (40% and 60% sensitivity), with little variation between them.

Familial risks according to proband MDD subtype—There were six subtypes of MDD, with overlap among them (Supplementary Table S4). Neither the proportion of cases with a family history of MDD nor the proportion of relatives reported to be affected varied substantially among these subtypes. The family history rates for depressed cases ranged from 44% (single-episode MDD) to 56% (recurrent-episode MDD). The proportions of case relatives reported to have MDD ranged from 10% (late-onset MDD) to 15% (recurrent, early-onset).

Discussion

To date, there are no known published family studies of MDD in AAs, despite evidence that MDD exerts considerable burden in this population. Our primary study finding was that trauma exposure appeared to amplify the effect of family history on MDD risk. Similarly, family history of MDD appeared to exacerbate the effect of trauma on risk for MDD. These findings differ from those of previous family studies of MDD, which used Caucasian samples, and showed a two- to five-fold increased risk associated with family history, regardless of trauma exposure (Sullivan, Neale, & Kendler, 2000). This study therefore represents an important step in addressing familial MDD risks in an urban AA population.

One possible explanation for this result is that depressed probands may have been more likely than controls to recall both traumatic events and family MDD history. However, although probands with MDD more often reported a family history if they had high trauma vs. low trauma, this was not true among controls without MDD. The lack of association between family history of MDD and trauma exposure in controls argues against the idea that trauma is driving recall of family history.

In our cohort analysis of MDD rates in the relatives, we evaluated MDD in the relatives in relation to trauma exposure in the proband. This is less straightforward to interpret than the findings of the case-control analysis, in which the proband's trauma exposure is considered in relation to his/her own risk of MDD. However, the proband's trauma exposure also has implications for the relatives. As we have shown previously (Ottman, 1996), under a model

of synergistic interaction between a genotype and an environmental exposure, exposed probands are more likely to have the high-risk genotype than are unexposed probands. This is also the basis for the case-only method of testing for gene-environment interaction, which evaluates whether a genotype is associated with an exposure in cases but not in the source population (Khoury & Flanders, 1996; VanderWeele, Hernandez-Diaz, & Hernan, 2010). In the context of this interpretation, our finding of increased risk for depression in the relatives of depressed probands with high exposure to trauma is consistent with a synergistic effect of trauma and a genetic susceptibility to MDD. In the absence of this synergism, probands with high and low exposure levels would not be expected to differ in the likelihood of having a genetic susceptibility to MDD, and hence no difference would be expected in the risks of MDD in their relatives.

The findings of our analysis lend support to a model of gene-environment interaction in which a genotype exacerbates the effect of a known risk factor for a disorder, but does not confer increased risk in the absence of the risk factor (Ottman, 1996). One example of this model is the serotonin transporter gene, which has been found in some populations to affect MDD risk only among individuals exposed to stressful life events (Caspi et al., 2003; Karg et al., 2011). Although AAs have been shown to have a greater prevalence of the protective long *L*-allele in their genotypes (Lotrich et al., 2003; Odgerel et al., 2013), the gene-disorder association observed in Caucasian populations has not been found among AA groups studied to-date (Lotrich et al., 2003; Odgerel et al., 2013).

Other competing explanations for which there has been some empirical support are gene-environment correlations in which those with a genetic predisposition to MDD may be at heightened risk of being exposed to trauma, which in turn contributes to their MDD (Inslicht et al., 2010); and shared genetic factors contributing to both trauma exposure and MDD (Fu et al., 2007; Sartor et al., 2012). These gene-environment correlations require additional empirical investigation before conclusions relevant to our results can be drawn.

In addition to the main study finding of an interaction between proband trauma and family MDD history, some of our secondary findings show interesting trends that warrant additional inquiry. We found a non-significant two-fold increased MDD risk among parents, but not among offspring and siblings of depressed cases relative to controls. Previous family studies showed less underreporting by probands of psychiatric disorders in parents and siblings than in offspring (Kosten, Anton, & Rounsaville, 1992; Weissman et al., 2000). The greater RR in parents in our study may have been explained by less underreporting in parents than in other relatives.

Before considering the scientific or clinical implications of our findings, some study limitations must be addressed. First, the lack of direct interviews with relatives or review of medical records may have increased the influence of recall bias or underreporting in the probands. The sensitivity analysis with additional informants suggests that probands underreported depression in their relatives, regardless of case/control status. Although this non-differential misclassification may not have affected the MDD relative risks among family members, the odds ratios for family history may have been biased toward the null hypothesis. Previous research has shown that multiple informants, direct interviews of

relatives and use of medical records can improve the accuracy of the risk estimates over sole reliance on the FHS (Milne et al., 2009; Ptak, Seeher, Jessen, Papassotiropoulos, & Heun, 2001; Weissman et al., 2000). However, in this study, where those options were not available or sparse, we urge caution in interpreting the estimates of the main effect of family history, which are likely conservative. We were reassured that our analysis found no instances of reports of MDD presence by the probands not corroborated by the relative, which allows us to tentatively assert that the main effect of family history is likely higher (but not lower) than observed in the present analyses. The overall trend of lower sensitivity ($< 70\%$) and high specificity ($< 90\%$) has been consistent with previous family studies using the FHS (Weissman et al., 2000). Along with future family studies of MDD in AA populations, it might be beneficial to calibrate the extent to which proband reports from current measures underestimate the effect of family history, and the implications for the interactions with other exposures on the MDD outcomes.

A second limitation is that underpowered analyses due to small sample sizes may have resulted in null findings or non-significant trends. For example, the family cohort relative risks of 2.0 or greater that were not statistically significant should be interpreted with caution. The heterogeneity of MDD also presented a challenge with smaller samples, resulting in non-significant trends for familial risks based on MDD subtypes.

A third limitation pertains to the convenience sample, which may limit the generalizability of our findings to other AA communities. Moreover, individuals of African ancestry in the US are diverse in SES, education, and cultural practices. Accordingly the interactions between genetics, trauma, and structural factors may impact AA subgroups differently. Recent epidemiological studies have highlighted significant differences between second-generation Black immigrants from the Caribbean and African Americans in MDD risk factors and outcomes (Assari & Caldwell, 2017; D. R. Williams et al., 2007). The limitations of convenience samples as well as the variability within AA subgroups underscore the need for future family studies in population-based cohorts that account for AA diversity.

Conclusions

This study highlights the plausibility of trauma as an important influence on the familial aggregation of depression in an urban AA community. Contributing factors could be of both genetic and environmental origin, with a plausible interaction between them. Given that this is the first family study of major depression in African Americans, additional research on the chronology, types, and symptom specificity of trauma and depression is necessary to sort out these factors. Underreporting of family depression in research studies can be mitigated by inclusion of medical records, direct interviews, and careful selection of family informants. Studies with larger, population-based samples are necessary for producing analyses that are adequately powered, and for addressing issues related to the heterogeneity of MDD and the diversity of AAs.

Clinicians who work in low-income, urban communities are especially likely to be in contact with AA patients who have experienced high levels of trauma and may be at risk for depression (Alim et al., 2006). AAs in treatment have more severe MDD that is associated

with greater impairment and disability than their white counterparts. A history of trauma exposure may influence the severity and impairment associated with MDD in AAs. MDD may be underreported or undetected by patients for several reasons including mental health stigma and a perceived lack of family history of the disorder (Bell et al., 2011). Attention to patients' personal trauma history and family MDD history may be beneficial in such settings even when they deny past or current MDD. Consideration of these factors may help to minimize under-detection in primary preventive care and treatment settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Proband selection for family study depression

Table 1

Proband characteristics and MDD case-control status

	Cases (N=63)	Controls (N=33)	<i>p</i> -value
RECRUITMENT MODE: <i>N</i> (%)			
Flyers	6 (9.5)	2 (6.0)	.43
Word of Mouth	56 (88.9)	29 (87.9)	
Other	1 (1.6)	2 (6.0)	
GEOGRAPHIC LOCATION: <i>N</i> (%)			
Manhattan	36 (57.1)	22 (66.7)	.81
Bronx	16 (25.4)	7 (21.2)	
Brooklyn	9 (14.2)	3 (9.1)	
Queens	2 (3.2)	1 (3.0)	
DEMOGRAPHICS			
Female: <i>N</i> (%)	41 (65.0)	15 (46.0)	.10
Age in years: <i>M</i> (<i>SD</i>)	52.5 (8.3)	53.8 (11.5)	.53
Years of education: <i>M</i> (<i>SD</i>)	12.6 (2.0)	12.2 (1.4)	.38
SOCIOECONOMIC STATUS (SES) INDICES			
Community Distress Index: <i>M</i> (<i>SD</i>)	73.7 (15.0)	76.3 (7.1)	.36
Percent below poverty level	31.7 (7.6)	32.0 (4.3)	.84
Median Income Ratio – MRI	60.5 (23.0)	58.2 (10.4)	.60
FAMILY SIZE & COMPOSITION			
Avg. No. Relatives per family: <i>M</i> (<i>SD</i>)	10 (4.0)	10 (4.2)	.72
Avg. No. Relatives per family whose Psych. History is known: <i>M</i> (<i>SD</i>)	9 (3.9)	9 (3.5)	.53
Female relatives: <i>N</i> (%)	228 (52.4)	108 (48.6)	.36
RELATIVE TYPE: <i>N</i> (%)			
Mothers	57 (13.1)	31 (14.0)	
Fathers	41 (9.4)	20 (9.0)	
Full siblings	132 (30.3)	46 (20.7)	
Half siblings	82 (18.9)	70 (31.5)	
Offspring	123 (28.3)	55 (24.8)	
PSYCHIATRIC HISTORY: <i>N</i> (%)			
Alcohol Dependence	23 (36.5)	10 (30.3)	.54
Drug Dependence	43 (68.3)	19 (57.6)	.30
Anxiety Disorders	17 (27.0)	5 (15.2)	.19
PTSD	22 (35.0)	3 (9.0)	.01
MEDICAL HISTORY			
Chronic Illness Index: <i>M</i> (<i>SD</i>)	0.19 (0.11)	0.2 (0.14)	.33
Body Mass Index: <i>M</i> (<i>SD</i>)	30.5 (6.8)	27.9 (5.9)	.07
TRAUMATIC EVENTS SCORE: <i>M</i> (<i>SD</i>)	0.4 (0.24)	0.3 (0.15)	.02

Note. Independent samples *t*-tests used to test for group differences in age, SES, years of education, chronic illness index, body mass index, and traumatic events score. Pearson chi-square or Fisher's exact test used to test for differences in categorical variables.

Table 2Odds ratios for major depression according to family history and trauma exposure level^a

Family history	Case	Control	Odds Ratio (95% C.I.)	Odds Ratio ^b (95% C.I.)
Positive	32	15	1.2 (0.53-2.88)	1.1 (0.47-2.73)
Negative	31	18	1.0 (referent)	1.0 (referent)
Trauma level				
High	39	12	3.0 (1.22-7.17)	2.8 (1.10-7.10)
Low	22	20	1.0 (referent)	1.0 (referent)
High Trauma, positive family history	26	6	3.1 (0.96-9.70)	3.2 (0.92-11.34)
High trauma, negative family history	13	6	1.5 (0.45-5.17)	1.6 (0.43-6.25)
Low trauma, positive family history	5	8	0.4 (0.12-1.68)	0.3 (0.10-1.37)
Low trauma, negative family history	17	12	1.0 (referent)	1.0 (referent)

^aThree probands (two cases and one control) had missing data for trauma exposure.^bAdjusted for family sibling status (full siblings only, half-siblings only, half-siblings and full siblings)

Table 3

Relative risks for depression among relatives of cases and controls

	Total N	Affected	Morbidity risk	Relative Risk (95% CI) ^a	
				Unadjusted	Adjusted ^b
Relatives of cases	435	53	12.2%	1.5 (0.87-2.57)	1.4 (0.84-2.47)
Relatives of controls	222	18	8.1%	1.0 (referent)	1.0 (referent)
Relatives of: ^c					
Cases with high trauma	273	43	15.8%	2.4 (1.22-4.53)	2.2 (1.16-4.24)
Cases with low trauma	146	7	4.8%	0.7 (0.26-1.79)	0.6 (0.25-1.71)
Controls with high trauma	73	7	9.6%	1.5 (0.62-3.72)	1.4 (0.59-3.53)
Controls with low trauma	140	9	6.4%	1.0 (referent)	1.0 (referent)

^aRelative risk (RR) estimates obtained through Poisson regression models, using generalized estimating equations to adjust for within-family correlations.^bAdjusted for relative age at time of death or interview and relative gender^c6 relatives of cases and 9 relatives of controls excluded from stratified analyses due to missing data on proband trauma

Table 4

Relative risks of MDD among relatives of cases and controls according to relationship and gender.

Relationship to proband	Relatives of Cases		Relatives of Controls		Morbidity risk (%)	Morbidity risk (%)	Relative Risk (95% CI) ^a
	Affected	Unaffected	Affected	Unaffected			
Parents	17	81	4	47	17.3	7.8	2.1 (0.77-5.75)
Siblings	29	185	11	104	13.6	9.6	1.3 (0.60-2.64)
Offspring	7	116	3	53	5.7	3.6	1.2 (0.34-4.48)
Gender							
Male	21	186	6	107	10.1	5.3	1.8 (0.77-4.38)
Female	32	196	12	97	14.0	11.0	1.2 (0.64-2.38)
Sibling type							
Full	16	116	5	40	12.1	11.1	1.1 (0.36-3.31)
Maternal half	11	47	4	48	19.0	7.7	1.9 (0.54-6.84)
Paternal half	2	22	2	16	8.3	11.1	0.5 (0.08-3.67)

^aRelative risk (RR) estimates obtained through Poisson regression models using generalized estimating equations (GEE), adjusted for relative age at death or interview and relative gender.