Early life depression: Social moderation of the influences of neurotransmitter candidate genes and physical attractiveness

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Abstract

DANIEL E. ADKINS: Early life depression: Social moderation of the influences of neurotransmitter candidate genes and physical attractiveness
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Understanding the social determinants of depression has remained a primary concern in the mental health literature for decades. Investigation into the topic has been productive, yielding a number of robust empirical findings and organizing theoretical frameworks. Thus, social scientists have made substantial progress in elucidating how social factors including stressful events, social support and socio-economic status influence depression over the life course. However, it is also clear that there are considerable individual differences in the impact of social factors, with some individuals showing greater vulnerability than others. This fact suggests that much of the variance in depression is due to interactions between social factors and personal characteristics not typically examined in social science research. This dissertation elaborates this line of reasoning, investigating social moderation of the influence of five neurotransmitter candidate genes and physical attractiveness on depression using data from the National Longitudinal Study of Adolescent Health.

In the first empirical chapter, the direct and interactive influences of candidate genes and various dimensions of social environmental risk on depression are examined. Using false discovery rate (FDR) methods to account for multiple testing, evidence suggests possible interactions between the *MAOA* VNTR promoter polymorphism, particularly the 2 repeat and 3.5/4 repeat variants, and social support among females. In the second empirical

chapter, temporal variation in the influence of neurotransmitter candidate genes across early life is examined. Again using FDR methods to account for multiple testing, results indicate temporal variation in the effects of the *DRD4* dopamine receptor gene (5 repeat variant) for the full sample, and the *MAOA* VNTR promoter polymorphism (3.5 repeat) among males. The final substantive chapter examines the depressogenic influence of another source of individual differences rarely considered by social scientists—physical attractiveness. Results indicate that attractiveness becomes increasingly influential on depression as individuals age through adolescence and young adulthood, and that less attractive individuals are more resilient to the effects of eventful stress than their more attractive counterparts. Overall, this research demonstrates that, in addition to their main effects on depression, social factors represent important moderators of the influence of genetic variation and physical attractiveness.

To my mother, Margaret Ann Cothran

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Chapter 1: Introduction

As one of the world's three leading causes of disability (Murray and Lopez 1997), depression is highly prevalent, costly, and associated with increased risk of morbidity and mortality (Kessler et al. 1994; Greenberg et al. 1993; Ustun et al. 1999). As such, substantial attention has been devoted to understanding the etiology of depression from various academic disciplines. The sociological perspective on mental health has proven particularly useful in this respect, as it has robustly demonstrated the importance of social factors in structuring exposure to stress and access to buffering psychological resources—factors known to be proximate determinants of depression. Indeed, this literature has been consolidated in a series of related theories including the *stress process* (Pearlin 1989) and *fundamental causes* (Link and Phelan 1995) perspectives, which provide convincing and coherent models of how social factors shape individuals' experiences to perpetuate mental health disparities.

Despite these important contributions to understanding the etiology of depression, sociological perspectives on mental health are characterized by limitations that have become increasingly obvious over the past decade. Research has shown that even with high quality data and sophisticated modeling, conventional social psychological approaches still fall short of providing comprehensive models of depression (Costello et al. 2002). One primary reason for this shortcoming is variation across individuals in sensitivity to social factors. It has been shown that individuals differ markedly in their ability to take advantage of protective factors and in their vulnerability to adversity (Monroe and Simons 1991; Zuckerman 1999). In response to this fact researchers have elaborated the *diathesis-stress* model that posits unobserved individual,

primarily genetic, differences as important moderators of the social determinants of depression. Thus, research suggests that substantial improvements to existing models of depression etiology are likely to be driven by the inclusion of data on sources of individual difference not typically considered in the social sciences, such as genetics.

Fortunately, technological advances in genotyping have led to unprecedented amounts of molecular genetic data becoming available over the past decade. This has resulted in exponential growth of molecular genetic studies of disease, including psychiatric disorders. But while research into the molecular underpinnings of depression has been conducted in parallel to social science approaches over the past decade, there has been little exchange between the literatures. This lack of synthesis has weakened research produced by both perspectives. In the case of sociological research, the pervasive exclusion of genetic factors has led to a serious omitted variable bias compromising much of the causal inference drawn from this research (Rowe 1994; Turkheimer 2004). Conversely, in genetics there is a burgeoning realization that for complex disorders like depression, genetic influence is likely to act through gene-environmental interactive paths and failure to model this interaction significantly weakens the ability to detect effects (Risch 2000; Moffitt et al. 2005). Despite this, gene-environment interaction (GxE) studies remain rare and when environmental measures are present in genetics research they are generally proximate measures such as stressful life events (SLE) (Moffitt et al. 2005). This practice is unfortunate as it threatens to marginalize the role of distal, structural causes of depression such as childhood poverty. As Pearlin (1989) noted over two decades ago, research focusing strictly on the effect of proximate stressors on mental health miss the vital sociological insight that exposure to stress, as well the presence of buffering psychological resources, is significantly influenced by one's social position.

Broadly, this project incorporates the individual differences perspective from psychology and behavior genetics to explain variation in the effects of the social determinants of depression. More concretely, it explores the role of established social predictors of depression as moderators of the influence of individual differences in constitutional factors—namely, five neurotransmitter candidate gene polymorphisms and physical attractiveness. Within this effort, special attention is paid to developing a context for addressing the current disjunct between sociological and genetic mental health literatures by incorporating sociology's more nuanced conceptualization of the social environment into the GxE perspective on depression. This is achieved through systematically testing for GxE between candidate genes and various sources of proximate and distal environmental risk, examining temporal variation in genetic effects using a life course perspective and accounting for multiple testing using advanced statistical genetics methods. Finally, in addition to examining the social and developmental moderation of genetic variation, the project also examines the influence of another understudied factor—physical attractiveness—from a social moderation perspective.

This dissertation is organized as three separate articles. Each article is based on an analysis of longitudinal data from the National Longitudinal Study of Adolescent Health using growth curve models to investigate social moderation of the influence of constitutional factors. The study has three specific aims:

Aim 1: Assess the influence of candidate genes, the stress process and GxE on depression in early life. Using linear mixed effects regression models, the direct and interactive influences of candidate genes 5-HTTLPR, *DRD4, MAOA, DRD2,* and DAT1) and social determinants on depression are examined. In accordance with stress process theory (Pearlin 1989), proximate and distal environmental risk are distinguished, and various dimensions of both types of

environmental risk are tested for GxE effects on depression. Finally, in order to conduct a rigorous, comprehensive examination of several genes, multiple specifications of allelic effects, and various dimensions of environmental risk, false discovery rate (FDR) methods are used to account for multiple testing.

Aim 2: Develop comprehensive longitudinal models of genetic, environmental and GxE influences on trajectories of depression. It is now well-established that depression follows a normative, inverted U-shaped trajectory across early life—peaking in late adolescence and falling in young adulthood (Ge et al. 2006; Adkins et al 2008). However, it is also clear that there is significant between-individual variation around mean trajectories (Adkins et al 2008; Adkins et al. 2009). Explaining these individual differences in early life depression trajectories has proven a difficult task, with well-specified models including exhaustive lists of social risk factors explaining only modest amounts of trajectory variance (Adkins et al. 2009, Natsuaki et al. 2009). This has led to growing interest in the role of genetics in explaining individual differences in depression development, with experts increasingly drawing on the diathesis-stress perspective to empirically investigate GxE in depression (e.g., Costello et al. 2002; Caspi et al. 2003). Despite this interest, virtually no research has considered gene × age interaction effects for candidate genes on depression trajectories in early life. The gap in the literature is addressed by investigating gene × age interaction on early life depression trajectories for five monoaminergic candidate genes, 5-HTTLPR, *DRD4, MAOA, DRD2,* and DAT1, using False Discovery Rate methods to control for the risks of false discoveries due to multiple testing.

Aim 3. Investigate social and developmental moderation in the influence of physical attractiveness in early life depression. Although a pervasive aspect of social reality and a central preoccupation of contemporary culture, physical attractiveness remains an understudied topic in

social science research. This is unfortunate because, as recent economic research on wage premiums has demonstrated (e.g., Biddle and Hamermesh 1998; Hamermesh 2006), the influence of physical attractiveness on outcomes of interest to social scientists can be considerable. In order to address this limitation, comprehensive models of social and developmental moderation of the effects physical attractiveness on age-based trajectories of depressive symptoms are developed. Several key questions guide the analyses. First, does physical attractiveness have an association to depression? Second, does this association vary in strength across adolescence and young adulthood? Finally, does physical attractiveness moderate the influence of social determinants of depression? Specifically, does attractiveness buffer against the deficits associated with gender and racial/ethnic minority status? And does it reduce the detrimental effects of childhood poverty, SLEs and social support deficits?

Theoretical Framework

The overarching intent of this study is to examine how social adversity interacts with constitutional individual differences to influence depression in early life. As such, the study draws together several perspectives in developing its theoretical framework. First, the present research synthesizes the GxE perspective emerging from psychiatric genetics (e.g., Moffitt et al. 2005) with the stress process theory of mental illness (Pearlin 1989). Next, it expands the GxE perspective to consider developmental, life course moderation of genetic effects. Finally, the project takes up the undertheorized topic of physical attractiveness, integrating psychological perspectives on the internalization of social perceptions into a sociological approach to mental health.

Gene-Environment Interaction and the Stress Process

The GxE perspective, building on *diathesis-stress* theory, conceptualizes depression as a neurological phenomenon caused by stable characteristics of the individual (e.g., direct genetic effects) interacting with physiological response to (primarily social) environmental adversity (Moffitt et al. 2005; Caspi et al. 2003). This paradigm represents a significant step forward from the strictly main effects analyses that predominant in the genetics literature, in that it explicitly acknowledges, and promotes the study of, social moderation of genetic effects. One prominent shortcoming of the GxE perspective, however, is its limited conception of the social environment, often narrowly restricting focus to proximate factors such as SLEs. Conversely, sociology offers a markedly richer conceptualization of the social environment. Pearlin's stress process paradigm (1981, 1989), in particular, offers a well-developed theoretical perspective on the matter, modeling environmental adversity as a system of proximate factors (e.g., life events, social support deficits), and distal structural influences (e.g., socioeconomic status). More specifically, this empirically verified stress process model posits low childhood SES to predispose individuals to experience stress, which, in turn, predisposes individuals to experience depression (e.g., Turner and Lloyd 1999; Turner and Butler 2003). The GxE perspective theorizes that while some of the effect of this environmental adversity is likely to be invariant across individuals due to genetic homogeneity (e.g., direct effect of childhood SES and SLE), some of it will vary according to genetic heterogeneity in sensitivity to adversity (e.g., GxE) (Rutter 2005; Moffitt et al. 2005). Thus, by synthesizing the GxE perspective with stress process theory a model is developed that maps how social adversity influences the individual and interacts with their genetic predispositions to produce depression.

Developmental Moderation of Genetic Influence

While social science research has effectively demonstrated a normative, inverted U-

shaped pattern in the development of depression and depressed affect in early life, it has been less successful in explaining the significant between-individual variation around these mean trajectories (Adkins et al 2008; Adkins et al. 2009). The recognition that exhaustive models of social risk explain only modest amounts of trajectory variance has stimulated interest in the role of genetics in explaining individual differences in depression development. Thus, experts have increasingly gravitated toward diathesis-stress perspectives to investigate gene × social environment interaction in depression (e.g., Costello et al. 2002; Caspi et al. 2003).

Moreover, several lines of inquiry within genetics have suggested the plausibility of temporal variation in the genetic effects. For instance, biometric genetics research has shown that the heritability of depression significantly varies across early life, suggesting that the influence of various genes may increase or decrease across this important developmental period (Bergen, Gardner, and Kendler 2006). This conclusion is further supported by epigenetics research showing substantial gene expression changes during early life, as developmental mechanisms "turn various genes off and on" (Whitelaw and Whitelaw 2006). Beyond suggesting consistent genetic effects across early life, contemporary genetics research has indicated that the influence of specific genetic loci may vary over the period. Thus, while empirical studies have been largely lacking, convergent evidence from the social sciences and genetics strongly suggest temporal variation in genetic influences on depression.

Social and Developmental Contingencies in the Effects of Physical Attractiveness

Given the central role of attractiveness in our social experience, it is surprising how little social science research has focused on the topic, outside of relatively insular literatures in personality and evolutionary psychology. This shortcoming has recently begun to be redressed, particularly in the area of labor economics, where a growing body of research has shown that

attractiveness is associated with a substantial wage premium (e.g., Biddle and Hamermesh 1998; Hamermesh 2006; Hamermesh and Biddle 1994). However, research focusing on the social implications of attractiveness is still in its infancy, with some of the most basic effects of attractiveness poorly understood. In particular, the effect of attractiveness on affective characteristics, such as depression, has received very little attention in the literature, in spite of being among the most direct, fundamental results of the trait.

Given the paucity of research on the influence of attractiveness on depression, it is not surprising that virtually nothing is known of how attractiveness interacts with developmental and social processes influencing depression in early life. However, there are several well-established social science perspectives that suggest such interaction. Regarding development, former longitudinal research has shown that developmental processes influence both normative trajectories of depressive symptoms in early life (Adkins et al. 2009; Ge et al. 1994, 2006), and the effects of key predictors. For instance, the influence of gender, which is recognized as one of the strongest and most consistent predictors of depression in adulthood (Nolen-Hoeksema 1990), is known to gradually emerge in early adolescence and thought to be related to pubertal changes (e.g., Angold et al. 1998). Given such developmental trends, it seems plausible that the impact of attractiveness on affect, and self-perception more generally, may also be developmentally moderated, increasing during adolescence as individuals begin to internalize social identities, develop sexual awareness and enter into more competitive milieus.

Similarly, while no empirical research has yet examined potential interactions between the social determinants of depression and attractiveness, prominent theoretical perspectives suggest a likely pattern.. Specifically, theories under the rubric of cumulative disadvantage (see McLeod and Owens 2004) posit that the presence of a given social disadvantage depletes an

individual's coping resources, leaving them more vulnerable to the pernicious effects additional adversity. Thus, this perspective suggests that sources of social disadvantage are apt have multiplicative detrimental effects on mental health when occurring in combination. Further, empirical support of cumulative disadvantage has been found in studies of early life depression. For instance, former research has shown that the detrimental effects of low socio-economic status (SES) are greater among demographic groups showing higher levels of depression—females and racial/ethnic minorities (Adkins et al. 2009). This raises the possibility that physical attractiveness may also function to moderate vulnerability to social determinants of depression, including demographic factors (i.e., gender and race/ethnicity) and components of the stress process (e.g., social support and stressful life events (SLEs).

Chapter 2: Gene-Environment Interaction in Early Life Depression: An Analysis of Interplay between the Stress Process And Five Monoamine Genes

Introduction

Over the past three decades, the sociological study of mental health has considerably advanced understanding of depression. More than any other approach, the sociological perspective has demonstrated the importance of social structural factors in the etiology of depression. Among the various theories of social influence on depression, Pearlin's stress process model (1981; 1989) is notable for both its longevity and breadth. In essence, the stress process model holds that the social location of individuals influences stress exposure and vulnerability that, in turn, produce distress response. But while research conducted from the stress process perspective, and complementary approaches such as Link and Phelan's fundamental causes theory (1995), have made critical contributions to our knowledge of depression, this success has, in a sense, jeopardized the future relevance of the perspective as an active research frontier in mental health. That is, by establishing such comprehensive models of social influence on depression, researchers have satisfied many of the primary goals of the approach, suggesting that future research conducted from a strictly structural perspective will likely meet with only incremental gains.

This does not imply, however, that the sociological study of depression has reached an impasse. Rather, it suggests that substantial future advances in understanding the function of social determinants will likely be driven by investigating their interactive effects with sources of individual differences not typically examined by social scientists, such as genetic variation. This observation is supported by research showing that even with high quality data and exhaustive, well-specified models, conventional social science approaches still fall short of providing

comprehensive models of depression (see Costello et al. 2002 for an official NIMH statement on the matter). A principal reason for this shortcoming is individual variation in sensitivity to social factors, with individuals differing substantially in their ability to take advantage of protective factors and in their vulnerability to social adversity (Monroe and Simons 1991; Zuckerman 1999). Although some of this variation may eventually be explained by improved measurement and modeling of social influences, there is a growing recognition that, as posited by the diathesis-stress model, much of it is likely due to constitutional differences.

Undoubtedly then, the diathesis-stress model, and the related GxE approach, have great potential to improve understanding of depression. These emerging perspectives are, however, characterized by serious theoretical shortcomings of their own—notably including a relatively weak conceptualization of the social environment. This lack of strong social theory in GxE research has lead to a general lack of conceptual rigor in separating proximate and distal environmental risks, with some studies analyzing composite measures aggregating the two (e.g., Eley et al. 2004). Furthermore, research to date from the GxE perspective has largely focused on proximate environmental factors, such as SLEs, to the neglect of more distal, and fundamental, structural causes. This bias has recently been formalized, as Moffitt et al. (2005) have explicitly called for a focus on proximate environmental factors, and the exclusion of distal ones, in their GxE research guidelines. This recommendation, though warranted in many cases, threatens to marginalize the role of distal, structural causes of depression such as childhood poverty. As Pearlin (1989) noted almost two decades ago, research focusing strictly on the effect of proximate stressors on mental health miss the vital sociological insight that exposure to stress, as well the presence of buffering psychological resources, is significantly influenced by one's structural position.

The current study has investigated these issues using data from the National Longitudinal Study of Adolescent Health and linear mixed effects regression models to systematically examine several candidate genes and apply a more comprehensive conceptualization of environmental risk. In accordance with stress process theory (Pearlin 1989), proximate and distal environmental risk were distinguished, and various dimensions of both types of environmental risk were tested for GxE effects on depression. Finally, in order to conduct a rigorous, comprehensive examination of several genes, multiple sources of individual differences not typically examined by social scientists, such as genetic specifications of allelic effects, and various dimensions of environmental risk, false discovery rate (FDR) methods were used to account for multiple testing.

Background

Early life depression

Adolescence is a life stage characterized by transition into more complex social environments increasing exposure to a wide array of stressors and life-shaping choices. And while the majority of individuals successfully negotiate this developmental period without any major psychological or emotional disorders, adolescents do evidence higher rates of depression[1] relative to most other age groups (e.g., Allgood-Merten et al. 1990; Adkins et al. 2008, 2009). Thus, major affective disorders often begin during adolescence and, unfortunately, for many adolescents experiencing depression (30-50%) this experience will be recurrent across the life course (Lewinsohn et al. 1999; Rao et al. 1999). Further, research indicates that early-onset

[1] "Depression" is herein defined as a psychological state characterized by low mood and persistent sadness. This state is often further characterized by secondary symptoms including anhedonia, disturbed sleep or appetite, low energy, poor concentration and interpersonal difficulties. Thus, the term "depression" is used in a generalized sense and not to refer to the clinical designation, "major depressive disorder" per se.

depressive disorders may be particularly informative for the study of GxE causation, due to an increased role of genetics in early-onset cases (Nobile et al. 2004). For instance, increased risk of affective disorders has been documented in the children of early-onset major depressive disorder cases relative to the children of later-onset cases (Weissman et al. 1988; Wickramaratne and Weissman 1998).

Genetic factors in depression

Epidemiological research offers strong evidence for genetic factors in depression with family studies indicating first-degree relatives of depressed probands to be 2.84 times more likely to experience major depression than controls, and twin studies indicating the heritability of unipolar depression to be 31-42% (Sullivan et al. 2000). However, despite substantial advances in understanding aggregate genetic effects in depression, progress in understanding the molecular architecture of the phenotype has been slow.

Candidate genes. Since reserpine and antidepressant pharmacology first suggested the role of monoamine neurotransmission in depression (Schildkraut 1965), various hypotheses of neurotransmitter dysregulation in mood disorders have been advanced. While no consensus has yet been reached regarding the primary molecular mechanism underlying mood disorder susceptibility, a confluence of neurobiological, pharmacological and molecular genetic evidence has supported an important role for monoaminergic neurotransmission, particularly the serotonergic and dopaminergic systems. Among the many candidate gene variants influencing these systems, polymorphisms in: 5-HTTLPR, *DRD4, MAOA* and DAT1 are among the most

promising.[2]

Serotonin Transporter (5HTT, locus symbol *SLC6A4*). Among neurotransmission systems the serotonergic system has received the most attention for its involvement in several processes including brain development and synaptic plasticity. Located at 17q11.2, the serotonin transporter gene (5-HTT) encodes a protein critically involved in the control of 5-HT function. Allelic variations in the 5′ flanking transcriptional region of 5-HTT gene (5-HTTLPR which controls 5-HTT expression and function) have been associated with personality traits including anxiety and aggressiveness (Anguelova et al. 2003). Short (S) and long (L) 5-HTTLPR variants differentially influence transcription activity of the 5-HTT gene promoter, protein concentration, and the consequent 5-HT uptake in lymphoblastoid cells. Further, recent research has shown 5-HTTLPR substantially influences the human amygdala-cingulate feedback circuit, indicating a developmental, systems-level mechanism underlying normal emotional reactivity and genetic susceptibility for depression (Pezawas et al. 2005).

While results of main effects of 5-HTTLPR on depression have been mixed (Anguelova et al. 2003), Caspi et al. (2003) has drawn together several lines of experimental genetic research to theorize that although the 5-HTT gene may not be directly associated with depression, it may moderate the serotonergic response to stress. Investigating this hypothesis, Caspi et al. (2003) found individuals possessing the S allele of 5-HTTLPR to present more depression in relation to stressful life events (SLEs) than individuals homozygous for the L allele. Since this study, several studies have attempted replication, yielding both positive (e.g., Gillespie et al. 2005) and

[2] While monoamine candidates represent the strongest family of depression candidate genes, other strong candidates have been advanced, notably including BDNP (Karege et al. 2002). Further, within the monoaminergic system several likely candidates exist beyond those examined here, including 5HTR2A, TH, TPH1, and COMT (see Levinson 2006 for review). Future studies should apply the analytical framework developed here to systematically search for GxE between these polymorphisms and leading social determinants.

negative results (e.g., Surtees et al. 2006).[3]

Dopamine D4 Receptor (*DRD4*)**.** The *DRD4* gene maps 11p15.5 and spans 3.4 kb. A functional variable number of tandem repeats (VNTR) polymorphism has been identified in the third exon in the *DRD4* gene, the region coding for the third intracellular loop of the receptor (Van Tol et al. 1992). The genetic variant is a 16 amino acid (48 bp) repeat polymorphism, which is repeated two to 11 times, with two (D4.2), four (D4.4), and seven (D4.7) repeats being the most common alleles (Van Tol et al. 1992). The mRNA distribution profile of *DRD4* shows elevated levels in limbic areas involved in the pathophysiology of major psychoses (Van Tol et al. 1991), and has high levels of expression in the frontal area of the brain and the nucleus acumbens, areas associated with lack of motivation, anhedonia, and affective and emotional behaviors (Emilien et al 1999; Oak et al 2000). While several lines of research have suggested *DRD4* as a candidate gene for mood disorders, association results have been mixed. Significant associations have been reported between *DRD4* and unipolar and bipolar depressive disorders (e.g., Manki et al 1996; Muglia et al 2002), but other studies have failed to confirm these findings (e.g., Bocchetta et al 1999; Serretti et al 2002). It has been suggested that these failures to replicate may have been due to underpowered samples (Lohmueller et al 2003), a view supported by a recent, comprehensive meta-analysis which found a strong significant association between the *DRD4*.2 allele and unipolar depression (Lopez et al. 2005).

The mechanism by which dopamine D4 receptor expression is regulated is not yet fully understood (Wang et al 2004). Most research to date has focused on the *DRD4*.7 allele, which in vitro studies suggest has decreased affinity for dopamine, and transmits weaker intracellular signals in comparison with other *DRD4* alleles (Asghari et al. 1995). While the *DRD4*.7 allele

[3] See Uher and McGuffin (2008) for a meta-analysis and explanation of heterogeneity in replication estimates (focusing on sample variation in age and gender, as well as variable specifications of environmental adversity).

has been consistently associated with attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and novelty seeking, it is the *DRD4*.2 allele which has been implicated in depression. One potential mechanism through which this effect may operate regards the role of D4 receptors in inhibiting adenylyl cyclase activity and thereby reducing conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) (Sanyal and Van Tol 1997; Watts et al 1999). It has been reported that dopamine *DRD4*.2 receptors are less potent than *DRD4*.4 and *DRD4*.10 in coupling to adenylyl cyclase and show a blunted ATP to cAMP conversion (e.g., Asghari et al 1995; Watts et al 1999). Thus, the D4 receptors with a suboptimal functionality, e.g., *DRD4*.2, may influence depression.

Monoamine Oxidase A promoter (MAOA-uVNTR). Two primary lines of evidence have indicated *MAOA* as a likely depression candidate gene. First, *MAOA* has a central role in controlling amine disposability at the synaptic cleft, preferentially metabolizes serotonin and norepinephrine (Bach et al., 1988). Second, *MAOA* inhibitors have been found effective in the treatment of depression (Murphy et al. 1994). Thus, while precise mechanism are not fully understood, these two findings provide compelling evidence for considering *MAOA* in candidate genes studies, as they demonstrate its modulation of the serotonergic system, one of the two leading biological pathways in the etiology of depression, and show robust pharmacological evidence that *MAOA* inhibition results in depressive symptom reduction, at least in a subgroup of patients. The *MAOA* gene is located on the short arm of the X chromosome (Xp11.23) (Sabol et al. 1998). While several different polymorphisms in the *MAOA* gene have been identified, only a polymorphism located 1.2 kb upstream of the *MAOA* coding sequences has been shown to affect the transcriptional activity of the *MAOA* gene promoter. This polymorphic region consists of a 30 bp repeated sequence present in 2, 3, 3.5, 4, or 5 copies. Alleles with 3.5 or 4 copies of the

repeat sequence are transcribed two to 10 times more efficiently than those with 2, 3 or 5 copies of the repeat (Sabol et al., 1998). While this promoter VNTR has shown association with several affective disorders including recurrent major depression (Preisig et al., 2000; Schulze et al., 2000), other studies have reported negative associations of this polymorphism with mood disorders (Furlong et al. 1999; Kunugi et al. 1999). Similar controversial results exist for GxE between the low activity alleles and childhood maltreatment for antisocial behavior (e.g., Caspi et al. 2002; Haberstick et al. 2005).

Dopamine Transporter (DAT1, locus symbol: *SLC6A3*). The dopamine transporter gene, DAT1 (locus symbol: *SLC6A3*), has been mapped to chromosome 5p15.3 (Vandenbergh et al. 1992). DAT1 has a 40 bp VNTR; ranging from 3-11 copies in the 3 untranslated region of the gene. In the central nervous system, the dopamine transporter protein, DAT1, mediates reuptake of dopamine from the synaptic cleft and thus, is largely responsible for the intensity and duration of dopaminergic neurotransmission (Storch et al. 2004). Given the central role of the dopaminergic system in neurobiological theories of depression, DAT represents a plausible depression candidate, although further functional research is needed to elucidate a precise biological mechanism linking the polymorphism to depression. However, pharmacological animal studies have been instructive in this regard, demonstrating that drugs affecting DAT function such as cocaine or amphetamines enhance dopaminergic signaling, which in turn can result in hyperactivity and other changes in mood and behavior. The importance of correct DAT function for normal behavior has been demonstrated in DAT knockout mice (Giros et al. 1996). Owing to the lack of the transporter protein, these animals have constantly elevated dopaminergic neurotransmission resulting in hyperactive behavior and thus, are unaffected by the psychostimulants cocaine and amphetamines. Genetic association studies have implicated the

DAT gene in the etiology of psychopathologies including ADHD (e.g., Cook et al. 1995), avoidant behavior (Blum et al. 1997), and bipolar affective disorders (Waldman et al. 1997; Kelsoe et al. 1996).

Dopamine D2 receptor (*DRD2*, rs1800497). The 3′ TaqI A polymorphism of the dopamine D2 receptor is a T to C transition in the 3′ non-coding region of the gene, 10.5 kb downstream of the stop codon and 9.4 kb downstream of the polyA signal (Bunzow et al. 1988, Grandy et al. 1989). The polymorphism has been suggested to be functionally relevant, affecting dopamine receptor D2 availability in postmortem striatal samples (Noble and Cox 1997; Thompson et al. 1997) and moderating dopamine density and glucose metabolic rate in dopaminergic regions in the human brain (Noble et al. 1997). Consequently, the polymorphism has been studied as a candidate for affective disorders, with studies generally focusing on the A1 minor allele as a risk variant, as functional studies of both humans and mice have shown individuals with the A1 allele to have lower density of dopamine D2 receptors throughout the brain (Nobel et al. 1997; Noble and Cox 1997). Empirical findings of main effect have been mixed, however, with some studies finding significant associations (Li et al. 1999) and others not (e.g., Serretti et al. 2000). Recent research has attempted to resolve this discrepancy using a GxE approach, finding a significant interaction between DRD2 and stressful life events SLEs on depressive symptomology (Elovainio et al. 2007).

Gene-environment interaction. Recently Moffitt et al. (2005) have advanced a rubric for selecting both candidate genes and environmental risk factors in GxE studies.[4] Regarding the

[4] As noted by Shanahan et al. (2007), gene-environment correlation (rGE) represents an important and frequently neglected process in molecular genetics research. Building on a longstanding behavior genetics literature, Shanahan and colleagues demonstrate that rGE and GxE are complementary mechanisms in attaining tertiary education in the

selection of candidate genes, they recommend the following criteria: common polymorphic variants, a direct gene-to-disorder association, and/or functional significance in relation to the environmental pathogen. The authors cite 5-HTTLPR as an exemplar, as the vulnerability conferring S allele is common and has been indicated to have functional significance in relation to environmental stress in animal studies prior to being analyzed in humans. For each of the other four candidate genes considered in this proposal: *DRD4*, *MAOA*, DAT1 and *DRD2*, the first condition is satisfied—the most probable risk alleles (i.e. 5-HTT-S, *DRD4*.2, *DRD4*.7, *MAOA*.3.5-4 and DAT1.9) are common in the study population. Further, condition two is satisfied because, as elaborated above, substantial pharmacological, experimental and association studies have suggested roles for each of these alleles in depression etiology. Though analysis results of these candidate gene's main effects on depression have been mixed, this is plausible if GxE are the primary effect path.

Regarding the selection of environmental risk factors, Moffitt and colleagues (2005) recommend environmental factors that have proven causal effects, demonstrated variability in response across individuals, and plausible biological mechanisms. As discussed further below, the conceptualization of environmental adversity in the current study is derived from the long-standing stress process perspective. Thirty years of research in this perspective has strongly indicated that each of the environmental risks examined here—stressful life events, social support, and childhood socio-economic environment—satisfy these criteria (see Turner and Scheiman 2008 for review).

The stress process perspective on environmental risk

Add Health genetic subsample examined here. While rGE was not examined here due to space constraints, it is clearly a substantively important issue deserving investigation in future research.

A longstanding axiom in the sociological study of health is that variation in health outcomes is largely a product of differences in social experiences. This perspective asserts that structural dimensions (e.g., socio-economic status [SES], race/ethnicity and gender) position individuals in social locations more or less conducive to health. Stress process theory extends this logic, theorizing the mechanisms through which social structure impacts health. In the seminal statement of the theory, Pearlin and colleagues (1981) argue that stress exposure is a primary determinant of mental health. They develop a conceptual model in which stress exposure is categorized in two classes, acute and chronic stress and theorize that the impact of stress is mediated and/or moderated by buffering personal resources such as social support, mastery and self-esteem. In later work Pearlin (1989) explicitly contextualizes this stress process model, arguing that individuals' exposure to stress and access to buffering resources is largely a function of their structural position in society. This stress process paradigm guides the conceptualization of environmental risk in this study. Thus, in the following discussion I conceptualize environmental risk in depression as a dichotomy of distal, structural causes and proximate sources of stress and support.[5]

Distal environmental risk: Childhood socio-economic disadvantage and depression. Despite consistent findings of association between SES and depression (Lorant et al. 2003 for meta-analysis), research has long stressed the importance of distinguishing the causal direction of this relationship, or as it is commonly phrased in the literature—distinguishing social

[5] The distinction of proximate and distal is particularly useful in the context of GxE studies. This is because as proximate influences often mediate the influence of distal factors, these influences are typically moderately to strongly correlated (e.g., Turner and Butler 2003). Thus, they may proxy for one another in GxE models, giving misleading, or suboptimal models of the GxE mechanism. It is only through systematically screening various proximate and distal factors that the optimal model can be determined.

causation from social selection[6]. While most research on the topic has been non-experimental and unable to allow strong causal inference, the small body of experimental and quasi-experimental evidence to date has generally offered support for social causation in mental health outcomes, though not precluding selection effects (Gennetian and Miller 2002; Costello et al. 2003 [see Case 2004]). For instance, Costello et al. (2003) examined data from the Great Smoky Mountains Study, in which a casino opened midway through the study giving every American Indian an income supplement. This exogenous shock raised 14% of sample families out of poverty, resulting in a significant reduction in emotional (i.e. depression and anxiety) symptoms for the children transitioning out of poverty (see Case 2003). This and other analyses using robust analytic approaches have indicated substantial social causation effects (e.g., Hass 2006).[7]

Also relevant is the multi-dimensionality of SES--although socio-economic factors correlate moderately, it has been shown that the various factors are often differentially influential (e.g., Braveman et al. 2005; Goodman 1999, Mirowsky and Ross 1998). For instance, analyzing a variety of datasets, Braveman and colleagues (2005) have shown that for most health outcomes, both income and education evidence independent significant effects. These findings have been collaborated for several outcomes in the presently analyzed National Longitudinal Study of Adolescent Health (Add Health) (Goodman 1999), including depression (Adkins et al. 2008). Moreover, this line of research has suggested that in early life, parental income and education are the most robustly influential commonly surveyed socio-economic indicators, with occupational status showing less consistent independent effects (Goodman 1999).

[6] The social causation model posits that stress associated with low SES leads to increased levels of depression; while the social selection hypothesis asserts that individuals suffering from depression are more likely to drift into, or fail to rise out of, poverty (Dohrenwend et al. 1992).

[7]In the current study we have largely avoided the risk of confounding social selection effects through focusing on parental SES during the subject's youth. Thus, social selection effects are likely to be minimized as the children's mental health is generally unlikely to have a dramatic influence on their parent's SES, particularly given that a major component of SES—parental education, was generally determined prior to the subjects' births.

In line with the guidelines advanced by Moffitt and colleagues (2005), GxE is indicated by the considerable variation in depression within the lowest socio-economic strata, with some individuals proving more resilient to the adversity of poverty than others (Costello et al. 2003). And though little empirical research on the interaction of candidate genes with socio-economic environment has been conducted, with most GxE studies focusing on more proximate environmental risks such as SLEs, there is evidence suggesting GxE with SES. For instance, Eley et al. (2004) included parental education in their index of family environmental risk, and found 5-HTT-S to significantly interact with family environmental risk to promote depression among females. Further, though not explicitly addressing depression, Manuck et al. (2005) found significant interaction between both personal SES and mean community SES with 5-HTT-S in brain serotonergic responsivity. Thus, childhood SES remains a promising and under-investigated environmental factor in GxE studies of depression.

Proximate environmental risk: Stressful life events, social support and depression. In the past 30 years many studies have examined the influence of recent SLEs on depression, providing consistent evidence of significant association in both adulthood (e.g., Paykel 1978; Kendler et al. 1999) and early life (e.g., Goodyer et al. 1985, 1987). Furthermore, research using robust co-twin methods has demonstrated that though a portion of the association is non-casual due to selection into risky environments by individuals predisposed to depression, the majority of the effect of SLEs on depression is causal (Kendler et al. 1999). However, not all individuals experiencing a SLE react depressively, and many researchers have suggested that genetic differences are a key factor in explaining differential sensitivity to SLEs (Costello 2002; Caspi 2003). Indeed, in one of the first proof of principle studies in molecular GxE research, Caspi and colleagues (2003)

presented evidence that SLEs and the short 5-HTT allele interact to promote depression in young adults. While subsequent replication efforts have yielded mixed results, SLEs continue to be viewed as a likely environmental risk factor in GxE mental health studies.

Social support is another key component of the stress process perspective, with seminal theoretical perspectives arguing that psychosocial resources, such as social support, are primary protective factors buffering the negative effects of stress on mental health (Pearlin et al. 1981; Pearlin 1989). Empirical analyses have consistently supported this proposition, indicating social support to be among the strongest buffering psychosocial resources typically examined (Turner and Lloyd 1999). However, as is the case with other social determinants of depression, individuals differ in their ability to capitalize on the protective effects of social support (Adkins et al. 2008), and genetic variation is likely to explain a portion of this differential vulnerability.[8]

One overlooked issue in the literature to date is the lack of effective distinction between various proximate and distal environmental risk factors in depression GxE research. For instance, as one of the more robust findings to date, the 5-HTT-SLE interaction is considered an important proof of principle for GxE in psychiatric genetics (Moffitt et al. 2005). However, closer examination reveals considerable heterogeneity in the operationalization of life stress in this research. While Caspi et al. (2003) define life stress exclusively as SLE occurring over the past five years; other specifications include social support (Grabe et al. 2005; Kaufman et al. 2004) and parental educational attainment (Eley et al. 2004). The proposed study will clarify the issue of proximate and distal environmental risk, systematically testing all major components of the stress process for GxE on depression in early life.

[8] Most GxE candidate studies to date have operated under the expectation that risk alleles will be "activated" in adverse environments, thus implying that individuals with the risk alleles will have greater distress response to environments that have general deleterious effects in all, or most individuals. This would suggest that social support deficits will have outsized effects on individuals at genetic risk.

Data and Methods

Sample

Data were analyzed from three waves of the National Longitudinal Study of Adolescent Health (Add Health). Add Health is a large nationally representative, longitudinal sample of adolescents and young adults. The National Quality Education Database was used as the baseline sample frame, from which 80 high schools were selected with an additional 52 feeder middle-schools. The overall response rate for the 134 participating schools was 79 percent. Of the over 90,000 students who completed in-school surveys during the 1994-1995 academic year, a sample of 20,745 adolescents in grades 7-12 were selected and have been interviewed 3 times in 1994–1995, 1995–1996, and 2001–2002. A questionnaire was also administered to a selected residential parent of each adolescent. Further details of Add Health's sampling design, response rates, and data quality are well-documented (http://www.cpc.unc.edu/projects/addhealth/design).

The current study analyzes data from the Add Health sibling subsample, for which DNA measures are available. The sibling sample is composed of pairs of respondents residing in the same household, and includes individuals of various degrees of biological relatedness, ranging from monozygotic twins to unrelated individuals. Respondents were included in the analysis sample if they had nonmissing values on all variables on at least one assessment.[9] The total analysis sample consisted of 5627 observations for 1914 individuals, with each individual contributing an average of 2.9 observations. Individuals were nested within 1131 households, with each household containing 1-4 individuals (1.7 on average).

***M**easures*

[9] As per the casewise deletion method of handling missing data.

Depression. Depression was measured using a 9-item scale derived from the conventional 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977). The 20-item CES-D is composed of questions on a number of physical and psychological symptoms of depression, which cluster into four factors: somatic, depressed affect, positive affect, and interpersonal relations (Ensel 1996; Radloff 1977).[10] The scale has been validated using confirmatory factor analysis (CFA) in adult samples of Whites and Blacks (Blazer et al. 1998).[11] It has also been validated in samples of adolescents and young adults (Radloff 1991). Fortunately, a 19-item CES-D was collected in the first two waves of Add Health and a comparison with the subscale (9 items) indicated a high correlation (r = 0.91 and 0.92 in waves one and two, respectively). Individual items were coded on a four-point scale to indicate the frequency of symptoms occurring during the past week, ranging from never or rarely (0) to most or all of the time (3). The primary outcome used in this analysis is the simple average of the 9 items.[12]

In addition to using a simple average of the 9 items available across in all three survey waves[13], sensitivity analyses were conducted using: 1) a CFA factor score of the 9 items, 2) an

[10] One common issue arising in research on affective issues is the relationship of depressive symptoms to clinical diagnosis of depression (i.e., major depressive disorder). While the nature of this relationship continues to be debated, it is well-established that the CES-D is very strongly associated with MDD diagnosis (Fetchner-Bates et al. 1994). Thus, regardless of their exact relationship, the consensus among clinical practitioners is that symptom questionnaires, such as CES-D, tap much of the same construct as DSM IV-TR diagnoses, and thus, are adequate to identify clinical depressed individuals (Williams et al. 2002).

[11] While Blazer and colleagues (1998) found racial measurement invariance across most items, see Perreira et al. (2005) for contrasting findings indicating widespread measurement invariance across racial groups for the CES-D.

[12] This 9 item average CES-D specification matches the conceptual definition of depression given above in that each of the four major dimensions of the depression construct are represented by items in the CES-D measure. However, as some psychometric research has found that a simple summary of all four dimensions does not adequately fit the data, a measure composed of the 3 items found to represent negative affect and have desirable psychometric properties (Perreira et al. 2005) was analyzed, in addition to the 9 item measure.

[13] While a factor analytic approach yields improved measurement, simple sum/average measures of depression questionnaire items are, by far, the predominant specification in the literature. Thus, the current project analyzes

average of the 3 depressed affect items collected in all waves, which have been shown to be measurement invariant across racial/ethnic and immigrant groups (Perreira et al .2005), and 3) a factor score of these 3 items. It has been shown previously that the use of factor scores for phenotypic measurement refinement can improve power to detect genetic effects (e.g., van den Oord et al. 2008). Further, analyses of the current data indicate that allowing factor loadings to vary significantly improves model fit for both the 9 and 3 item measures. In addition to measurement invariance characteristics, the use of the 3 item subscale was also indicated by both notably higher factor loadings for these items relative to the other 6 indicators, as well as stronger theoretical correspondence of the items to the depression construct (see Perreira et al. 2005). Correlations were high between all 4 specifications of the depression variable (r = 0.84-0.98). A constant was added to the factor scores setting their minimum values equal 0, in order increase comparability of model parameters across depression specifications. Finally, to assure that results are not driven by multidimensionality in the CES-D or measurement variance across racial/ethnic groups, more rigorous SEM sensitivity analyses are conducted, modeling the 3 items that have been demonstrated to be measurement invariant depressed affect indicators as latent variable repeated measures.

Parental socioeconomic status. Add Health allows respondents to report parental education levels for up to four parents—resident mother and father figures, and for cases in which biological parents live outside of the respondent's household, nonresident biological mother and father. These variables describe the highest level of education that the parent has completed, and range from "never went to school" to "professional training beyond a four year

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questionnaire averages, as well as factor scores, to provide continuity with previous research and facilitate replication in other samples where factor loading may differ from those estimated here.

college or university". Based on previous analyses these items were coded as continuous variables (Adkins et al. 2008). Finally, for each respondent, the mean was then taken of all reported parental education levels, which improved the explanatory power of the variable relative to any single parent's level. Household income was ascertained from the parental questionnaire and includes all sources of income from the previous year (measured in thousands of dollars), and was logged in these analyses. Correlation between parental education and logged household income was moderate (r = 0.45), indicating collinearity was not problematically high. SES indicators were mean-centered to aid in model interpretation.

Stressful life events. An additive index was used to measure cumulative exposure to stressful life events. Presented in Appendix 2.1, the SLE index used here is derived from one developed by Ge et al. (1994). Established criteria for the development of the SLE index were used in modifying and expanding the measure for the Add Health survey (Turner and Wheaton 1995).[14] For instance, only acute events of sudden onset and of limited duration that occurred within 12 months of the interview were included (Turner and Wheaton 1995).[15] Further, given previous research indicating that undesirable life events are more likely to adversely affect health (e.g., Compas 1987), only negative life events were included in the index. To ensure a complete

[14] Previous research has explicitly indicated that as SLE indices are based on the concept of allostatic load, a typical (effect) factor analytic approach to measuring SLEs is not appropriate (see Turner and Wheaton 1995). This is because, in accordance with the allostatic load perspective, stress is viewed as a cumulative biological process. Regardless of whether stressful events are correlated (which the effect factor analytic model assumes), each additional event is judged to increase allostatic load. Thus, the ideal measurement model for the SLE index is a *causal indicator* factor model, in which each event has an independent causal effect on a latent allostatic load construct (see Bollen and Davis 2009). However, due to the complexity of the current model, optimization problems precluded the estimation of such a causal indicator model of allostatic load. Future research should focus on improving the measurement of SLEs using this innovative latent variable approach.

[15] The 12 month window for SLEs ensures that, for the vast majority of cases, the events occurred prior to the depression evaluation, which questions respondents on depressive symptoms experienced in the past week. The temporal precedence of SLEs helps identify the causal direction of the relationship of SLEs to depression as the direction of causality cannot flow from depression at the time of evaluation to determine a previously occurring SLE.

coverage of stressful events, approximately 50 items from various domains of life (e.g., family, romantic and peer conflicts, academic problems, involvement/exposure to violence, death of family and friends) were included. A major challenge of operationalizing SLEs is longitudinal accountability—as adolescents make the transition into adulthood, some stressors become irrelevant (e.g., expulsion from school) and other stressors become relevant (e.g., divorce or entering military service). Thus, to ensure stress was appropriately measured at different life stages, slightly different set of items is used in wave III to capture the different life experiences. Finally, similar items (such as miscarriage and still birth) were grouped together to avoid making the measurement overly specific. A simple, additive index was created from the selected items and is mean-centered in the current analysis.

Social support. The social support index shown in Appendix 2.2 is a composite measure of perceived social support across waves I and II. It assesses how the respondents feel about their relationship with their closest social ties including family, teachers and parents. A CFA of the items indicated marginally adequate fit (CFI = 0.971; RMSEA = 0.06) when including wave-specific factors and item-specific correlated errors between the two waves. A simple average of all the social support items was calculated and mean-centered in this analysis. To address potential concerns with the simplified specification of social support used in the mixed model analyses, the construct is modeled as the CFA described above in the SEM sensitivity analyses.

Race/ethnicity. Add Health allows respondents to indicate as many race and ethnic categories as deemed applicable. Approximately 4% of the participants report a multiracial/ethnic identity. Following criteria developed by Add Health data administrators, we

assign one racial identity for persons reporting multiple backgrounds.[16] This method combines Add Health's five dichotomous race variables and the Hispanic ethnicity variable as following: respondents identifying a single race were coded accordingly; respondents identifying as Hispanic were coded as such regardless of racial designation; those identifying as "black or African American" and any other race were designated as Black; those identifying as Asian and any race other than Black were coded as Asian, those identifying as Native American or "other" were coded as Native American, and those identifying only as "other" were coded as such.[17]

Candidate genes. In Wave III in 2002, DNA samples were collected from a subset of the Add Health sample. Genomic DNA was isolated from buccal cells at the Institute for Behavioral Genetics, University of Colorado (Smolen and Hewitt, www.cpc.unc.edu/projects/addhealth/), using a modification of published methods (Lench et al. 1988; Meulenbelt et al. 1995; Spitz et al. 1996; Freeman et al. 1997). The average yield of DNA was 5871 mg. All of the Wave III buccal DNA samples are of excellent quality and have been used to assess nearly 48,000 genotypes.

DAT1: The allelic distribution of the 40 base pair (bp) VNTR in the 3' untranslated region (UTR) of the gene has been determined in duplicate (two separate PCR amplifications and analyses, 5224 genotypes). The allelic distributions in bp and number of repeats (#R) were: 320 bp (6R), 0.0002%; 360 bp (7R), 0.003%; 400 bp (8R), 0.004%; 440 bp (9R), 21.0%; 480 bp (10R), 77.0%; and 520 bp (11R), 0.009%. *DRD4*: The 48 bp VNTR element in the third exon was determined in duplicate as above (5224 genotypes). The allelic distributions were: 379 bp (2R), 0.09%; 427 bp (3R), 0.03%; 475 bp (4R), 65.0%; 523 bp (5R), 0.01%; 571 bp (6R),

[16] http://www.cpc.unc.edu/projects/addhealth/data/using/code/race

[17] Former research comparing this coding approach with another in which only individuals identifying as one race/ethnic group were coded as such and all other individuals were coded as "multiracial" suggest that findings are generally robust across coding schemes (Adkins et al. 2009).

0.008%; 619 bp (7R), 20.0%; 667 bp (8R) 0.009%; 715 bp (9R), 0.0006%; and 763 bp (10R), 0.002%. *SLC6A4*: The 44 bp addition/deletion in the 5' regulatory region was determined in duplicate as above (5224 genotypes). The allelic distributions were: 484 bp ("short allele), 43.0%; and 528 bp ("long allele"), 57.0%. MAOA-uVNTR: The 30 bp VNTR in the promoter was determined in duplicate as above (5224 genotypes). The allelic distributions were: 291 bp (2R), 1.1% (males), 0.01% (females); 321 bp (3R), 40.9% (males), 38.0% (females); 336 bp (3.5R), 0.8% (males), 0.01% (females); 351 bp (4R), 55.3% (males), 58.0% (females); 381 bp (5R), 1.38% (males), 0.01% (females). *DRD2* TaqIA: The polymorphic TaqI restriction endonuclease site was determined in duplicate as above (5224 genotypes). The allelic distributions were: 178 bp, 72.8%; 304 bp, 27.2%.

Analytical strategy

Linear mixed effects models (i.e., hierarchical linear models) were used to assess the effects of candidate genes, and their interactions with environmental risks, on depression. Mixed models have long been established in the statistical literature for the analysis of clustered, non-independent data (Searle 1971; Searle et al. 1992), and have recently been used in similar molecular genetic analysis of Add Health data (e.g., Guo et al. 2006). The following equation describes a simplified version of the general mixed regression model of depression (DS):

$$DS_{jit} = \beta_0 + \beta_1 Gene + \beta_2 Envir.Risk + \beta_4 GxE + \beta_k Controls + \mu_{j0} + \upsilon_{ji0} + e_{jit}$$

where *j, i,* and *t* index the three levels of data: sibling cluster (i.e., household), individual, and assessment, respectively. Thus, the model allows random effects at both the sibling cluster and

individual levels. Conditional on the random intercepts μ_{j0} and υ_{ji0} at the sibling cluster and individual levels, the siblings and repeated assessments were assumed to be independent. The household level random effect should, in principle, capture much of the influence of population stratification on the results. This because it accounts for intercept variation in depression between households, with the assumption that the household cluster should be a decent proxy for "identical by descent" genetic similarity. Further control of population stratification is gained by the inclusion of self-identified race/ethnicity in all models.[18]

The base model, without genetic effects, controls for race/ethnicity, gender, age, age^2, social support, parental education, household income, and SLEs.[19] This model is consistent with stress process theory and has been empirically tested by the author in previous analyses of Add Health (see Adkins et al. 2008, Adkins et al. 2009). Building on the base model, five sets of primary analyses were conducted here. The first set of analyses investigated genetic main effects, with each estimated model including a genetic variable in addition to the base model. The second through fifth sets of analyses investigated GxE. In these GxE analyses, in addition to the base model, each estimated model included a genetic variable and an interaction term between the genetic variable and an environmental risk factor—household income in the second set of analyses, parental education in the third, SLEs in the fourth, and social support in the fifth set. All five sets of analyses were repeated for each of the three sensitivity outcomes. After identifying the most promising models, the robustness of these models are tested in two final sensitivity analyses; first, by square root transforming the CES-D and rerunning the promising models to eliminate the possibility that results are driven by outliers. And, in the final sensitivity

[18] While self-identified race/ethnicity is clearly a social construct, it has been shown to correlate strongly to primary genomic ancestral dimensions (Tang et al. 2005).

[19] The effects of age and age^2, as well as those of all other predictors, are modeled as fixed effects. This specification was made to facilitate model optimization.

analyses, fitting the promising models as structural equation models (SEM) to allow more accurate measurement of the several latent constructs modeled (i.e., depression, social support, parental education).

For DAT1, *DRD4, SLC6A4,* and *DRD4,* analyses were conducted on the full sample of both males and females. An alternative approach was used for *MAOA*, as its location on the X chromosome complicates direct comparisons between males and females. This is because males have a single allele at this locus, making their characterization straightforward, while females have two alleles, one of which may be silenced to some degree due to X-inactivation (Meyer-Lindenberg et al. 2006; Jansson et al. 2005). Given this ambiguity, analyses of *MAOA* were stratified by gender, while the full sample is jointly analyzed for all other genes.[20]

The case of *MAOA* in females is illustrative of a more pervasive issue—it is often unclear what the correct specifications of allelic effect are (e.g., Lee et al. 2008). Examples of both additive effects, in which there is a dose-response relationship between number of the risk alleles and the phenotype, and dominance effects, where a single allele is sufficient to give the full phenotypic effect, abound in the psychiatric genetics literature. Moreover, in psychiatric genetics there are also documented instances of *heterosis*, a situation in which heterozygosity at a given locus is associated with a greater or lesser phenotypic effect, compared to homozygotes of either allele (Chen et al. 1994; Guo et al. 2007). And though former human genetics research, animal studies, and functional analyses can be informative in selecting allelic effect specifications, this knowledge is incomplete at best, and expectations are frequently overturned. *DRD4* is instructive in this regard—while functional studies have generally implicated the 7R allele (Asghari et al.

[20] While there is a possibility of gender differences in the function of examined candidate genes other than *MAOA*, I have chosen to analyze pooled samples for all polymorphisms other than *MAOA*. This represents a decision to maximize power and reduce the influence of multiple testing, potentially at the expense precision. Future research should expand the current topic by considering gender differences in candidate gene effects.

1995), a recent meta-analysis instead only showed significant association between the 2R allele and unipolar depression (Lopez et al. 2005). The case of *MAOA* and delinquency is similarly instructive as Caspi et al. (2002) have reported GxE between the *MAOA* 3R and maltreatment, while Guo and colleagues (2008a, 2008b) have instead shown evidence of both main effects and GxE with the 2R allele, offering no support for a role of the 3R allele in delinquency.

Overall, the frequency of unexpected associations combined with relatively weak theory of genetic mechanisms suggests that approaches relying strictly on precedent to specify allelic effects are vulnerable to missing true associations. This line of logic recommends an empirical approach to systematically screen various allelic effect specifications and GxE configurations. Moreover, in practice researchers conducting candidate gene studies often tacitly employ such empirical, exploratory methods, but do not adjust significance criteria to account for multiple testing (Colhoun et al. 2003). Indeed, the enormous problem of false discoveries in candidate gene research, with 19 out every 20 associations currently reported in the literature thought be false, is largely due to researchers conducting multiple tests, but only reporting significant findings (Colhoun et al. 2003; van den Oord 2008). Given these facts, experts have argued that optimal methods for genetic discovery should cast a wide net, using exhaustive exploratory techniques, yet explicitly recognize the reduced confidence in any single association and adjust significance criteria accordingly (van den Oord 2008; van den Oord 2005). Research has indicated that controlling for the false discovery rate (FDR) is a superior method for achieving these aims in candidate gene studies with correlated tests, such as the current analysis (van den Oord and Sullivan 2003; van den Oord 2005).

False discovery rate

For each allele of the five monoamine genes investigated in this study, additive, dominance and heterosis allelic effects were tested, each in a separate mixed model; and in the GxE analyses, each of these allelic effect specifications were tested for interaction with each of the four environmental risk factors, each in separate mixed model. Thus, in the primary analysis there were 80 allelic effect specifications tested (counting *MAOA* alleles separately for male and females) in 5 sets of analyses—1) main genetic effects, and GxE for 2) household income, 3) parental education, 4) SLEs, and 5) social support. Therefore, 400 models were estimated for the primary analysis, and an additional 400 models were estimated for each of the 3 sensitivity analyses of alternative depression measures, with 1600 models estimated in total.

Standard p-values for the genetic and GxE effects from each estimated mixed model were collected and FDRs were estimated from the p-value data. FDRs can be estimated in various ways and many standard statistical packages (e.g., R, SAS) have such estimation procedures implemented. The current study estimates a FDR for a chosen threshold p-value *t*. If the *m* p-values are denoted p_i, $i = 1 \ldots m$, this can be done using the formula:

$$\widehat{\mathrm{FDR}}(t) = \frac{mt}{\#\{p_i \leq t\}}$$

Thus, the FDR is estimated by dividing the estimated number of false discoveries (the number of tests times the probability *t* of rejecting a marker without effect) by the total number of significant markers (i.e. total number of p-values smaller than *t*) that includes the false and true positives. To avoid arbitrary choices, each of the observed p-values can be used as a threshold p-value *t*. The resulting FDR statistics are then called q-values. Associations with $q < 0.15$ were considered "significant", indicating the 1.5 out of 10 reported findings would be expected to be a

false discovery[21],[22]. Data management and statistical analyses were conducted using Stata 10 (StataCorp LP; www.stata.com) and FDRs were calculated using R 2.7.2 (http://www.r-project.org/index.html).

Results

Table 2.1 presents descriptive statistics for the 4 specification of the CES-D and the environmental predictors at Wave I by gender. Several notable trends were evident. First, consistent with former analyses of Add Health and other samples, females reported higher levels of depression than males for all for all specification of the CES-D.[23] Differences between the 4 specifications of the CES-D were observed, with means, SDs, and ranges smaller for the factor scores than the averages. Demographically, the sample included slightly more females than males, and Add Health's minority oversample was apparent with all minority racial/ethnic groups representing higher proportions of the sample than the national population. The sample was primarily of high school age in Wave I, and both genders generally reported comparably high levels of perceived social support. Measures of SES indicated that the mean yearly household income for respondents is approximately $45,000-$50,000 and the mean highest parental educational attainment was slightly greater than a high school degree. Finally, SLEs were more frequently reported by males (mean = 2.75) than females (mean = 1.85).

[21] While $q < 0.15$ represents a relatively liberal q-value threshold, this fact is balanced by the numerous sensitivity analyses conducted. Final judgment of the importance of findings is, thus, contingent on the overall robustness of the result and not any single measure of statistical significance.

[22] While FDR is generally viewed as a superior method for adjusting significance criteria for multiple testing, it is not without limitations. Chief among these are its difficulty in detecting true minor effects with very modest effects sizes and a tendency to be overly liberal in analyses with small to moderate numbers of tests (see van den Oord 2008 for review).

[23] The issue of gender-based measurement invariance in the CES-D has been examined by Meadows et al. (2006). The authors find the instrument invariant across genders.

Table 2.2 shows the number of significant genetic and GxE effects at various *q*-value thresholds. The first 5 rows of Table 2.2 show that for the primary outcome, the 9 item CES-D average, 7 out of the approximately 720 genetic and GxE effects tested[24] were significant at $q < 0.15$, and 2 were significant at $q < 0.05$. All significant findings were for models examining *MAOA* × social support interaction among females. In addition to the significant findings for the primary outcome, the sensitivity analyses of alternate CES-D specifications indicated that out approximately 2160 parameters tested, 11 effects were significant at $q < 0.15$, and 2 were significant at $q < 0.05$. This indicates that there were a small number of effects with *p*-values significantly lower than expected by chance given the number of tests, suggesting the presence of several true effects.

Table 2.3 describes the top hits from the analysis ($q < 0.15$, hereafter referred to as significant). The first 7 and latter 11 rows describe significant findings for the primary and sensitivity outcomes, respectively. Findings from both sets of outcomes were sorted by *p*-values in ascending order. All significant findings involved GxE models for either *MAOA* among females (various alleles and environmental risks) or 8R DAT1 genotype in the full sample. The strongest associations for both the primary and sensitivity outcomes were for models of GxE for the 2R *MAOA* allele among females. The very strongest associations ($p = 9.71E\text{-}05$ and $p = 0.0006$) were for 2R/2R *MAOA* × SLEs interactions on the average and factor score 3 item CES-D measures, respectively. However, as the MAO 2R/2R genotype is exceedingly rare (0.10% of the female sample), this result is considered of limited interest and further discussion is focused on other more common variants.[25]

[24] Eighty allelic effects for the main genetic effects analysis and 80 main effects + 80 GxE effects for each of the 4 GxE analyses equals a total of 720 effects considered in the FDR analysis. This figure is considered approximate because in a few models 1 of the 2 parameters of interest in the GxE analyses was dropped due to collinearity.

All other significant findings for the *MAOA* polymorphism among females were interactions with social support. Results indicate that females with the relatively uncommon 2R MAO allele (2.3% of the female sample) do not benefit from the buffering effects of social support on depression. This was found for various specifications of the *MAOA* 2R allele for the primary outcome (p = 0.002 for no 2R, p = 0.001 for 2R/other, and p = 0.006 for additive effect of number of 2R alleles), as well as for the no 2R specification for the 9 item factor score outcome.[26] Table 2.4 shows all estimates from the MAO no 2R × social support model for each of the 4 outcome specifications. *P*-values were higher for the 3 item CES-D specifications (p = 0.052 and 0.058), than for the 9 item specifications. Additional sensitivity analyses provided consistent results. Specifically, as shown in Appendix 2.4, taking the square root of the CES-D to increase the normality of the distribution and reduce the influence of outliers did not substantially effect the significance of the 2R × social support interaction (p = 0.004 and 0.077 for the 9 and 3 item CES-D average, respectively). Likewise, Appendix 2.5 shows that in a SEM of 3 item specification the MAO no 2R × social support coefficient is in the expected direction, with a comparable *p*-value (p = 0.066). For all outcome specifications, coefficients indicate that only females without any 2R *MAOA* alleles were significantly influenced by social support. This is illustrated in Figure 2.1, which plots predicted probabilities of depression at various levels of social support by *MAOA* 2R genotype for females. These results are suggestive of possible GxE between social support and *MAOA* 2R among females, but the strongest effects appears to be on CES-D items other than those capturing the negative affect construct.

The vast majority of the female sample had some combination of the of 3.5R and/or 4R

[25] Model estimates shown for all outcome specifications in Appendix 2.3.

[26] Given that there were only 3 observations with the *MAOA* 2R/2R genotype, these three specifications are very highly correlated.

MAOA genotypes (83.1%), which were commonly grouped together as high activity alleles (Caspi et al. 2003). Several specifications for these alleles were found to significantly interact with social support.[27] Specifically, among females with the 3.5R or 4R *MAOA* genotype, social support was generally less influential in buffering depression, though still significant. While only the 9 item CES-D specifications satisfied the $q < 0.15$ threshold ($p = 0.015$ and $p = 0.012$, for the 9 item average and factor score, respectively), as shown in Table 2.5, the *p*-values were less than 0.05 for all outcome mixed model specifications. These results were upheld in additional sensitivity analyses showing significant results for square root transformed specifications of the CES-D (Appendix 2.7). Further, in the final SEM sensitivity analysis this interaction was in the expected direction, but the *p*-value was slightly higher (Appendix 2.8). This relationship is illustrated for the primary outcome in Figure 2.2. Thus, females with the low activity allele were indicated to be more susceptible to the detrimental effects of social support deficits.

The final significant finding regards the rare DAT1 8R genotype in the full sample (0.61%). This allele was indicated to a have a significant main effect in the social support GxE model for the 3 item factor score CES-D specification; and multiple specifications of the allele significantly interacted with parental education for the 9 item factor score. Individuals with 8R allele were characterized by elevated depression and heightened sensitivity to the influence of parental education on depression. However, given that the 8R allele is quite rare and completely uncharacterized by either functional research or genetic association studies, these findings are not further discussed.[28]

[27] The other significant results for *MAOA* among females regards the 3R/3R genotype, which is not discussed as it is essentially the inverse of the no 3.5R or 4R genotype described above (r = 0.94). Estimates for all outcome specifications of the *MAOA* 3R/3R × social support model for females are shown in Appendix 2.6.

[28] Estimates for all 4 outcome specifications of the DAT1 8R/8R × parental education model are shown in Appendix 2.9.

Discussion

The sociological study of mental health has long emphasized the importance of social environmental factors as fundamental causes of depression. Specifically, research from the stress process perspective has shown the distal influence of SES and the proximate impacts of eventful stress and social support as primary factors in the environmental etiology of the disorder (Pearlin et al. 1981; Pearlin 1989). However, one limitation of the stress process perspective on depression, and the sociology of mental health more broadly, is the inability to explain individual differences in response to depressogenic environmental factors. Given that from very young ages individuals vary widely in their vulnerability to environmental insult, leading theories have suggested that, to some degree, genetic variation underlies these differences (e.g., Caspi et al. 2003). But while new movements in genetics have called for integrating genetic and social perspectives in GxE research (Moffitt et al. 2005), few comprehensive empirical studies have yet been conducted. Furthermore, the nascent GxE literature in the social sciences has yet to address what has come to be seen in molecular genetics as the central weakness of candidate gene studies—multiple testing and the risk of false discoveries (Colhoun et al. 2003; van den Oord 2005). Using the Add Health genetic subsample, this study has addressed these issues through comprehensively testing the interactive effects of primary components of the stress process and 5 monoamine genes on early life depression, while employing FDR methods to control the risk of false discoveries.

The most promising associations detected were for interactions between the *MAOA* VNTR promoter polymorphism and social support among females. Specifically, while on average both females and males showed highly significant buffering effects for social support,

females with the rare 2R *MAOA* allele showed no influence of social support on depression. Similarly, females with high activity 3.5R or 4R *MAOA* alleles showed less sensitivity to social support than those with low activity alleles (i.e., primarily 3R homozygotes), however all genotypes other than 2R showed some degree of significant influence for social support. These results, while promising, should be viewed with some degree of skepticism, given that they were not entirely robust in all sensitivity analyses. The results will, therefore, require replication before the possibility of false discoveries can be conclusively ruled out.

Despite these concerns, however, there are compelling reasons for giving the current results serious consideration. *MAOA* has long been considered a leading candidate gene for psychiatric conditions as the enzyme it encodes acts as a catalyst in the degradation of neurotransmitters, primarily serotonin and norepinephrine (Bach et al. 1988), and inhibitors of the enzyme have been found effective in the treatment of depression (Murphy et al. 1994). However, studies of main genetic effects for *MAOA* on various affective disorder phenotypes have failed to provide robust support for a significant association (e.g., Furlong et al. 1999). And while the combination of functional evidence and inconsistent candidate gene results is strongly indicative of potential GxE for *MAOA* on depression, very little research in this vein has been conducted, with only two methodologically limited, small sample analyses published to date (Eley et al. 2004; Cicchetti et al. 2007).

In contrast to the dearth of *MAOA* GxE research for depression, a much larger literature has accumulated for the role of *MAOA* in GxE for aggression and antisocial behavior in males. Beginning with Caspi et al. (2002), several studies have shown that males with low activity *MAOA* genotypes were more likely to respond to childhood maltreatment by developing antisocial behavior problems than males with high activity variants (see Kim-Cohen et al. 2006

for meta-analysis). This finding has recently been extended by Guo and colleagues (2008a, 2008b) who have found evidence of both main effects and interactions with school-related social control mechanisms for the 2R *MAOA* genotype among young males. Given the relative robustness of this discovery, researchers have begun searching for underlying biological mechanisms, finding structural and functional brain differences between individuals with high and low activity alleles. For instance, individuals with low activity alleles have been characterized by smaller limbic volumes, greater amygdala response to emotional arousal, as well as diminished reactivity in prefrontal regions involved in emotional regulation[29], compared with the high expression allele (Meyer-Lindenberg et al. 2006).

Studies of functional and structural brain differences by *MAOA* genotype have also revealed gender × *MAOA* genotype differences (Meyer-Lindenberg et al. 2006). These results have suggested that *MAOA* genotype influences the volume of frontal cortex areas responsible for emotional regulation, and the functional connectivity between these regulatory areas and the amygdala, among males but not females. This has been offered as a potential mechanism in explaining greater frequency of violent behavior among males, and the increased role of *MAOA* variation in explaining violence among males relative to females (Meyer-Lindenberg et al. 2006).

Considered in tandem with social science research on gendered response to social adversity, this neurobiological research presents an interesting potential explanation for the gender differences in the influence of *MAOA* on depression observed here. That is, social science research has consistently found gendered differences in response to the same sources of social adversity (e.g., Hagan and Foster 2003; Meadows 2007). For instance, Meadows (2007) found that social support generally has stronger associations to delinquent behavior among males and

[29] Specifically, the bilateral lateral orbitofrontal cortex.

depression among females. Meyer-Lindenberg and colleagues' (2006) research offers a potential neurobiological and, by extension, a genetic explanation for this gendered response to adversity by showing that *MAOA* functions to moderate the influence of aversive stimuli on aggression in males more than females. This finding raises the possibility that *MAOA* may be a key filter in differentiating emotional response to adversity between the genders. The missing element in synthesizing these lines of neurobiological and social research is, of course, evidence that *MAOA* functions to moderate the effect of adversity on depression disproportionately among females relative to males—and that is precisely the evidence provided by the current study. While this conclusion requires replication and extension via neurobiological studies, it suggests the interesting possibility that *MAOA* may function via "gendered pleiotropy" to help explain sex differences in response to social adversity.

Beyond the substantive conclusions, this study shows the value of combining sociological theory with comprehensive empirical statistical approaches to optimize the search for GxE relationships. This can be seen from multiple aspects of the current study. First, without an exhaustive exploration of various allelic specifications beyond those conventionally assessed, highly significant associations for the rare 2R *MAOA* and 8R DAT1 alleles would have been undetected. Also, using the stress process paradigm to expand the environmental risks considered beyond the previously examined SLEs enabled the detection of strong GxE associations for social support—an understudied factor in GxE studies. Finally, and perhaps most importantly, the use of FDR methods allowed these comprehensive empirical explorations of the data by controlling the risk of false discoveries. Thus, in the current analysis, 2880 genetic and GxE coefficients were examined for significant association to depression and only 18 parameters, relating to 4 alleles, were found significant at an FDR level of $q < 0.15$. The contrast of this FDR

approach to the usual tacit exploratory approach is striking when you consider that had a conventional $p < 0.05$ significance criterion been used 131 significant results, with median q-value = 0.57, would have been reported. The importance of this is illustrated by considering that if a researcher began ad hoc testing from the class of models examined here, roughly 6 of every 10 associations meeting the $p < 0.05$ criterion would be expected to be false discoveries—flooding the literature with erroneous findings and encouraging the misallocation of time, energy, and funds in future replication efforts.

More generally, this research highlights the promise and perils that recent advances in molecular genetics pose to the social sciences. Molecular genetics technology is now sufficiently developed that large amounts of genotype data are becoming increasingly available to social science researchers. Thus, we are witnessing the opening of an unprecedented frontier in behavioral research—it is now possible to go beyond estimating average social environmental effects across different genotypes, to empirically investigate the long-standing problem of individual differences in resilience and susceptibility. However, along with this opportunity comes pitfalls, many of which are poorly understood in the social sciences. Chief among these poorly recognized risks is that of false discoveries—it has been estimated that as many as 19 out of 20 published genetic findings are in fact false discoveries (Colhoun et al. 2003). Given the magnitude of this problem, it has become a focal point for method development in statistical genetics and effective techniques to control for this risk are readily available (van den Oord 2008; van den Oord 2005). But while these techniques are being increasingly employed at the vanguard of genomics (e.g., van den Oord et al. 2009), they have not yet been incorporated into the burgeoning GxE literature in the social sciences. As the current study illustrates, these methods can be easily integrated into sociologically oriented GxE research, pairing the theory-

based strengths of sociology with empirical insights of statistical genetics. In order for social science researchers to credibly and responsibly conduct GxE research it is imperative that we import not only variables from molecular genetics, but also the hard-earned methodological advances of the discipline.

Table 2.1. Descriptive Statistics

	Male (n = 926)				Female (n = 988)			
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max
CES-D 9 item avg	0.58	0.41	0	2.67	0.73	0.50	0	2.78
CES-D 9 item factor score	0.35	0.32	0	2.04	0.47	0.39	0	2.08
CES-D 3 item avg	0.40	0.52	0	3	0.60	0.63	0	3
CES-D 3 item factor score	0.29	0.39	0	2.18	0.44	0.48	0	2.18
White	0.60	0.49	0	1	0.63	0.48	0	1
Hispanic	0.14	0.35	0	1	0.13	0.34	0	1
Black	0.17	0.38	0	1	0.16	0.37	0	1
Asian	0.06	0.24	0	1	0.05	0.21	0	1
American Indian	0.02	0.13	0	1	0.02	0.14	0	1
Other Race	0.01	0.09	0	1	0.01	0.07	0	1
Age	16.12	1.65	12	21	16.01	1.66	12	20
Social Support	4.04	0.54	1.7	5	4.07	0.54	1.4	5
Parental Education (mean)	5.96	1.75	2	9	5.78	1.78	2	9
Household income	45.36	45.53	0	999	50.28	61.68	0	999
SLEs	2.75	2.87	0	20	1.85	2.15	0	17

Table 2.2. Number of associations below various *q*-values thresholds

		Full Sample (no *MAOA*)				Males (*MAOA*)				Females (*MAOA*)			
Outcome	Predictor	0.01	0.05	0.1	0.15	0.01	0.05	0.1	0.15	0.01	0.05	0.1	0.15
CES-D 9 item avg	Gene main effect	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 9 item avg	GxE, Household income	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 9 item avg	GxE, Parental education	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 9 item avg	GxE, SLEs	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 9 item avg	GxE, Social support	0	0	0	0	0	0	0	0	0	2	3	7
CES-D 9 item factor	Gene main effect	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 9 item factor	GxE, Household income	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 9 item factor	GxE, Parental education	0	0	0	2	0	0	0	0	0	0	0	0
CES-D 9 item factor	GxE, SLEs	0	0	0	0	0	0	0	0	0	0	0	1
CES-D 9 item factor	GxE, Social support	0	0	0	0	0	0	0	0	0	0	0	5
CES-D 3 item avg	Gene main effect	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item avg	GxE, Household income	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item avg	GxE, Parental education	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item avg	GxE, SLEs	0	0	0	0	0	0	0	0	1	1	1	1
CES-D 3 item avg	GxE, Social support	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item factor	Gene main effect	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item factor	GxE, Household income	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item factor	GxE, Parental education	0	0	0	0	0	0	0	0	0	0	0	0
CES-D 3 item factor	GxE, SLEs	0	0	0	0	0	0	0	0	1	1	1	1
CES-D 3 item factor	GxE, Social support	0	0	0	1	0	0	0	0	0	0	0	0

Table 2.3. Associations with *q*-values less than 0.15

CES-D Specification	Sample	Environmental Risk	Coefficient	b	se	z stat	p-value	q-value
9 Item Avg	Female	Social Support	*MAOA* 2R/other × Social Support	0.467	0.137	3.419	0.001	0.026
9 Item Avg	Female	Social Support	*MAOA* no 2R × Social Support	-0.432	0.138	-3.136	0.002	0.035
9 Item Avg	Female	Social Support	*MAOA* # 2R × Social Support	0.363	0.133	2.736	0.006	0.085
9 Item Avg	Female	Social Support	*MAOA* 3R/3R × Social Support	-0.121	0.049	-2.454	0.014	0.122
9 Item Avg	Female	Social Support	*MAOA* no 3.5 or 4R × Social Support	-0.115	0.047	-2.436	0.015	0.122
9 Item Avg	Female	Social Support	*MAOA* no 4R × Social Support	-0.110	0.047	-2.350	0.019	0.128
9 Item Avg	Female	Social Support	*MAOA* # 3R × Social Support	-0.058	0.026	-2.276	0.023	0.134
3 Item Avg	Female	SLEs	*MAOA* 2R/2R × SLEs	1.447	0.371	3.898	0.000	0.004
3 Item Factor Score	Female	SLEs	*MAOA* 2R/2R × SLEs	1.056	0.280	3.776	0.000	0.007
9 Item Factor Score	Female	SLEs	*MAOA* 2R/2R × SLEs	0.689	0.229	3.012	0.003	0.109
9 Item Factor Score	Female	Social Support	*MAOA* 2R/other × Social Support	0.319	0.108	2.938	0.003	0.135
9 Item Factor Score	Female	Social Support	*MAOA* no 2R × Social Support	-0.281	0.109	-2.579	0.010	0.135
9 Item Factor Score	Female	Social Support	*MAOA* no 3.5 or 4R × Social Support	-0.094	0.037	-2.522	0.012	0.135
9 Item Factor Score	Female	Social Support	*MAOA* 3R/3R × Social Support	-0.096	0.039	-2.478	0.013	0.135
9 Item Factor Score	Female	Social Support	*MAOA* no 4R × Social Support	-0.088	0.037	-2.387	0.017	0.139
3 Item Factor Score	Full	Social Support	DAT1 8R/8R	0.704	0.222	3.168	0.002	0.147
9 Item Factor Score	Full	Parental Education	DAT1 #8R × Parental Education	-0.093	0.030	-3.094	0.002	0.150
9 Item Factor Score	Full	Parental Education	DAT1 no 8R × Parental Education	0.141	0.048	2.938	0.003	0.150

Table 2.4. Parameter estimates (*p*-values) of linear mixed models among females: Effects of stress process and *MAOA* 2R genotype on 4 specifications of depression

	9 item avg	9 item factor	3 item avg	3 item factor
MAOA no 2R	-0.060	-0.016	0.047	0.026
	(0.445)	(0.801)	(0.624)	(0.722)
MAOA no 2R * Support	-0.432**	-0.281**	-0.328	-0.242
	(0.002)	(0.010)	(0.052)	(0.058)
Hispanic	0.036	0.017	0.038	0.020
	(0.300)	(0.526)	(0.374)	(0.526)
Black	0.007	0.008	0.005	-0.002
	(0.832)	(0.762)	(0.904)	(0.947)
Asian	0.206***	0.106**	0.128*	0.083
	(0.000)	(0.008)	(0.037)	(0.073)
American Indian	0.099	0.099	0.160	0.110
	(0.194)	(0.100)	(0.086)	(0.119)
Other Race	-0.216	-0.157	-0.194	-0.140
	(0.125)	(0.159)	(0.264)	(0.284)
Age	0.011	0.026**	0.033*	0.030**
	(0.291)	(0.003)	(0.020)	(0.005)
Age Squared	-0.002**	-0.002**	-0.003***	-0.002**
	(0.002)	(0.004)	(0.001)	(0.005)
Social Support	0.157	0.087	0.076	0.050
	(0.250)	(0.420)	(0.650)	(0.693)
Parental Education (mean)	-0.030***	-0.019***	-0.025**	-0.018**
	(0.000)	(0.001)	(0.005)	(0.008)
Household income (logged thousands)	-0.002	-0.006	-0.011	-0.012
	(0.910)	(0.633)	(0.569)	(0.404)
SLE	0.060***	0.051***	0.081***	0.061***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.733***	0.378***	0.426***	0.303***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Household level)	0.179***	0.135***	0.199***	0.154***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.144***	0.108***	0.154***	0.113***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.379***	0.315***	0.512***	0.386***
	(0.000)	(0.000)	(0.000)	(0.000)
N	2904	2904	2904	2904
Log restricted likelihood	-1683.754	-1103.669	-2463.959	-1647.523

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Table 2.5. Parameter estimates (*p*-values) of linear mixed models among females: Effects of stress process and *MAOA* 3.5 and 4R genotype on 4 specifications of depression

	9 item avg	9 item factor	3 item avg	3 item factor
MAOA no 3.5 or 4R	-0.019	-0.014	-0.020	-0.014
	(0.512)	(0.551)	(0.575)	(0.598)
MAOA no 3.5 or 4R * Support	-0.115*	-0.094*	-0.146*	-0.104*
	(0.015)	(0.012)	(0.012)	(0.018)
Hispanic	0.032	0.014	0.032	0.017
	(0.360)	(0.610)	(0.443)	(0.603)
Black	0.012	0.009	-0.001	-0.005
	(0.700)	(0.724)	(0.977)	(0.854)
Asian	0.216***	0.115**	0.141*	0.092*
	(0.000)	(0.004)	(0.023)	(0.049)
American Indian	0.101	0.101	0.162	0.111
	(0.187)	(0.095)	(0.082)	(0.114)
Other Race	-0.214	-0.155	-0.190	-0.137
	(0.130)	(0.166)	(0.273)	(0.293)
Age	0.011	0.025**	0.033*	0.029**
	(0.302)	(0.004)	(0.021)	(0.006)
Age Squared	-0.002**	-0.002**	-0.003***	-0.002**
	(0.002)	(0.004)	(0.001)	(0.005)
Social Support	-0.243***	-0.169***	-0.215***	-0.165***
	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education (mean)	-0.030***	-0.019***	-0.025**	-0.018**
	(0.000)	(0.001)	(0.005)	(0.008)
Household income (logged thousands)	-0.004	-0.008	-0.016	-0.015
	(0.790)	(0.510)	(0.428)	(0.299)
SLE	0.060***	0.051***	0.082***	0.061***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.676***	0.364***	0.476***	0.330***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Household level)	0.176***	0.133***	0.196***	0.152***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.148***	0.110***	0.156***	0.114***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.379***	0.315***	0.512***	0.386***
	(0.000)	(0.000)	(0.000)	(0.000)
N	2904	2904	2904	2904
Log restricted likelihood	-1687.568	-1105.838	-2465.185	-1648.870

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Figure 2.1. Interactive effects of *MAOA* 2R genotype and social support on depression among females

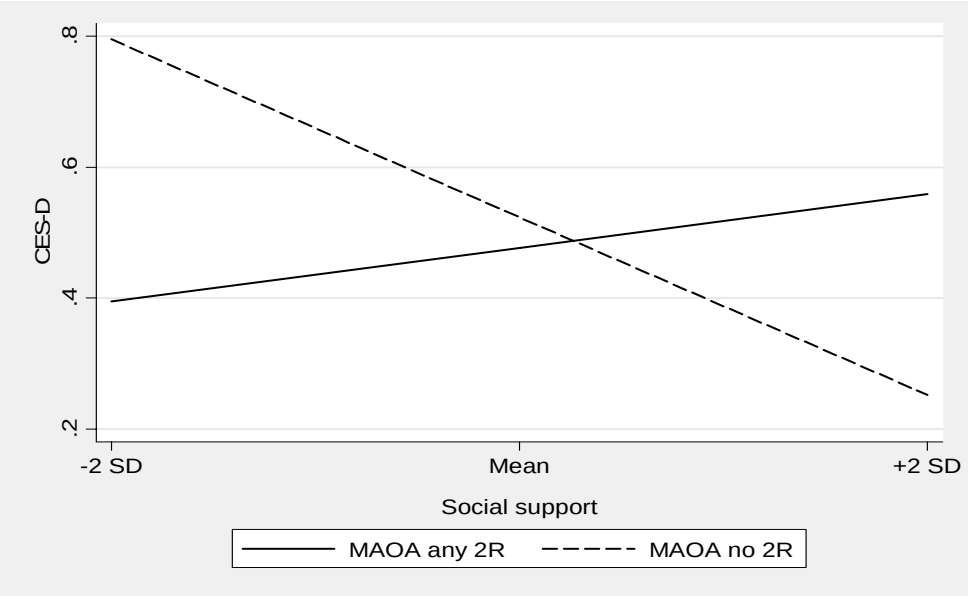
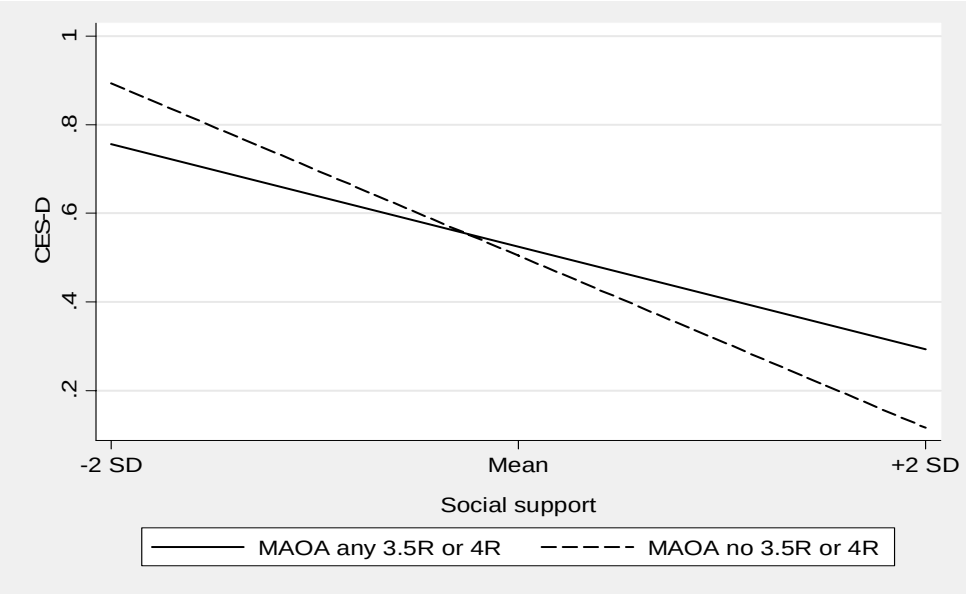


Figure 2.2. Interactive effects of *MAOA* 3.5 and 4R genotype and social support on depression among females



Chapter 3: The Influence of Five Monoamine Genes on Early Life Trajectories of Depression

Introduction

There is a burgeoning consensus among scholars that depression follows a normative, inverted U-shaped trajectory across early life—peaking in late adolescence and falling in young adulthood (Ge et al. 2006; Adkins et al 2008). Further, research has also consistently shown significant between-individual variation around mean trajectories (Adkins et al 2008; Adkins et al. 2009). Explaining these individual differences in early life depression trajectories has proven a difficult task, with well-specified models including exhaustive lists of social risk factors explaining only modest amounts of trajectory variance (Adkins et al. 2009, Natsuaki et al. 2009). This has led to growing interest in the role of genetics in explaining individual differences in depression development, with experts increasingly drawing on the diathesis-stress perspective to empirically investigate gene × environment interaction in depression (e.g., Costello et al. 2002; Caspi et al. 2002).

In addition to social science research implying a role of genetics in depression trajectories, several lines of inquiry within genetics have also suggested this highly plausible, but largely empirically uninvestigated process. For instance, biometric genetics research has shown that the heritability of depression significantly varies across early life, suggesting that the influence of various genes may increase or decrease across this

important developmental period (Bergen, Gardner, and Kendler 2006). This conclusion is further supported by epigenetics research showing substantial gene expression changes during early life, as developmental mechanisms "turn various genes off and on" (Whitelaw and Whitelaw 2006). Thus, beyond suggesting consistent gene effects across early life, contemporary genetics research has indicated that the influence of specific genetic loci may vary over the period. Given this knowledge, it is perhaps surprising that virtually no research has considered gene × age interaction effects for candidate genes on depression trajectories in early life. The current study addresses this gap in the literature by investigating gene × age interaction on early life depression trajectories for five monoaminergic candidate genes, 5-HTTLPR, *DRD4, MAOA, DRD2,* and DAT1, using False Discovery Rate methods to control for the risks of false discoveries due to multiple testing.

Background

Early life depression trajectories

Though longitudinal analyses of nationally representative data across adolescence and young adulthood remain uncommon, there is mounting evidence of a normative, inverted U-shaped trajectory of depression across this period of the life course. This conclusion is supported by longitudinal research finding curvilinear trajectories in samples of individuals moving through adolescence and young adulthood, as well as by research in younger samples showing linear increase through middle adolescence and studies of young adult samples showing linear decrease or stability through the twenties. For instance, inverted U-shaped trajectories have been found across ages 12-26 in former,

methodologically robust analyses of the National Longitudinal Study of Adolescence (Add Health) (Adkins et al. 2008; Adkins et al. 2009; Natsuaki et al. 2009). Similarly, analyzing eleven waves of longitudinal data covering ages 12-23, Ge et al. (2006) found curvilinear trajectories of depressive symptoms, rising in early and middle adolescence and declining in late adolescence. Furthermore, Wight et al. (2004) examined depressive symptoms in three datasets (one adolescent sample and two adult samples) and found increasing levels in the adolescent sample, while the adult samples showed both lower initial levels and a steady decline over time. Comparable findings have been reported in several other analyses (e.g., Wade et al. 2002; Hankin et al. 1998; Ge et al. 1994), collectively offering strong support for a normative curvilinear depression trajectory across this important developmental period.

In addition to elucidating average trajectories of depression in early life, research has also highlighted the longstanding issue of individual differences in the development of depression and depressive symptoms. For instance, recent trajectory analyses of Add Health using mixed effects modeling (Adkins et al. 2008; Natsuaki et al. 2009) and latent trajectory modeling (Adkins et al. 2009) have leveraged these powerful modeling techniques to show that both intercept and slope trajectory components vary significantly across individuals, showing the majority of variance in the depression measure is comprised by individual differences in these trajectory components. And though some of this variation may eventually be explained by improved measurement and modeling of social influences, there is a growing recognition that, as posited by the *diathesis-stress* model, much of it is likely due to genetic factors (Costello et al. 2002; Caspi et al. 2002).

Genetic factors in depression

Epidemiological research has offered strong evidence of the importance of genetics, with family studies indicating first-degree relatives of depressed probands to be 2.84 times more likely to experience major depression than controls, and twin studies indicating the heritability of unipolar depression to be 31-42% (Sullivan et al. 2000). But despite the longstanding body of behavioral genetics research showing substantial genetic influence, advances in mapping the molecular underpinnings of the phenotype have been slow. And while no consensus has yet been reached regarding the primary molecular mechanisms underlying mood disorder susceptibility, a confluence of neurobiological, pharmacological and molecular genetic evidence has supported an important role for monoaminergic neurotransmission, particularly the serotonergic and dopaminergic systems. Among the many candidate gene variants influencing these systems, polymorphisms in: 5-HTTLPR, *DRD4, MAOA, DRD2,* and DAT1 are among the most promising.

Serotonin Transporter (5HTT, locus symbol *SLC6A4*). Among neurotransmission systems the serotonergic system has received the most attention for its involvement in several processes including brain development and synaptic plasticity. Located at 17q11.2, the serotonin transporter gene (5-HTT) encodes a protein critically involved in the control of 5-HT function. Allelic variations in the 5′ flanking transcriptional region of 5-HTT gene (5-HTTLPR which controls 5-HTT expression and function) have been associated with personality traits including anxiety and aggressiveness (Anguelova et al. 2003). Short (S) and long (L) 5-HTTLPR variants differentially influence transcription activity of the 5-HTT gene promoter, protein concentration, and the consequent 5-HT

uptake in lymphoblastoid cells. And while results of main effects of 5-HTTLPR on depression have been mixed (Anguelova et al. 2003), Caspi et al. (2003) has drawn together several lines of experimental genetic research to theorize that although the 5-HTT gene may not be directly associated with depression, it may moderate the serotonergic response to stress. Investigating this hypothesis, Caspi et al. (2003) found individuals possessing the S allele of 5-HTTLPR to present more depression in relation to SLE than individuals homozygous for the L allele. Since this study, several studies have attempted replication, yielding both positive (e.g., Gillespie et al. 2005) and negative results (e.g., Surtees et al. 2006).

Dopamine D4 Receptor (*DRD4*)**.** The *DRD4* gene maps 11p15.5 and spans 3.4 kb. A functional variable number of tandem repeats (VNTR) polymorphism has been identified in the third exon in the *DRD4* gene, the region coding for the third intracellular loop of the receptor (Van Tol et al. 1992). The genetic variant is a 16 amino acid (48 bp) repeat polymorphism, which is repeated two to 11 times, with two (D4.2), four (D4.4), and seven (D4.7) repeats being the most common alleles (Van Tol et al. 1992). The mRNA distribution profile of *DRD4* shows elevated levels in limbic areas involved in the pathophysiology of major psychoses (Van Tol et al. 1991), and has high levels of expression in the frontal area of the brain and the nucleus acumbens, areas associated with lack of motivation, anhedonia, and affective behaviors (Emilien et al 1999; Oak et al 2000). While several lines of research have suggested *DRD4* as a candidate gene for mood disorders, association results have been mixed. Significant associations have been reported between *DRD4* and unipolar and bipolar depressive disorders (e.g., Manki et al 1996; Muglia et al 2002), but other studies have failed to confirm these findings (e.g.,

Bocchetta et al 1999; Serretti et al. 2002). It has been suggested that these failures to replicate may have been due to underpowered samples (Lohmueller et al 2003), a view supported by a recent, comprehensive meta-analysis which found a strong significant association between the *DRD4*.2 allele and unipolar depression (Lopez et al. 2005).

The mechanism by which dopamine D4 receptor expression is regulated is not yet fully understood (Wang et al 2004). Most research to date has focused on the *DRD4*.7 allele, which in vitro studies suggest has decreased affinity for dopamine, and transmits weaker intracellular signals in comparison with other *DRD4* alleles (Asghari et al. 1995). While the *DRD4*.7 allele has been consistently associated with attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and novelty seeking, it is the *DRD4*.2 allele which has been implicated in depression. One potential mechanism through which this effect may operate regards the role of D4 receptors in inhibiting adenylyl cyclase activity and thereby reducing conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) (Sanyal and Van Tol 1997; Watts et al 1999). It has been reported that dopamine *DRD4*.2 receptors are less potent than *DRD4*.4 and *DRD4*.10 in coupling to adenylyl cyclase and show a blunted ATP to cAMP conversion (e.g., Asghari et al 1995; Watts et al 1999). Thus, the D4 receptors with a suboptimal functionality, e.g., *DRD4*.2, may influence depression.

Monoamine Oxidase A promoter (MAOA-uVNTR). Two primary lines of evidence have indicated *MAOA* as a likely depression candidate gene. First, *MAOA* has a central role in controlling amine disposability at the synaptic cleft, preferentially metabolizes serotonin and norepinephrine (Bach et al., 1988). Second, *MAOA* inhibitors have been found effective in the treatment of depression (Murphy et al. 1994). Thus,

while precise mechanism are not fully understood, these two findings provide compelling evidence for considering *MAOA* in candidate genes studies, as they demonstrate its modulation of the serotonergic system, one of the two leading biological pathways in the etiology of depression, and show robust pharmacological evidence that its inhibition results in depressive symptom reduction, at least in a subgroup of patients. The *MAOA* gene is located on the short arm of the X chromosome (Xp11.23) (Sabol et al. 1998). While several different polymorphisms in the *MAOA* gene have been identified, only a polymorphism located 1.2 kb upstream of the *MAOA* coding sequences has been shown to affect the transcriptional activity of the *MAOA* gene promoter. This polymorphic region consists of a 30 bp repeated sequence present in 2, 3, 3.5, 4, or 5 copies. Alleles with 3.5 or 4 copies of the repeat sequence are transcribed two to 10 times more efficiently than those with 2, 3 or 5 copies of the repeat (Sabol et al., 1998). While this promoter VNTR has shown association with several affective disorders including recurrent major depression (Preisig et al., 2000; Schulze et al., 2000), other studies have reported negative associations of this polymorphism with mood disorders (Furlong et al. 1999; Kunugi et al. 1999). Similar controversial results exist for GxE between the low activity alleles and childhood maltreatment for antisocial behavior (e.g., Caspi et al. 2002; Haberstick et al. 2005).

Dopamine Transporter (DAT1, locus symbol: *SLC6A3*). The dopamine transporter gene, DAT1 (locus symbol: *SLC6A3*), has been mapped to chromosome 5p15.3 (Vandenbergh et al. 1992). DAT1 has a 40 bp VNTR; ranging from 3-11 copies in the 3 untranslated region of the gene. In the central nervous system, the dopamine transporter protein, DAT1, mediates reuptake of dopamine from the synaptic cleft and

thus, is largely responsible for the intensity and duration of dopaminergic neurotransmission (Storch et al. 2004). Given the central role of the dopaminergic system in neurobiological theories of depression, DAT represents a plausible depression candidate, although further functional research is needed to elucidate a precise biological mechanism linking the polymorphism to depression. However, pharmacological animal studies have been instructive in this regard, demonstrating that drugs affecting DAT function such as cocaine or amphetamines enhance dopaminergic signaling, which in turn can result in hyperactivity and other changes in mood and behavior. The importance of correct DAT function for normal behavior has been demonstrated in DAT knockout mice (Giros et al. 1996). Owing to the lack of the transporter protein, these animals have constantly elevated dopaminergic neurotransmission resulting in hyperactive behavior and thus, are unaffected by the psychostimulants cocaine and amphetamines. Genetic association studies have implicated the DAT gene in the etiology of psychopathologies including ADHD (e.g., Cook et al. 1995), avoidant behavior (Blum et al. 1997), and bipolar affective disorders (Waldman et al. 1997; Kelsoe et al. 1996).

Dopamine D2 receptor (*DRD2*, rs1800497). The 3′ TaqI A polymorphism of the dopamine D2 receptor is a T to C transition in the 3′ non-coding region of the gene, 10.5 kb downstream of the stop codon and 9.4 kb downstream of the polyA signal (Bunzow et al. 1988, Grandy et al. 1989). The polymorphism has been suggested to be functionally relevant, affecting dopamine receptor D2 availability in postmortem striatal samples (Noble and Cox 1997; Thompson et al. 1997) and moderating dopamine density and glucose metabolic rate in dopaminergic regions in the human brain (Noble et al. 1997). Consequently, the polymorphism has been studied as a candidate for affective disorders,

with studies generally focusing on the A1 minor allele as a risk variant, as functional studies of both humans and mice have shown individuals with the A1 allele to have lower density of dopamine D2 receptors throughout the brain (Nobel et al. 1997; Noble and Cox 1997). Empirical findings of main effect have been mixed, however, with some studies finding significant associations (Li et al. 1999) and others not (e.g., Serretti et al. 2000). Recent research has attempted to resolve this discrepancy using a GxE approach, finding a significant interaction between DRD2 and stressful life events SLEs on depressive symptomology (Elovainio et al. 2007).

Age moderation of genetic influence

The period of adolescence to young adulthood is among the most developmentally intensive periods in the life course. It is characterized by important biological changes, such as puberty, and also a dramatic shift in social environment as children's parent-dominated social experience gives way to an expanding range of social options. Moreover, these changes have been linked to variation in the influence of genetic factors in ways that are potentially relevant to gene × age interaction in early life depression trajectories. For instance, there is ample evidence of extensive gene expression changes during adolescence, during which genes may be de/silenced (i.e., "turned on and off") through developmentally and environmentally induced epigenetic changes (Whitelaw and Whitelaw 2006). And while puberty represents a particularly striking example of phenotypic change in response to developmental epigenetic change (Whitelaw and Whitelaw 2006), both mouse and human studies have demonstrated that these epigenetic changes continue across young adulthood and, indeed, throughout the

life course (Barbot et al. 2002; Fraga et al. 2005). Although no research has yet focused on epigenetic regulation of monoamine genes in early life,[30] given the extensive epigenetic changes characterizing the period, it is plausible that these genes may be differential expressed across the period, suggesting a potential molecular mechanism for gene × age interaction in early life depression trajectories.

Biometric studies offer another source of evidence indicating changes in the influence of genetics on depression across early life. Analyzing twin, family, and adoptee data, biometric genetic studies decompose phenotype variance into aggregate genetic and environmental components without reference to molecular data. Many of these studies have examined depression at various points in early life (e.g., Silberg et al. 2001, Eley et al. 1999), and some have modeled how aggregate genetic influence (i.e., heritability) changes as a function of age (e.g., Nes et al. 2007). The results of this body of research are well-summarized by a recent meta-analysis by Bergen, Gardner, and Kendler (2007), who analyzed 6 studies with sample ages ranging from 8-28, showing that the heritability of depression significantly increases from approximately 21% at age 8 to 42% at age 28.

Bergen and colleagues (2007) offer two broad, non-mutually exclusive potential explanations for the increasing role of genetics in depression as individuals move through early life. First, they suggest that as individuals age out of childhood, the role of parental social control recedes and individuals begin to self-select into environments, allowing them to more readily express their genetic proclivities. For instance, with parent's no longer structuring their time, college students with depressive tendencies may fail to maintain social ties and drift towards isolation. The authors also offer the possibility that

[30] See Casey et al. (2009) for a useful model of age moderation on genetic influences, with the empirical example of life course variation in the influence of BDNF on cognitive and neuroanotomic development.

developmental epigenetic changes may "turn on" novel genes, providing additional sources of genetic variance. Further, the two mechanisms may interact, with novel environmental exposures triggering epigenetic changes. And while these possibilities can not be adjudicated between without longitudinal epigenetic data, they both provide convincing rationale for considering age variation in the effects of known depression candidate genes across early life.

Data and Methods

Sample

Data were analyzed from three waves of the National Longitudinal Study of Adolescent Health (Add Health). Add Health is a large nationally representative, longitudinal sample of adolescents and young adults. The National Quality Education Database was used as the baseline sample frame, from which 80 high schools were selected with an additional 52 feeder middle-schools. The overall response rate for the 134 participating schools was 79 percent. Of the over 90,000 students who completed in-school surveys during the 1994-1995 academic year, a sample of 20,745 adolescents in grades 7-12 were selected and have been interviewed 3 times in 1994–1995, 1995–1996, and 2001–2002. A questionnaire was also administered to a selected residential parent of each adolescent. Further details of Add Health's sampling design, response rates, and data quality are well-documented (http://www.cpc.unc.edu/projects/addhealth/design).

The current study analyzes the three waves of repeated measures data from the Add Health sibling subsample, for which DNA measures are available. The sibling sample is composed of pairs of respondents residing in the same household, and includes

individuals of various degrees of biological relatedness, ranging from monozygotic twins to unrelated individuals. Respondents were included in the analysis sample if they had nonmissing values on all variables on at least one assessment. The total analysis sample consisted of 5627 observations for 1914 individuals, with each individual contributing an average of 2.9 observations. Individuals were nested within 1131 households, with each household containing 1-4 individuals (1.7 on average).

Measures

Depression. Depression was measured using a 9-item scale derived from the conventional 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977). The 20-item CES-D is composed of questions on a number of physical and psychological symptoms of depression, which cluster into four factors: somatic, depressed affect, positive affect, and interpersonal relations (Ensel 1996; Radloff 1977).[31] The scale has been validated using CFA in adult samples of Whites and Blacks (Blazer et al. 1998).[32] It has also been validated in samples of adolescents and young adults (Radloff 1991). Fortunately, a 19-item CES-D was collected in the first two waves of Add Health and a comparison with the subscale (9 items) indicated a high correlation (r = 0.91 and 0.92 in waves one and two, respectively). Individual items were coded on a

[31] One common issue arising in research on affective issues is the relationship of depressive symptoms to clinical diagnosis of depression (i.e., major depressive disorder). While the nature of this relationship continues to be debated, it is well-established that the CES-D is very strongly associated with MDD diagnosis (Fetchner-Bates et al. 1994). Thus, regardless of their exact relationship, the consensus among clinical practitioners is that symptom questionnaires, such as CES-D, are adequate to identify clinical depressed individuals (Williams et al. 2002). Based on these findings, we assume that research on MDD is relevant to the current study, and vice versa.

[32] While Blazer and colleagues (1998) found racial measurement invariance across most items, see Perreira et al. (2005) for contrasting findings indicating widespread measurement invariance across racial groups for the CES-D.

four-point scale to indicate the frequency of symptoms occurring during the past week, ranging from never or rarely (0) to most or all of the time (3). The primary outcome used in this analysis is the simple average of the 9 items.

In addition to using a simple average of the 9 items available across in all three survey waves, sensitivity analyses were conducted using: 1) a confirmatory factor analysis (CFA) factor score of the 9 items, 2) an average of the 3 depressed affect items collected in all waves, which have been shown to be measurement invariant across racial/ethnic and immigrant groups (Perreira et al .2005), and 3) a factor score of these 3 items. It has been shown previously that the use of factor scores for phenotypic measurement refinement can improve power to detect genetic effects (e.g., van den Oord et al. 2008). Further, analyses of the current data indicate that allowing factor loadings to vary significantly improves model fit for both the 9 and 3 item measures. In addition to measurement invariance characteristics, the use of the 3 item subscale was also indicated by both notably higher factor loadings for these items relative to the other 6 indicators, as well as stronger theoretical correspondence of the items to the depression construct (see Perreira et al. 2005). Correlations were high between all 4 specifications of the depression variable ($r = 0.84$-0.98). A constant was added to the factor scores setting their minimum values equal 0, in order increase comparability of model parameters across depression specifications. Finally, to assure that results are not driven by multidimensionality in the CES-D or measurement variance across racial/ethnic groups, more rigorous SEM sensitivity analyses are conducted, modeling the 3 items that have been demonstrated to be measurement invariant depressed affect indicators, as latent variable repeated measures.

Parental socioeconomic status. Add Health allows respondents to report parental education levels for up to four parents—resident mother and father figures, and for cases in which biological parents live outside of the respondent's household, nonresident biological mother and father. These variables describe the highest level of education that the parent has completed, and range from "never went to school" to "professional training beyond a four year college or university". Based on previous analyses these items were coded as continuous variables (Adkins et al. 2008). Finally, for each respondent, the mean was then taken of all reported parental education levels, which improved the explanatory power of the variable relative to any single parent's level. Household income was ascertained from the parental questionnaire and includes all sources of income from the previous year (measured in thousands of dollars), and was logged in these analyses. Correlation between parental education and logged household income was moderate ($r = 0.45$), indicating collinearity was not problematically high. SES indicators were mean-centered to aid in model interpretation.[33]

Stressful life events. An additive index was used to measure cumulative exposure to stressful life events. Presented in Appendix 2.1, the SLE index used here is derived from one developed by Ge et al. (1994). Established criteria for the development of the SLE index were used in modifying and expanding the measure for the Add Health survey

[33] When continuous measures are mean-centered, the intercept and age parameters describe the mean trajectory in the sample. This is generally more substantively interesting than the age trajectory for (hypothetical) individuals with values equal to zero on all covariates, which is the interpretation when continuous predictors are left untransformed.

(Turner and Wheaton 1995).[34] For instance, only acute events of sudden onset and of limited duration that occurred within 12 months of the interview were included (Turner and Wheaton 1995).[35] Further, given previous research indicating that undesirable life events are more likely to adversely affect health (e.g., Compas 1987), only negative life events were included in the index. To ensure a complete coverage of stressful events, approximately 50 items from various domains of life (e.g., family, romantic and peer conflicts, academic problems, involvement/exposure to violence, death of family and friends) were included. A major challenge of operationalizing SLEs is longitudinal accountability—as adolescents make the transition into adulthood, some stressors become irrelevant (e.g., expulsion from school) and other stressors become relevant (e.g., divorce or entering military service). Thus, to ensure stress was appropriately measured at different life stages, slightly different set of items is used in wave III to capture the different life experiences. Finally, similar items (such as miscarriage and still birth) were grouped together to avoid making the measurement overly specific. A simple, additive index was created from the selected items and is mean-centered in the current analysis.

[34] Previous research has explicitly indicated that as SLE indices are based on the concept of allostatic load, a typical (effect) factor analytic approach to measuring SLEs is not appropriate (see Turner and Wheaton 1995). This is because, in accordance with the allostatic load perspective, stress is viewed as a cumulative biological process. Regardless of whether stressful events are correlated (which the effect factor analytic model assumes), each additional event is judged to increase allostatic load. Thus, the ideal measurement model for the SLE index is a *causal indicator* factor model, in which each event has an independent causal effect on a latent allostatic load construct (see Bollen and Davis 2009). However, due to the complexity of the current model, optimization problems precluded the estimation of such a causal indicator model of allostatic load. Future research should focus on improving the measurement of SLEs using this innovative latent variable approach.

[35] The 12 month window for SLEs ensures that, for the vast majority of cases, the events occurred prior to the depression evaluation, which surveys respondents on depressive symptoms experienced in the past week. The temporal precedence of SLEs helps identify the causal direction of the relationship of SLEs to depression as the direction of causality cannot flow from depression at the time of evaluation to determine a previously occurring SLE.

Social support. The social support index shown in Appendix 2.2 is a composite measure of perceived social support across waves I and II. It assesses how the respondents feel about their relationship with their closest social ties including family, teachers and parents. A CFA of the items indicated marginally adequate fit (CFI = 0.971; RMSEA = 0.06) when including wave-specific factors and item-specific correlated errors between the two waves. A simple average of all the social support items was calculated and mean-centered in this analysis. To address potential concerns with the simplified specification of social support used in the mixed model analyses, the construct is modeled as the CFA described above in the SEM sensitivity analyses.

Race/ethnicity. Add Health allows respondents to indicate as many race and ethnic categories as deemed applicable. Approximately 4% of the participants report a multiracial/ethnic identity. Following criteria developed by Add Health data administrators, we assign one racial identity for persons reporting multiple backgrounds.[36] This method combines Add Health's five dichotomous race variables and the Hispanic ethnicity variable as following: respondents identifying a single race are coded accordingly; respondents identifying as Hispanic were coded as such regardless of racial designation; those identifying as "black or African American" and any other race were designated as Black; those identifying as Asian and any race other than Black were coded as Asian, those identifying as Native American or "other" were coded as Native American, and those identifying only as "other" were coded as such.[37]

[36] http://www.cpc.unc.edu/projects/addhealth/data/using/code/race

Candidate genes. In Wave III in 2002, DNA samples were collected from a subset of the Add Health sample. Genomic DNA was isolated from buccal cells at the Institute for Behavioral Genetics, University of Colorado (Smolen and Hewitt, www.cpc.unc.edu/projects/addhealth/), using a modification of published methods (Lench et al. 1988; Meulenbelt et al. 1995; Spitz et al. 1996; Freeman et al. 1997). The average yield of DNA was 5871 mg. All of the Wave III buccal DNA samples are of excellent quality and have been used to assess nearly 48,000 genotypes.

DAT1: The allelic distribution of the 40 base pair (bp) VNTR in the 3' untranslated region (UTR) of the gene has been determined in duplicate (two separate PCR amplifications and analyses, 5224 genotypes). The allelic distributions in bp and number of repeats (#R) were: 320 bp (6R), 0.0002%; 360 bp (7R), 0.003%; 400 bp (8R), 0.004%; 440 bp (9R), 21.0%; 480 bp (10R), 77.0%; and 520 bp (11R), 0.009%. *DRD4*: The 48 bp VNTR element in the third exon was determined in duplicate as above (5224 genotypes). The allelic distributions were: 379 bp (2R), 0.09%; 427 bp (3R), 0.03%; 475 bp (4R), 65.0%; 523 bp (5R), 0.01%; 571 bp (6R), 0.008%; 619 bp (7R), 20.0%; 667 bp (8R) 0.009%; 715 bp (9R), 0.0006%; and 763 bp (10R), 0.002%. *SLC6A4*: The 44 bp addition/deletion in the 5' regulatory region was determined in duplicate as above (5224 genotypes). The allelic distributions were: 484 bp ("short allele), 43.0%; and 528 bp ("long allele"), 57.0%. MAOA-uVNTR: The 30 bp VNTR in the promoter was determined in duplicate as above (5224 genotypes). The allelic distributions were: 291 bp (2R), 1.1% (males), 0.01% (females); 321 bp (3R), 40.9% (males), 38.0% (females); 336

[37] Former research comparing this coding approach with another in which only individuals identifying as one race/ethnic group were coded as such and all other individuals were coded as "multiracial" suggest that findings are generally robust across coding schemes (Adkins et al. 2009).

bp (3.5R), 0.8% (males), 0.01% (females); 351 bp (4R), 55.3% (males), 58.0% (females); 381 bp (5R), 1.38% (males), 0.01% (females). *DRD2* TaqIA: The polymorphic TaqI restriction endonuclease site was determined in duplicate as above (5224 genotypes). The allelic distributions were: 178 bp, 72.8%; 304 bp, 27.2%.

Analytical strategy. Add Health is typical among longitudinal datasets, in that it is organized by wave of assessment with variability in chronological age at each wave. However, given that developmental research has clearly demonstrated age to be a more meaningful time metric than wave for the study of depression trajectories (e.g., Hankin et al. 1998; Ge et al. 1994), the data have been restructured in this analysis to provide age-based measurements. Fortunately, the statistical method employed—linear mixed effects models—has been shown to effectively accommodate features of the restructured data, including unbalanced repeated measures, variable data schedules, and missing observations (Diggle and Kenward 1994; Willett et al. 1998).

Linear mixed effects models have long been established in the statistical literature for the analysis of clustered, non-independent data (Searle 1971; Searle et al. 1992), and are known to be particularly advantageous for growth curve analyses of longitudinal data (Willett et al. 1998). The following equation describes a simplified version of the general mixed regression model used to investigate age variation in the effects of the candidate genes on depression (DS):

$$DS_{jit} = \beta_0 + \beta_1 Gene + \beta_2 Gene \times Age + \beta_3 Gene \times Age^2 + \beta_k Controls + \mu_{j0} + \upsilon_{ji0} + e_{jit}$$

where *j, i,* and *t* index the three levels of data: sibling cluster (i.e., household), individual, and assessment, respectively. Thus, the model allows random effects at both the sibling cluster and individual levels. Conditional on the random intercepts μ_{j0} and υ_{ji0} at the sibling cluster and individual levels, the siblings and repeated assessments are assumed to be independent. The household level random effect should, in principle, capture much of the influence of population stratification on the results. This because it accounts for intercept variation in depression between households, with the assumption that the household cluster should be a decent proxy for identical by descent genetic similarity. Further control of population stratification is gained by the inclusion of self-identified race/ethnicity in all models.[38]

The base model, without genetic effects, controls for race/ethnicity, gender, age, age^2, social support, parental education, household income, and SLEs.[39] This model is consistent with prevailing environmental theories of depression and has been empirically tested by the author in previous analyses of Add Health (see Adkins et al. 2008, Adkins et al. 2009). For the primary set of analyses, in addition to the base model, each estimated model included a genetic variable and interaction terms between the genetic variable and both age and age^2; thus examining variation in genetic effects across age by modeling genetic effects on each of the three trajectory components—intercept, linear age slope, and quadratic age slope. Sensitivity analyses repeat this procedure for each of the three alternate specifications of depression. After identifying the most promising models, the robustness of these models are tested in two final sensitivity analyses; first, by square

[38] While self-identified race/ethnicity is clearly a social construct, it has been shown to correlate strongly to primary ancestral dimensions (Tang et al. 2005).

[39] The effects of age and age^2, as well as those of all other predictors, are modeled as fixed effects. This specification was chosen to facilitate model optimization.

root transforming the CES-D and rerunning the promising models to eliminate the possibility that results are driven by outliers. And, in the final sensitivity analyses, fitting the promising models as structural equation models (SEM) to allow more accurate measurement of the several latent constructs modeled (i.e., depression, social support, parental education).

For DAT1, *DRD4, SLC6A4,* and *DRD4,* analyses were conducted on the full sample of both males and females. An alternative approach was used for *MAOA*, as its location on the X chromosome complicates direct comparisons between males and females. This is because males have a single allele at this locus, making their characterization straightforward, while females have two alleles, one of which may be silenced to some degree due to X-inactivation (Meyer-Lindenberg et al. 2006; Jansson et al. 2005). Given this ambiguity, analyses of *MAOA* are stratified by gender, while the full sample is jointly analyzed for all other genes.

The case of *MAOA* in females is illustrative of a more pervasive issue—it is often unclear what the correct specifications of allelic effect are. Examples of both additive effects, in which there is a dose-response relationship between number of the risk alleles and the phenotype, and dominance effects, where a single allele is sufficient to give the full phenotypic effect, abound in the psychiatric genetics literature. Moreover, in psychiatric genetics there are also documented instances of *heterosis*, in which heterozygosity at a given locus is associated with a greater or lesser phenotypic effect, compared to homozygotes of either allele (Chen et al. 1994; Guo et al. 2007). And though former human genetics research, animal studies, and functional analyses can be informative in selecting allelic effect specifications, this knowledge is incomplete at best,

and expectations are frequently overturned. *DRD4* is instructive in this regard—while functional studies have generally implicated the 7R allele (Asghari et al. 1995), a recent meta-analysis instead only showed significant association between the 2R allele and unipolar depression (Lopez et al. 2005). The case of *MAOA* and delinquency is similarly instructive as Caspi et al. (2002) have reported GxE between the *MAOA* 3R and maltreatment, while Guo and colleagues (2008a, 2008b) have instead shown evidence of both main effects and GxE with the 2R allele, offering no support for a role of the 3R allele in delinquency.

Overall, the frequency of unexpected associations combined with relatively weak theory of genetic mechanisms suggests that approaches relying strictly on precedent to specify allelic effects are vulnerable to missing true associations. This line of logic recommends an empirical approach to systematically screen various allelic effect specifications and gene × age configurations. Moreover, in practice researchers conducting candidate gene studies often tacitly employ such empirical, exploratory methods, but do not adjust significance criteria to account for multiple testing (Colhoun et al. 2003). Indeed, the enormous problem of false discoveries in candidate gene research, with 19 out every 20 associations currently reported in the literature thought be false, is largely due to researchers conducting multiple tests, but only reporting significant findings (Colhoun et al. 2003; van den Oord 2008). Given these facts, experts have argued that optimal methods for genetic discovery should cast a wide net, using exhaustive exploratory techniques, yet explicitly recognize the reduced confidence in any single association and adjust significance criteria accordingly (van den Oord 2008; van den Oord 2005). Research has indicated that controlling for the false discovery rate

(FDR) is a superior method for achieving these aims in candidate gene studies with correlated tests, such as the current analysis (van den Oord and Sullivan 2003; van den Oord 2005).

False discovery rate

For each allele of the five monoamine genes investigated in this study, additive, dominance and heterosis allelic effects were tested, each in a separate mixed model. Thus, the primary analysis consisted of 80 models, one of each of the 80 allelic effect specifications tested (counting *MAOA* alleles separately for male and females). In each of the 80 models of the primary analysis, there were three coefficients of substantive interest, the direct genetic effect and the gene × age and gene × age^2 interaction effects, resulting in 240 coefficients of interest from the primary analysis. This procedure was repeated for each of the three sensitivity outcomes, producing 960 coefficients of interest in total.

Standard p-values for the genetic, gene × age, and gene × age^2 coefficients from each estimated mixed model were collected and FDRs were estimated from the p-value data. FDRs can be estimated in various ways and many standard statistical packages (e.g., R, SAS) have such estimation procedures implemented. The current study estimates a FDR for a chosen threshold p-value t. If the m p-values are denoted p_i, $i = 1 \ldots m$, this can be done using the formula:

$$\widehat{\mathrm{FDR}}(\mathrm{t}) = \frac{\mathrm{mt}}{\#\{\mathrm{p_i} \leq \mathrm{t}\}}$$

Thus, the FDR is estimated by dividing the estimated number of false discoveries (the

number of tests times the probability *t* of rejecting a marker without effect) by the total number of significant markers (i.e. total number of p-values smaller than *t*) that includes the false and true positives. To avoid arbitrary choices, each of the observed p-values can be used as a threshold p-value *t*. The resulting FDR statistics are then called q-values. Associations with $q < 0.15$ are considered "significant", indicating the 1.5 out of 10 reported findings would be expected to be a false discovery.[40] Data management and statistical analyses were conducted using Stata 10 (StataCorp LP; www.stata.com) and FDRs were calculated using R 2.7.2 (http://www.r-project.org/index.html).

Results

Figure 3.1 plots means for each of the four CES-D specifications examined, by age and gender. Notable patterns include elevated symptom counts in late adolescence for all CES-D specifications and both genders, with symptom counts peaking around age 18. Females exhibit substantially higher symptom levels than males across all ages for all outcomes. Lower symptom levels were observed for the 3 item and factor score CES-D specifications relative to the primary 9 item outcome, indicating that depressed affect symptoms occurred less frequently than symptoms of other dimensions. All outcomes exhibited roughly the same over-time pattern.

Table 3.1 presents descriptive statistics for the environmental predictors at Wave I by gender. Several trends are evident. Demographically, the sample included slightly fewer males than females, and Add Health's oversample of minorities was apparent with

[40] While FDR is generally viewed as a superior method for adjusting significance criteria for multiple testing, it is not without limitations. Chief among these are its difficulty in detecting true minor effects with very modest effects sizes and a tendency to be overly liberal in analyses with small to moderate numbers of tests (see van den Oord 2008 for review).

all non-White racial/ethnic groups representing higher proportions of the sample than the national population. Respondents were primarily of high school age in Wave I, and both genders generally reported comparable levels of perceived social support. Measures of SES indicated that respondent's mean yearly household income was approximately $45,000-$50,000 and the mean highest parental educational attainment was slightly greater than a high school degree. Finally, SLEs were more frequently reported by males (mean = 2.75) than females (mean = 1.85).

Table 3.2 shows the number of significant gene, gene × age and gene × age^2 effects at various *q*-value thresholds. The first row of Table 3.2 show that for the primary outcome, the 9 item CES-D average, 9 coefficients were significant at $q < 0.1$, and 3 coefficients were significant at $q < 0.05$, out of 240 coefficients tested. All significant results from the primary results were for models examining *DRD4* in the full sample. In addition to the significant findings for the primary outcome, the sensitivity analyses of alternate CES-D specifications indicated that out approximately 720 parameters tested, 29 effects were significant at $q < 0.15$, 20 were significant at $q < 0.05$, and 2 were significant at $q < 0.01$. This indicates that there were a moderate number of effects with *p*-values significantly lower than expected by chance given the number of tests, suggesting the presence of several true effects.

Table 3.3 describes the top hits from the analysis ($q < 0.15$, hereafter referred to as "significant"). The first 9 and latter 29 rows describe significant findings for the primary and sensitivity outcomes, respectively. Findings from both sets of outcomes are sorted by *p*-values in ascending order. All significant findings involved either *DRD4* (3R or 5R alleles) in the full sample, *MAOA* 2R/2R genotype among females, or *MAOA* 3.5R

genotype among males. The strongest associations overall were for models of the 2R/2R *MAOA* genotype among females, where all three genetic coefficients—*MAOA* 2R/2R, *MAOA* 2R/2R × age, and *MAOA* 2R/2R × age^2—were highly significant for all three of the sensitivity outcomes ($p < 0.005$ for all genetic coefficients); and approached significance in the primary outcome ($p < 0.05$). However, as the MAO 2R/2R genotype is exceedingly rare (0.10% of the female sample), this result is considered of limited interest and further discussion is focused on other more common variants.

The strongest associations for the primary outcome were for the effects of the *DRD4* 3R/3R genotype in the full sample ($p < 0.0005$ for all genetic coefficients). However, as this genotype is extremely rare (0.08% of the full sample), it is of questionable robustness and generalizability, and consequently, not further discussed. All other significant findings in the full sample, for both primary and sensitivity outcomes, regard the *DRD4* 5R allele. Results indicate that individuals with the relatively uncommon 5R *DRD4* allele (2.76% of the full sample) experience unique trajectories of depression across early life, characterized by U-shaped depression development, with relatively high levels as pre-teens at baseline, declining through adolescence, and rising in young adulthood. As illustrated in Figure 3.2, this trajectory is roughly opposite the normative, inverted U-shaped pattern commonly seen across the period. This was found for various specifications of the *DRD4* 5R allele for the primary outcome, as well as for multiple specification for the 9 item and 3 item CES-D factor score sensitivity outcomes.[41] Table 3.4 shows all estimates from the *DRD4* no 5R allele model for each of the 4 outcome specifications. *P*-values were highest for the primary 9 item average CES-

[41] Given that there were only 2 observations with the DRD4 5R/5R genotype, the no 5R, # 5R, and 5R/other specifications are very highly correlated.

D specifications ($p < 0.005$ for gene × age and gene × age^2 coefficients), but gene × age and gene × age^2 interaction terms were also $p < .01$ for all 3 sensitivity CES-D specifications. Additional sensitivity analyses also supported the robustness of this finding. As shown in Appendix 3.1, taking the square root of the CES-D to improve the normality of the distribution and reduce the influence of outliers substantially *increased* the significance of the parameters of interest ($p < 0.005$ for gene × age and $p < 0.001$ gene × age^2 coefficients). Further, as shown in Appendix 3.2, an SEM sensitivity analysis also upheld the robustness of this finding ($p < 0.05$ for gene × age and gene × age^2 coefficients). Overall, these results suggest, with a high degree of confidence, that individuals with the *DRD4* 5R genotype exhibit a unique trajectory, characterized by relatively low depression levels in adolescence and relatively high levels in early adulthood.

The final significant finding regards the uncommon *MAOA* 3.5R genotype among males (0.79% of the male sample). This allele was found to significantly interact with age and age^2 in both the 9 and 3 item CES-D factor score outcomes. As shown in Figure 3.3, compared to the normative pattern males with the 3.5R genotype, exhibited a similar, but markedly more curvilinear, inverted U-shaped trajectory. While only the factor score CES-D specifications satisfied the $q < 0.15$ threshold ($p < 0.005$ for 3 item factor score, and $p < .02$ for 9 item factor score, gene × age and gene × age^2 coefficients), as shown in Table 3.5, gene × age and gene × age^2 interaction terms were $p < .05$ for all CES-D specifications. These results were largely supported by additional sensitivity analyses showing significant results for square root transformed specifications of the CES-D

(Appendix 3.3).[42] SEM sensitivity analysis of the 3 item CES-D specification, shown in Appendix 3.4, also demonstrated the robustness of the findings ($p < .01$ for gene × age and gene × age^2 coefficients). These results suggest that males with the *MAOA* 3.5R genotype may experience a particularly distressful adolescence, before converging with there peers in early adulthood.

Discussion

Leading social science perspectives have long stressed the importance of accounting for temporality and life course variation in models of mental health (Elder et al. 1996; Elder 1998). A primary insight of this perspective is that the importance of various depressogenic social factors fluctuates across developmental trajectories (Elder et al. 1996). For instance, prominent social science paradigms like *cumulative disadvantage* suggest the deleterious impact of persistent social disadvantage amplifies as individuals move through the life course (e.g., McLeod and Owens 2004; O'Rand 1996). The current study endeavors to wed this perspective to molecular genetic approaches to depression. While psychiatric molecular genetics has made advances toward elucidating the link between genetic variation and depression, virtually all of this research has been atemporal. The weakness of this static perspective on the genetic determinants of depression is highlighted not only by developmental social science perspectives, but also by newer research within genetics showing that epigenetic mechanisms "turn genes off and on" in response to developmental and environmental cues (Whitelaw and Whitelaw 2006). Using the Add Health genetic subsample, this study has addressed the issue of

[42] With the exception of the gene × age coefficient, which became marginally nonsignificant ($p = 0.068$) in the 3 item square root transformed CES-D model.

variation in genetic influences across early life through comprehensively testing the effects of 5 monoamine genes on depression trajectories, while employing FDR methods to control the risk of false discoveries.

The most promising associations detected were for interactions between the *DRD4* dopamine receptor gene and age trajectory components in the full sample, and the MAOA VNTR promoter polymorphism and age trajectory components among males. Specifically, in the case of the *DRD4* finding individuals with the 5R allele were found to exhibit a roughly opposite trajectory compared to the normative inverted-U pattern. Thus, individuals with any 5R alleles were shown to have relatively low depression levels through late adolescence, before experiencing increases in early adulthood. This pattern suggests that carriers of the *DRD4* 5R allele navigate their high school years with relative psychological ease compared to others, but begin to experience elevated psychological distress as they transition into adult roles. Interpreting the molecular mechanism underpinning this finding is problematized by the fact that there very little is known about the 5R allele. Given its relatively low allele frequency (2.76% of the full sample), it has not been well-characterized in functional studies; thus, its gene expression profile is poorly understood.

However, one potential explanation of the *DRD4* 5R finding stems from association studies linking *DRD4* to substance abuse. The *DRD4* 5R allele[43] has shown evidence of association to abuse of various substances, including alcohol (e.g., Muramatsu et al. 1996) and heroin (e.g., Li et al. 1997). And while these findings remain controversial (see Lusher et al. 2001), their potentially relevance to the current *DRD4* finding becomes apparent when considering the life course context of substance abuse.

[43] In some cases coded together with other "long" alleles.

Specifically, social control factors limiting access and abuse of substances, such as parental monitoring and legal obstacles, are relatively strong in adolescence. However, in the late teens and early twenties, after individuals leave their parents' homes and can legally purchase alcohol, social control mechanisms weaken and impediments to substance abuse are removed. Given that the upswing in depression for *DRD4* 5R carriers observed here closely corresponds to the transition to adulthood, and that substance abuse and depression are highly correlated and frequently clinically comorbid (e.g., Grant and Harford 1995), it seems likely that loosening social control is a key explanatory factor of the elevated distress levels observed among 5R carriers in young adulthood. However, as the direction of causality between substance abuse and depression is debated and likely reciprocal to some degree (e.g., Aneshensel and Huba 1983), future research will be needed to replicate this finding and disentangle the web of causality between *DRD4*, substance abuse, and depression.

The other notable substantive finding was an association between the *MAOA* 3.5R allele and depression trajectory components in the male sample. Specifically, males with the 3.5R genotype had more curvilinear depression trajectories than the normative pattern, with higher peaks in late adolescence and sharper declines in early adulthood. Thus, males with the 3.5 genotype were shown to have a particular distressful time during high school and the subsequent transition to adulthood, but converge with their peers in early adulthood. This age variation in the influence of *MAOA* may explain inconsistencies in former *MAOA*-depression association results, which have shown both elevated depression levels among male carriers of the 3.5R and other long *MAOA* alleles (Du et al. 2004; Yu et al. 2005), and also no significant association (Kunugi et al. 1999).

Furthermore, the current results may shed light on results from a recent meta-analysis of six *MAOA*-depression association studies, which found a strong trend toward increased depression among carriers of the 3.5R and other long *MAOA* alleles falling just short of statistical significance (OR = 0.86; 95% CI: 0.74–1.01).[44] Interestingly, this meta-analysis found strong evidence of heterogeneity in effect sizes across studies. Results of the current study offer a potential explanation for this heterogeneity, suggesting that age differences across samples may be driving effect differences.

Beyond the substantive results, this study shows the value of combining temporally dynamic, social science perspectives with comprehensive empirical statistical approaches to optimize the search for genetic influences across the life course. This can be seen from various aspects of the current study. First, without an exhaustive exploration of various allelic specifications beyond those conventionally assessed, highly significant associations for the 3.5R *MAOA* and 5R *DRD4* alleles would not have been detected. Also, employing a developmental perspective to consider age variations in genetic enabled the detection of very strong nonlinear gene × age interactions that would have otherwise been missed. Finally, the use of FDR statistical methods allowed these comprehensive empirical explorations of the data by controlling the risk of false discoveries—a major problem in genetic research (Colhoun et al. 2003), that social scientists interested in incorporating genetic perspectives have yet to sufficiently address.

[44] Reverse coded –i.e., *MAOA* 3.5 and 4 coded 0 and other *MAOA* alleles coded 1.

Table 3.1. Descriptive statistics, environmental predictors

	Male (n = 926)				Female (n = 988)			
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max
White	0.60	0.49	0	1	0.63	0.48	0	1
Hispanic	0.14	0.35	0	1	0.13	0.34	0	1
Black	0.17	0.38	0	1	0.16	0.37	0	1
Asian	0.06	0.24	0	1	0.05	0.21	0	1
American Indian	0.02	0.13	0	1	0.02	0.14	0	1
Other Race	0.01	0.09	0	1	0.01	0.07	0	1
Age	16.12	1.65	12	21	16.01	1.66	12	20
Social Support	4.04	0.54	1.7	5	4.07	0.54	1.4	5
Parental Education (mean)	5.96	1.75	2	9	5.78	1.78	2	9
Household income	45.36	45.53	0	999	50.28	61.68	0	999
SLEs	2.75	2.87	0	20	1.85	2.15	0	17

Table 3.2. Number of associations below various *q*-values thresholds

	Full Sample (no *MAOA*)				Males (*MAOA*)				Females (*MAOA*)			
Outcome	0.01	0.05	0.1	0.15	0.01	0.05	0.1	0.15	0.01	0.05	0.1	0.15
CES-D 9 item avg	0	3	9	9	0	0	0	0	0	0	0	0
CES-D 9 item factor	0	0	9	9	0	0	0	2	0	0	3	3
CES-D 3 item avg	0	0	0	0	0	0	0	0	3	3	3	3
CES-D 3 item factor	0	0	0	7	0	0	2	2	3	3	3	3

Table 3.3. Associations with *q*-values less than 0.15

CES-D Specification	Sample	Coefficient	b	se	z stat	p-value	q-value
9 Item Avg	Full	*DRD4* 3R/3R	3.692	0.949	3.890	0.000	0.014
9 Item Avg	Full	*DRD4* 3R/3R × Age	-1.050	0.287	-3.660	0.000	0.014
9 Item Avg	Full	*DRD4* 3R/3R × Age Sq	0.067	0.019	3.620	0.000	0.014
9 Item Avg	Full	*DRD4* # 5R × Age	-0.117	0.039	-3.020	0.003	0.055
9 Item Avg	Full	*DRD4* no 5R × Age	0.117	0.039	3.002	0.003	0.055
9 Item Avg	Full	*DRD4* 5R/other × Age	-0.116	0.039	-2.969	0.003	0.055
9 Item Avg	Full	*DRD4* # 5R × Age Sq	0.007	0.003	2.959	0.003	0.055
9 Item Avg	Full	*DRD4* no 5R × Age Sq	-0.007	0.003	-2.952	0.003	0.055
9 Item Avg	Full	*DRD4* 5R/other × Age Sq	0.007	0.003	2.932	0.003	0.055
3 Item Avg	Female	*MAOA* 2R/2R	50.520	12.862	3.928	0.000	0.003
3 Item Avg	Female	*MAOA* 2R/2R × Age	-10.443	2.724	-3.833	0.000	0.003
3 Item Avg	Female	*MAOA* 2R/2R × Age Sq	0.508	0.134	3.791	0.000	0.003
3 Item Factor Score	Female	*MAOA* 2R/2R	36.873	9.697	3.802	0.000	0.005
3 Item Factor Score	Female	*MAOA* 2R/2R × Age	-7.638	2.054	-3.719	0.000	0.005
3 Item Factor Score	Female	*MAOA* 2R/2R × Age Sq	0.372	0.101	3.681	0.000	0.005
9 Item Factor Score	Female	*MAOA* 2R/2R	24.246	7.925	3.059	0.002	0.057
9 Item Factor Score	Female	*MAOA* 2R/2R × Age	-5.051	1.678	-3.010	0.003	0.057
9 Item Factor Score	Female	*MAOA* 2R/2R × Age Sq	0.248	0.083	3.001	0.003	0.057
3 Item Factor Score	Male	*MAOA* 3.5R × Age Sq	-0.017	0.006	-2.793	0.005	0.069
3 Item Factor Score	Male	*MAOA* 3.5R × Age	0.209	0.079	2.666	0.008	0.069
9 Item Factor Score	Full	*DRD4* 3R/3R	2.690	0.789	3.409	0.001	0.071
9 Item Factor Score	Full	*DRD4* 3R/3R × Age	-0.771	0.239	-3.226	0.001	0.071
9 Item Factor Score	Full	*DRD4* 3R/3R × Age Sq	0.049	0.016	3.182	0.001	0.071
9 Item Factor Score	Full	*DRD4* no 5R × Age	0.093	0.032	2.875	0.004	0.088
9 Item Factor Score	Full	*DRD4* # 5R × Age	-0.092	0.032	-2.868	0.004	0.088
9 Item Factor Score	Full	*DRD4* 5R/other × Age	-0.093	0.032	-2.865	0.004	0.088
9 Item Factor Score	Full	*DRD4* no 5R × Age Sq	-0.006	0.002	-2.789	0.005	0.088
9 Item Factor Score	Full	*DRD4* 5R/other × Age Sq	0.006	0.002	2.784	0.005	0.088
9 Item Factor Score	Full	*DRD4* # 5R × Age Sq	0.006	0.002	2.781	0.005	0.088
9 Item Factor Score	Male	*MAOA* 3.5R × Age Sq	-0.013	0.005	-2.736	0.006	0.112
9 Item Factor Score	Male	*MAOA* 3.5R × Age	0.153	0.062	2.489	0.013	0.115
3 Item Factor Score	Full	*DRD4* no 5R × Age	0.114	0.040	2.861	0.004	0.130
3 Item Factor Score	Full	*DRD4* # 5R × Age	-0.114	0.040	-2.858	0.004	0.130
3 Item Factor Score	Full	*DRD4* 5R/other × Age	-0.114	0.040	-2.848	0.004	0.130
3 Item Factor Score	Full	*DRD4* no 5R × Age Sq	-0.007	0.003	-2.795	0.005	0.130
3 Item Factor Score	Full	*DRD4* # 5R × Age Sq	0.007	0.003	2.789	0.005	0.130
3 Item Factor Score	Full	*DRD4* 5R/other × Age Sq	0.007	0.003	2.785	0.005	0.130
3 Item Factor Score	Full	*DRD4* 3R/3R	2.666	0.981	2.718	0.007	0.137

Table 3.4. Parameter estimates (*p*-values) of linear mixed models among full sample: Effects of *DRD4* 5R genotype on depression trajectories for 4 outcome specifications

	9 item avg	9 item factor	3 item avg	3 item factor
DRD4 no 5R	-0.340*	-0.258*	-0.382*	-0.297*
	(0.013)	(0.022)	(0.037)	(0.032)
DRD4 no 5R * Age	0.117**	0.093**	0.144**	0.114**
	(0.003)	(0.004)	(0.007)	(0.004)
DRD4 no 5R * Age Sq	-0.007**	-0.006**	-0.009**	-0.007**
	(0.003)	(0.005)	(0.008)	(0.005)
Female	0.122***	0.106***	0.163***	0.121***
	(0.000)	(0.000)	(0.000)	(0.000)
Hispanic	0.032	0.020	0.041	0.023
	(0.210)	(0.320)	(0.184)	(0.315)
Black	0.064**	0.048**	0.054	0.041*
	(0.005)	(0.007)	(0.050)	(0.050)
Asian	0.160***	0.086**	0.102*	0.071*
	(0.000)	(0.002)	(0.018)	(0.030)
American Indian	0.022	0.035	0.079	0.041
	(0.683)	(0.422)	(0.245)	(0.425)
Other Race	-0.009	-0.023	-0.043	-0.037
	(0.921)	(0.757)	(0.712)	(0.669)
Age	-0.095*	-0.058	-0.097	-0.072
	(0.013)	(0.066)	(0.064)	(0.066)
Age Squared	0.005	0.004	0.005	0.005
	(0.052)	(0.065)	(0.119)	(0.063)
Social Support	-0.225***	-0.158***	-0.203***	-0.155***
	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education (mean)	-0.028***	-0.017***	-0.021**	-0.015**
	(0.000)	(0.000)	(0.001)	(0.002)
Household income (logged thousands)	-0.005	-0.005	-0.009	-0.009
	(0.684)	(0.569)	(0.518)	(0.409)
SLE	0.035***	0.029***	0.042***	0.031***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.848***	0.477***	0.631***	0.452***
	(0.000)	(0.000)	(0.001)	(0.001)
Random intercept SD (Household level)	0.164***	0.121***	0.182***	0.138***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.181***	0.138***	0.199***	0.150***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.345***	0.288***	0.476***	0.360***
	(0.000)	(0.000)	(0.000)	(0.000)
N	5627	5627	5626	5626
Log restricted likelihood	-2880.390	-1759.997	-4471.703	-2894.409

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Table 3.5. Parameter estimates (*p*-values) of linear mixed models among male sample: Effects of *MAOA* 3.5R genotype on depression trajectories for 4 outcome specifications

	9 item avg	9 item factor	3 item avg	3 item factor
MAOA 3.5R	-0.332	-0.321	-0.504	-0.487*
	(0.130)	(0.075)	(0.093)	(0.031)
MAOA 3.5R * Age	0.165*	0.153*	0.228*	0.209**
	(0.025)	(0.013)	(0.028)	(0.008)
MAOA 3.5R * Age Sq	-0.014*	-0.013**	-0.019*	-0.017**
	(0.012)	(0.006)	(0.014)	(0.005)
Hispanic	0.047	0.036	0.064	0.041
	(0.170)	(0.170)	(0.122)	(0.192)
Black	0.110***	0.083***	0.105**	0.082**
	(0.000)	(0.000)	(0.005)	(0.003)
Asian	0.130**	0.079*	0.098	0.074
	(0.004)	(0.025)	(0.076)	(0.075)
American Indian	-0.057	-0.034	-0.009	-0.035
	(0.447)	(0.566)	(0.923)	(0.617)
Other Race	0.177	0.119	0.157	0.104
	(0.152)	(0.216)	(0.298)	(0.365)
Age	0.022*	0.034***	0.048***	0.043***
	(0.016)	(0.000)	(0.000)	(0.000)
Age Squared	-0.002***	-0.002***	-0.003***	-0.002***
	(0.000)	(0.000)	(0.000)	(0.001)
Social Support	-0.179***	-0.121***	-0.151***	-0.114***
	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education (mean)	-0.022**	-0.011*	-0.012	-0.009
	(0.002)	(0.039)	(0.153)	(0.188)
Household income (logged thousands)	-0.006	-0.002	-0.003	-0.003
	(0.718)	(0.858)	(0.862)	(0.828)
SLE	0.026***	0.019***	0.026***	0.018***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.478***	0.195***	0.207***	0.120***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Household level)	0.175***	0.130***	0.208***	0.153***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.169***	0.126***	0.168***	0.133***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.302***	0.253***	0.429***	0.323***
	(0.000)	(0.000)	(0.000)	(0.000)
N	2701	2701	2700	2700
Log restricted likelihood	-1113.747	-573.268	-1919.846	-1164.920

P-values in parentheses

* p<0.05, ** p<0.01, *** p<0.001

Figure 3.1. Mean symptom levels for 4 specifications of the CES-D, plotted by age and gender

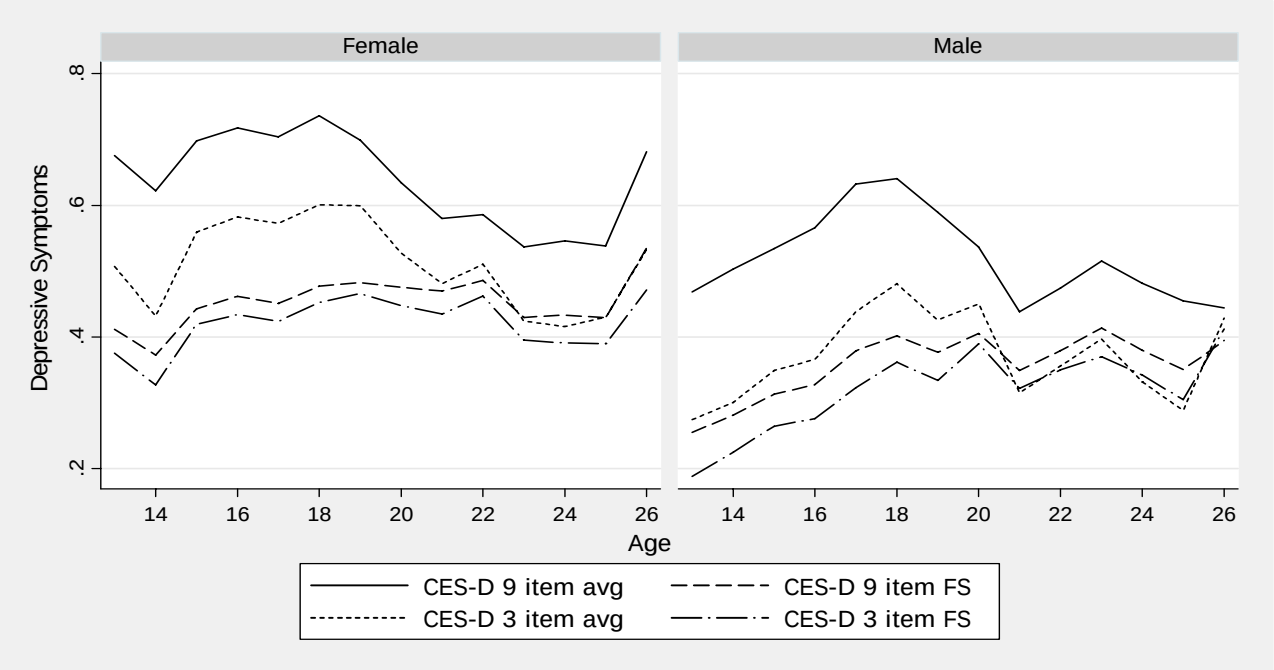


Figure 3.2. Depression age trajectory differences between *DRD4* 5R carriers and others

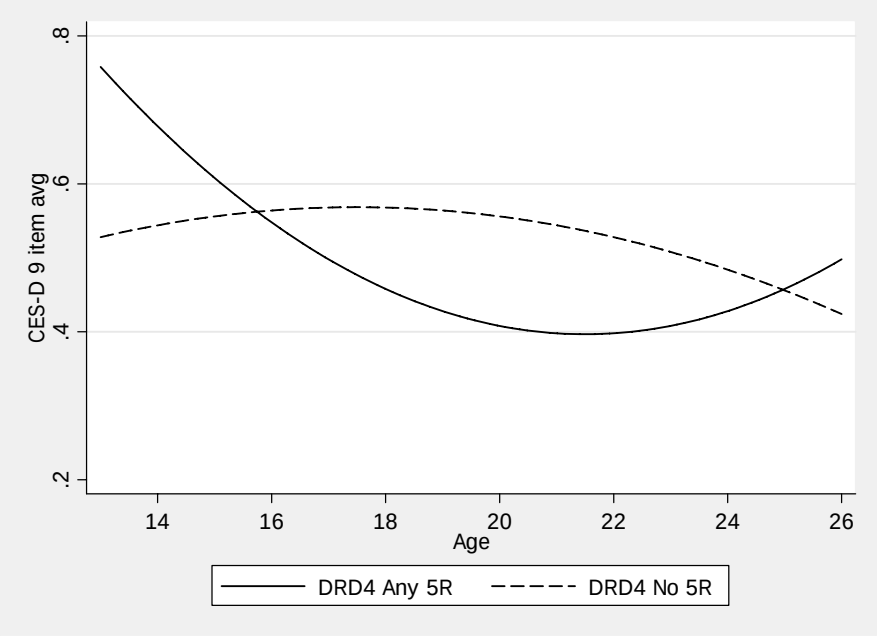
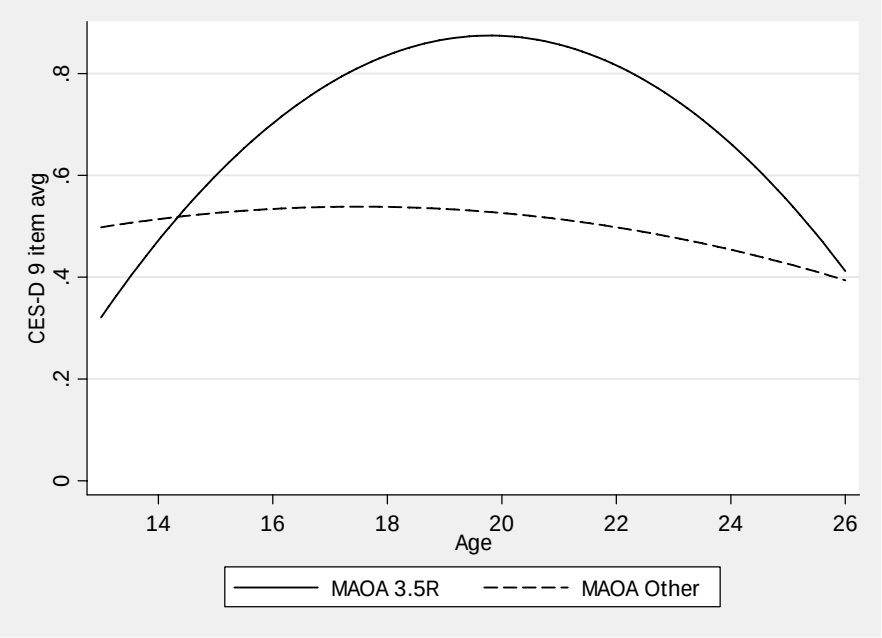


Figure 3.3. Depression age trajectory differences between male carriers of the *MAOA* 3.5 genotype and other males



Chapter 4: Social and Developmental Moderation of the Effects of Physical Attractiveness on Depression

Introduction

It would be difficult to overstate the importance of physical attractiveness in either contemporary American society or, more generally, human history. It has been a preoccupation of philosophers, poets and scientists since Antiquity and has spawned a $160 billion per year global beauty industry in contemporary times (Economist 2003). Given the perennial, central role of attractiveness in our personal and social lives, it is surprising how little social science research has focused on the topic, outside of relatively insular literatures in personality and evolutionary psychology. This deficiency has recently begun to be remedied, particularly in the area of labor economics, where a critical mass of research has shown that attractiveness is associated with a substantial wage premium (e.g., Biddle and Hamermesh 1998; Hamermesh 2006; Hamermesh and Biddle 1994). Despite these advances, some of the most basic effects of attractiveness are still poorly understood. In particular, the effect of attractiveness on affective characteristics, such as depression, has received very little attention in the literature, in spite of being among the most direct, fundamental results of the trait.

Given the dearth of research on the influence of attractiveness on depression, it is not surprising that virtually nothing is known of how attractiveness interacts with developmental

and social processes influencing depression in early life. However, assuming that attractiveness does indeed exert *some* influence on depression, there are several well-established social science perspectives that suggest interaction with developmental and social processes. Regarding development, longitudinal research has shown that developmental processes influence both normative trajectories of depressive symptoms in early life (Adkins et al. 2009; Ge et al. 1994, 2006), and the effects of key predictors. For instance, the influence of gender, which is recognized as one of the strongest and most consistent predictors of depression in adulthood (Nolen-Hoeksema 1990), is known to gradually emerge in early adolescence and thought to be related to pubertal changes (e.g., Angold et al. 1998). Given such developmental trends, it seems plausible that the impact of attractiveness on affect, and self-perception more generally, may also be developmentally moderated, increasing during adolescence as individuals begin to internalize social identities, develop sexual awareness and enter into more competitive milieus.

Similarly, while no empirical research has yet examined potential interactions between the social determinants of depression and attractiveness, prominent theoretical perspectives suggest a likely pattern in this regard. Specifically, theories under the rubric of cumulative disadvantage (see McLeod and Owens 2004) posit that the presence of a given social disadvantage depletes an individual's coping resources, leaving them more vulnerable to the pernicious effects of additional adversity. Thus, this perspective suggests that sources of social disadvantage are apt to have multiplicative detrimental effects on mental health when occurring in combination. Further, empirical support of cumulative disadvantage has been found in studies of early life depression. For instance, former research has shown that the detrimental effects of low socio-economic status (SES) are greater among demographic

groups showing higher levels of depression—females and racial/ethnic minorities (Adkins et al. 2009). This raises the possibility that physical attractiveness may also function to moderate vulnerability to social determinants of depression, including demographic factors (i.e., gender and race/ethnicity) and components of the stress process (e.g., social support and stressful life events (SLEs).

This study investigates these issues, modeling the main and interactive effects of physical attractiveness on age-based trajectories of depressive symptoms using a large nationally representative, longitudinal sample of U.S. adolescents and young adults. Several key questions guide the analyses. First, does physical attractiveness have an association to depression? Second, does this association vary in strength across adolescence and young adulthood? Finally, does physical attractiveness moderate the influence of social determinants of depression? Specifically, does attractiveness buffer against the deficits associated with gender and racial/ethnic minority status? And does it reduce the detrimental effects of childhood poverty, SLEs and social support deficits?

Background

Attractiveness and depression

While research has definitively shown that attractive individuals are *perceived* as less depressed and generally having better mental health (Feingold 1992; Langlois et al. 2000), the degree to which this perception corresponds to an actual depression gradient based on attractiveness is less certain. Empirical research into the question has been sparse and results have been mixed. Of the few studies focusing exclusively on depression, McGovern et al. (1996) found no association in a sample (N =1100) of adult females, as did Noles et al.

(1985) in a small, mixed gender sample of college students (N=225). Similarly, in a sample of young adolescents, Perkins et al. (1995) found that attractiveness did not predict depression, although it did predict several related social and behavioral measures. Conversely, Diener and colleagues (1995), conducting three small studies on a college sample, found a positive association to attractiveness and measures of subjective well-being and global happiness, part of which was explained by "appearance enhancers" (e.g., clothing and jewelry). Two meta-analyses have been conducted for the more general measure of "mental health" have similarly yielded conflicting results, with the earlier one yielding no significant association (Feingold 1992), but the more recent one indicating a modest mental health effect for attractiveness (Langlois et al. 2000).[45] Given that the later meta-analysis encompassed the earlier one, it would be accurate to say that, on balance, research suggests that the effect of attractiveness on mental health is significant but modest. It is also notable that the more recent meta-analysis indicated substantial heterogeneity across individual analysis estimates, suggesting that the influence of attractiveness may vary across subgroups (Langlois 2000).

While empirical findings have been mixed, there are ample reasons to expect an influence of attractiveness on depression. It is popularly held that more attractive individuals benefit from a social premium, as their social desirability tends to evoke warm regard and deference. Indeed, this has consistently been shown to be the case in many domains; so much so that the topic has spawned a considerable literature in psychology under the rubric of the

[45] While the literature on the effects of general attractiveness on depression is relatively small and characterized by heterogeneous results, more conclusive findings are available for related characteristics, such as BMI. Body size and shape are typically viewed as a component of attractiveness, and has robustly been shown to be associated with depression. For instance, in recent analysis of an extremely large sample (N = 177,407) Zhao and colleagues (2009) demonstrated that obese individuals exhibit substantially higher depression rates than individuals with normal range BMI.

"beauty is good" stereotype (e.g., Eagly et al. 1991). For instance, studies consistently show that on the basis of appearance alone, physically attractive individuals are rated as more competent, intelligent, mentally healthy, and more skilled in interpersonal interactions (see Langlois 2000; Feingold 1992; and Eagly 1991 for meta-analyses and review). Additionally, experiments show that subjects are more apt to engage in helping behavior toward attractive individuals, cooperate with them, and also view them as having more "integrity" (Langlois 2000; Eagly 1991). Further, it has been shown that these perceptions translate into tangible results, with attractive individuals enjoying a substantial wage premium (e.g., Hamermesh and Biddle 1994; Mobius and Rosenblat 2006).

Thus, the "beauty is good" literature has unequivocally demonstrated a strong, pervasive gradient in social treatment based on appearance. The cumulative benefits of this social windfall for the attractive, and unfortunately, the penalties for the unattractive, are apt to be internalized to some degree, influencing individuals' self-perceptions (Yeung and Martin 2003). As has been previously noted, this process is well-conceptualized by socialization and social expectancy theories (see Feingold 1992 and Langlois et al. 2000). Applied to the effects of attractiveness on depression, these perspectives suggest that variation in levels of attractiveness elicits differential expectations and treatment, as per the beauty is good stereotype, in which attractive individuals are generally treated more positively. Over time, individuals tend to internalize these differential perceptions, adopting the identity pervasively imputed to them in their social encounters. Once internalized, these socially imposed, cross-domain value judgments begin to influence self-esteem—bolstering a sense of self-worth among the attractive and fostering a sense personal deficits among the unattractive. Finally, as has long been established, such variation in self-esteem is strongly

tied to affective differences (Brown et al. 1990; Baumeister et al. 2003).

Though slightly tangential, it is important to note that this fundamentally social process of internalizing treatment differentials based on attractiveness is not incompatible with evolutionary theories of attractiveness and may validly be detached from other aspects of socialization and social expectancy theories. That is, while socialization and social expectancy theories would suggest that attractiveness and its associated stereotypes/expectations are social constructs, this is not essential to the process of internalizing social perceptions described above. Thus, the process described above could just as easily be driven by evolved universal preferences for attractive physical traits, such as symmetry, averageness and sexual dimorphism (Rhodes 2006). Regardless of the roots of attractiveness criteria, I contend that the influence of attractiveness on depression is driven by a fundamentally social process of gradual internalization of broadly held, societal perceptions.

Developmental variation in the influence of attractiveness on depression

Adolescence is a developmentally complex period characterized by biological changes, transitions to more challenging social environments and establishing identity and independence. As such, adolescence is marked by shifting normative pattern of depressive symptoms and the emergence of major depression differentials present in adulthood. Regarding the normative patterns of depressed affect, it is now well-established that adolescence and young adulthood are characterized by a inverted U-shaped pattern of rising depression levels during early and mid adolescence, peaking in late adolescence and declining levels in early adulthood (e.g., Adkins et al. 2009; Ge et al. 1994, 2006). While

various explanations for this pattern have been proposed, it is still not entirely clear what drives these changes. Clearly, developmental variation in effects of depressogenic factors account for a portion of the pattern (e.g., Nolen-Hoeksema and Girgus 1994). Given the importance of adolescence as a time of identity formation and burgeoning sexual awareness, in may be that the influence of attractiveness increases during adolescence, explaining part of the developmental variation in affect across the period.

Certainly, there is precedent for the emergence of depressogenic effects in this life stage. Gender is instructive in this regard, as it is not until early adolescence that the large female disadvantage characterizing adult depression epidemiology begins to emerge (Nolen-Hoeksema and Girgus 1994; Angold et al. 1998). Further, while it is debated what exactly drives this process—hormonal shifts, morphological changes associated with puberty and/or social responses evoked by these bodily changes—it is generally agreed upon that some aspect of pubertal development mediates the increasing levels of depressed affect experienced by females in adolescence (Angold et al. 1998). As a predominant aspect of adolescent development, pubertal changes also represent a likely mechanism driving an increase in the influence of attractiveness in the period. The development of sexual awareness is a particularly plausible mechanism, as it is not until adolescence that sexual attractiveness becomes a component of social status and desirability (McClintock and Herdt 1996; Udry and Billy 1987). According to this logic, as adolescents begin to signal romantic interest in peers, a new form of social power is generated, reinforcing any extant gradients in social desirability based on attractiveness.

Developmental changes related to puberty are not, however, the only reasons to expect an increase in the influence of attractiveness during adolescence. The socialization

process of internalizing attractiveness-based treatment differentials also suggests a trend toward increasing influence during adolescence. This is because treatment differentials based on attractiveness start early, with research demonstrating that even young children are subject to differential evaluation and treatment based on their attractiveness (Langlois et al. 2000). Thus, the social forces encouraging differential self-worth between the attractive and homely are present from very early in life. However, as with any identity forming socialization process, a certain level of development is required for this gradient in social treatment to be internalized. This is both a function of the cumulative nature of internalization and also, of the gradual nature of psychosocial development (Loevinger 1976). Thus, it seems likely that the affective influence of attractiveness gradually increases across adolescence in sync with the solidification of adult identity.

Attractiveness as a moderator of the social determinants of depression

In addition to developmental variations in the effects of attractiveness, theoretical perspectives and empirical research also suggest the plausibility of attractiveness as a moderator of social determinants of depression. Gender variations seem particularly likely as former research has consistently shown that physical attractiveness ranks more highly as a criterion for mate selection among males than females (e.g., Buss and Barnes 1986, Feingold 1990) and, perhaps relatedly, it has been suggested that females' self-esteem and self-worth are more strongly tied to physical attractiveness (e.g., Siever 1994; Wade and Cooper 1999; Pliner et la. 1990). Cumulatively, this research suggests that physical attractiveness may exert greater influence on depression among females than males, as it may be a more central component to female identity.

Beyond the specific relationship between gender and attractiveness, there are more general reasons to consider interactive effects between attractiveness and social determinants of depression, such as gender. The cumulative disadvantage perspective is particularly compelling in this regard. In this context, cumulative disadvantage refers to the process through which a given social disadvantage weakens an individual's ability to respond to additional sources of adversity (see McLeod and Owens 2004). Thus, the theory suggests that when disadvantaged statuses occur in tandem, they tend to have multiplicative detrimental effects, beyond the additive effects of each risk factor alone.

While the influence of attractiveness on depression has not yet been considered from a cumulative disadvantage perspective, former research has shown this process to operate for other, more established social determinants of depression in early life. For instance, analyzing longitudinal data on early adolescents, McLeod and colleagues (2004) found minority racial/ethnic groups to be particularly sensitive to the detrimental effects of poverty. Similarly, examining a slightly older longitudinal sample of adolescents and young adults, Adkins and colleagues (2009) found that Blacks, Hispanics, and females showed greater depressive response to the effects of low SES and, in the case of females, SLEs. Findings that racial/ethnic minority status increases vulnerability to other depressogenic social determinants may be especially relevant to considering attractiveness as a potential moderator. That is because, net of proxy effects for SES, most experts believe that the association of racial/ethnic minority status to diminished mental health is driven by appearance-based discrimination (Williams et al. 2003; Williams and Collins 1995). Given that the detrimental effects of unattractiveness probably stem from a comparable appearance-

based discrimination process, it may be that, similar to racial/ethnic minority status, unattractiveness functions to increase vulnerability to stressors.

Data and Methods

Sample

Data from the three waves of the National Longitudinal Study of Adolescent Health (Add Health) were used to examine the influence of physical attractiveness on depressive symptom trajectories. Add Health is a nationally representative, school-based sample of 20,745 adolescents in grades 7-12 surveyed during the 1994–1995 academic year. The National Quality Education Database was used as the baseline sample frame, from which 80 high schools were selected along with an additional 52 feeder middle-schools. The response rate for the 134 participating schools was 78.9%. Of the over 90,000 students who completed the in-school survey in 1994 a baseline sample of 20,745 adolescents was selected for further data collection. The adolescents were interviewed three times during a 7-year period in 1994–1995, 1995–1996, and 2001–2002. The overall sample is representative of United States schools with respect to region of the country, urbanicity, school type (e.g., public, parochial, private non-religious, military, etc.), and school size. Members of ethnic minority groups were over-sampled. Further details regarding the sample are available at http://www.cpc.unc.edu/projects/addhealth/. The smallest analysis sample for the current study consisted of 36,536 observations for 14,701 individuals, with each individual contributing an average of 2.5 observations.

Measures

Physical Attractiveness. Field interviewers evaluated the physical attractiveness of the respondents by responding to the questionnaire item: *How physically attractive is the respondent?*, with ratings ranging from 1 (very unattractive) to 5 (very attractive). The distribution of this attractiveness measure showed pronounced negative skew (skew = -.09), with above average ratings of attractiveness 7.75 times more common than below average ratings. Given the irregularity of the distribution, coupled with the likelihood of nontrivial measurement error due to subjective elements in the attractiveness ratings introduced by having only a single evaluator (Honekopp 2006), I considered respecifying the measure as a series of dummy variables. However, as exploratory analyses indicated that treating the measure as a 5 item continuous variable provided roughly equivalent explanatory power to the dummy series specification, the continuous specification was used in the analysis.[46]

Using data on the demographic characteristics of interviewers collected in Wave 3, I considered the possibility of systematic rater biases in the attractiveness measure across ethnic and gender groups. Specifically, as shown in Appendix 4.1, I examined the possibility that raters' systematically rated respondents' of their own ethnic/racial or gender groups differentially compared to respondents' of other demographic groups (Rhodes et al. 2005). Results showed some evidence of mild biases among certain rater demographic groups[47]; however, these biases accounted for very little variance in the attractiveness ratings (~1%) and thus, are not considered problematic source of measurement error.

[46] This findings suggest that, while it may be sensible to expect nonlinearities in the effects of attractiveness on depression, empirical results argue against such an patternn, instead indicating a linear relationship to fit the data well.

[47] Notably, Asian raters gave relatively low ratings to both Asian and, especially, Non-Asian respondents, and males gave other males relatively low ratings.

Depression. Depression was measured using a 9-item scale derived from the conventional 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977). The 20-item CES-D is composed of questions on a number of physical and psychological symptoms of depression, which cluster into four factors: somatic, depressed affect, positive affect, and interpersonal relations (Ensel 1996; Radloff 1977). The scale has been validated using CFA in adult samples of Whites and Blacks (Blazer et al. 1998).[48] It has also been validated in samples of adolescents and young adults (Radloff 1991). Fortunately, a 19-item CES-D was collected in the first two waves of Add Health and a comparison with the subscale (9 items) indicated a high correlation (r = 0.91 and 0.92 in waves one and two, respectively). Individual items were coded on a four-point scale to indicate the frequency of symptoms occurring during the past week, ranging from never or rarely (0) to most or all of the time (3). The primary outcome used in this analysis is the simple average of the 9 items.

In addition to using the 9 items available across in all three survey waves, sensitivity analyses were conducted using an average of the 3 depressed affect items collected in all waves, which have been shown to be measurement invariant across racial/ethnic and immigrant groups (Perreira et al. 2005). In addition to measurement invariance characteristics, the use of the 3 item subscale was also indicated by both notably higher factor loadings for these items relative to the other 6 indicators, as well as stronger theoretical correspondence of the items to the depression construct (see Perreira et al. 2005). Correlation was high between the 2 specifications of the depression variable (r = 0.86). To assure that results are not driven by multidimensionality in the CES-D or measurement variance across racial/ethnic groups, more rigorous SEM sensitivity analyses are conducted, modeling the 3

[48] While Blazer and colleagues (1998) found racial measurement invariance across most items, see Perreira et al. (2005) for contrasting findings indicating widespread measurement invariance across racial groups for the CES-D.

items that have been demonstrated to be measurement invariant depressed affect indicators as latent variable repeated measures.

Parental socioeconomic status. Add Health allows respondents to report parental education levels for up to four parents—resident mother and father figures, and for cases in which biological parents live outside of the respondent's household, nonresident biological mother and father. These variables describe the highest level of education that the parent has completed, and range from "never went to school" to "professional training beyond a four year college or university". Based on previous analyses these items were coded as continuous variables (Adkins et al. 2008). Finally, for each respondent, the mean was then taken of all reported parental education levels, which improved the explanatory power of the variable relative to any single parent's level. Household income was ascertained from the parental questionnaire and includes all sources of income from the previous year (measured in thousands of dollars), and was logged in these analyses. Correlation between parental education and logged household income was moderate ($r = 0.45$), indicating collinearity was not problematically high. SES indicators were mean-centered to aid in model interpretation.

Stressful life events. An additive index was used to measure cumulative exposure to stressful life events. Presented in Appendix 2.1, the SLE index used here is derived from one developed by Ge et al. (1994). Established criteria for the development of the SLE index were used in modifying and expanding the measure for the Add Health survey (Turner and Wheaton 1995).[49] For instance, only acute events of sudden onset and of limited duration

[49] Previous research has explicitly indicated that as SLE indices are based on the concept of allostatic load, a typical (effect) factor analytic approach to measuring SLEs is not appropriate (see Turner and Wheaton 1995).

that occurred within 12 months of the interview were included (Turner and Wheaton 1995).[50] Further, given previous research indicating that undesirable life events are more likely to adversely affect health (e.g., Compas 1987), only negative life events were included in the index. To ensure a complete coverage of stressful events, approximately 50 items from various domains of life (e.g., family, romantic and peer conflicts, academic problems, involvement/exposure to violence, death of family and friends) were included. A major challenge of operationalizing SLEs is longitudinal accountability—as adolescents make the transition into adulthood, some stressors become irrelevant (e.g., expulsion from school) and other stressors become relevant (e.g., divorce or entering military service). Thus, to ensure stress was appropriately measured at different life stages, slightly different set of items is used in wave III to capture the different life experiences. Finally, similar items (such as miscarriage and still birth) were grouped together to avoid making the measurement overly specific. A simple, additive index was created from the selected items and is mean-centered in the current analysis.

Social support. The social support index shown in Appendix 2.2 is a composite measure of perceived social support across waves I and II. It assesses how the respondents feel about their relationship with their closest social ties including family, teachers and

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This is because, in accordance with the allostatic load perspective, stress is viewed as a cumulative biological process. Regardless of whether stressful events are correlated (which the effect factor analytic model assumes), each additional event is judged to increase allostatic load. Thus, the ideal measurement model for the SLE index is a *causal indicator* factor model, in which each event has an independent causal effect on a latent allostatic load construct (see Bollen and Davis 2009). However, due to the complexity of the current model, optimization problems precluded the estimation of such a causal indicator model of allostatic load. Future research should focus on improving the measurement of SLEs using this innovative latent variable approach.

[50] The 12 month window for SLEs ensures that, for the vast majority of cases, the events occurred prior to the depression evaluation, which surveys respondents on depressive symptoms experienced in the past week. The temporal precedence of SLEs helps identify the causal direction of the relationship of SLEs to depression as the direction of causality cannot flow from depression at the time of evaluation to determine a previously occurring SLE.

parents. A CFA of the items indicated marginally adequate fit (CFI = 0.958; RMSEA = 0.07) when including wave-specific factors and item-specific correlated errors between the two waves. A simple average of all the social support items was calculated and mean-centered in this analysis. To address potential concerns with the simplified specification of social support used in the mixed model analyses, the construct is modeled as the CFA described above in the SEM sensitivity analyses.

Race/ethnicity. Add Health allows respondents to indicate as many race and ethnic categories as deemed applicable. Approximately 4% of the participants report a multiracial/ethnic identity. Following criteria developed by Add Health data administrators, we assign one racial identity for persons reporting multiple backgrounds.[51] This method combines Add Health's five dichotomous race variables and the Hispanic ethnicity variable as following: respondents identifying a single race were coded accordingly; respondents identifying as Hispanic were coded as such regardless of racial designation; those identifying as "black or African American" and any other race were designated as Black; those identifying as Asian and any race other than Black were coded as Asian, those identifying as Native American or "other" were coded as Native American, and those identifying only as "other" were coded as such.[52]

Analytical strategy

[51] http://www.cpc.unc.edu/projects/addhealth/data/using/code/race

[52] Former research comparing this coding approach with another in which only individuals identifying as one race/ethnic group were coded as such and all other individuals were coded as "multiracial" suggest that findings are generally robust across coding schemes (Adkins et al. 2009).

Linear mixed effects models (i.e., hierarchical linear models) were used to assess the effects of physical attractiveness, and its interactions with socio-demographic factors, on depression trajectories using age as the time metric. Mixed models have long been established in the statistical literature for the analysis of clustered, non-independent data (Searle 1971; Searle et al. 1992), and are known to be particularly advantageous for growth curve analyses of longitudinal data (Willett et al. 1998).

The current analysis begins by modeling the longitudinal functional form of the effect of physical attractiveness on depression to determine whether, and if so, how, the influence of physical attractiveness varies across the age range examined (12-28). After establishing the best-fitting longitudinal functional form, I then examine potential interactions between physical attractiveness and various socio-demographic factors. The following equation describes a simplified version of the general mixed regression model used to investigate the interactive effects of physical attractiveness (PA) and socio-demographic variables (SD) on depression (DS):

$$DS_{it} = \beta_0 + \beta_1 PA + \beta_1 PA \times Age + \beta_2 PA \times SD + \beta_k Base\ Model + \mu_{i0} + e_{it}$$

where i and t index the individual and assessment levels, respectively. Thus, the model allows random intercepts at the individual level. Conditional on the random intercept μ_{i0}, the repeated assessments are assumed to be independent. Random intercept μ_{i0} and the residual e_{it} are assumed uncorrelated and normally distributed with means equal zero.

The base model, without physical attractiveness effects, consists of age, age^2,

race/ethnicity, gender, social support, parental education, household income, and SLEs.[53] This model is consistent with prevailing environmental theories of depression and has been empirically tested by the author in previous analyses of Add Health (see Adkins et al. 2008, Adkins et al. 2009). Building on the base model and the age-varying effects of physical attractiveness, I sequentially test interactions between attractiveness and race/ethnicity, gender, SES, social support and SLEs. Finally, after identifying the best fitting model of the main and interactive effects of physical attractiveness, the robustness of the results are examined in a sensitivity analysis of the model using the 3 item CES-D subscale. Finally, after identifying the best fitting model using mixed modeling, the robustness of this model is tested in a structural equation modeling (SEM) framework, which allows more accurate measurement of the several latent constructs modeled (i.e., depression, social support, parental education).

Results

Descriptive statistics

Table 4.1 presents descriptive statistics for the analysis variables. The 9 item CES-D is shown to have a higher mean rating and less variance than the 3 item CES-D subscale. Mean physical attractiveness ratings are approximately midway between "average" and "attractive" and mean age is 20 with a range from 12 to 28. Demographically, the sample is approximately equally split between genders, and Add Health's minority oversample is apparent with Blacks and Hispanics representing higher proportions of the sample than the national population. The measures of SES show that the mean yearly household income for

[53] The effects of age and age^2, as well as those of all other predictors, are modeled as fixed effects. This specification was made to facilitate model optimization.

respondents is approximately $46,000 and mean highest parental educational attainment is slightly greater than a high school degree for both parents. The mean rating on items in the social support scale was 4 out of a possible 5 (most supportive), and the average respondent experienced approximately 2 SLEs in the past 12 months. Table 4.2 shows the distribution of the attractiveness measure and the CES-D means and SD at each level of attractiveness. As expected there is a discernable trend with depression levels higher among less attractive individuals for both the CES-D 9 and 3 item scales. However, the magnitude of this trend is relatively modest and shows some departure from linearity (i.e., flattening) in the lowest and highest attractiveness categories.

Physical attractiveness effects on depression trajectories

Table 4.3 shows the results of modeling the effects of attractiveness on trajectories of depression from ages 12-28. Model 1 shows random intercept model of the simple association of attractiveness to depression. Here it is shown that attractiveness has a highly significant negative association (b = -.016, p < .001) to depression. Model 2 demonstrates the robustness of the main effect of attractiveness, which increases in significance (b = -.019, p < .001) after controlling for the quadratic age variation in depression levels indicated by former analyses of Add Health. Model 3 examines whether the effects of attractiveness on depression vary as a function of age. Results indicate that effect of attractiveness increases linearly from ages 12 to 28 (b = -.002), with the inclusion of an attractiveness × age interaction term significantly improving model fit ($\Delta\chi^2$ = 6.1, df = 1, p = .01). Model 4 examined the possibility that the effect of attractiveness changes curvilinearly with age by adding an attractiveness × age^2 interaction term to the previous model, with results indicating

no improvement in model fit ($\Delta\chi^2 = 3.0$, $df = 1$, $p = .08$). Thus, as illustrated in Figure 4.1, the preferred longitudinal model of the effect of attractiveness is characterized by a marginal advantage for more attractive individuals at age 12, with this advantage increasing linearly to yield a substantial differential at age 28. These results are consistent with expectations, indicating that the salubrious influence of attractiveness develops gradually over adolescence.

Moderating effects of attractiveness on social determinants of depression

To consider whether the effects of well-established social predictors of depression may be moderated by physical attractiveness, we expand the preferred model from the previous set of analyses to include a set of social determinants (race/ethnicity, gender, household income, parental education, social support, and SLEs) indicated by former research on this sample (Adkins et al. 2009; 2008). In addition to the inclusion of these social determinants, each model tests interactions between a given social determinant and attractiveness to assess the moderating influence of attractiveness.[54] Table 4.4 shows results of models testing whether attractiveness moderates the influence of gender and race/ethnicity on depression. Model 1 presents the baseline social model. As expected, females and racial/ethnic minorities tend to have higher levels of depression, as do individual's coming from lower SES households, less supportive social environments and those experiencing more SLEs. More specifically, Asians are characterized by markedly higher, and Blacks and Hispanics moderately higher, depression levels relative to Whites. This is consistent with former research on this sample, which has shown moderate, persistent disadvantage for

[54] Three-way interactions between attractiveness × age × social determinants were also tested, but as none of these models yielded additional significant results, they are not presented.

Blacks and Hispanics relative to Whites, and considerably higher levels for Asians, primarily in late adolescence (Adkins et al. 2009). Model 2 introduces a gender × attractiveness interaction, which failed to improve model fit ($\Delta\chi^2 = 0.1$, $df = 1$, $p = .75$). Likewise, Model 3 examined interactions between race/ethnicity × attractiveness and yielded no evidence of moderation by attractiveness ($\Delta\chi^2 = 2.6$, $df = 4$, $p = .63$). In sum, results failed to support expectations for variability in attractiveness' effects across gender and racial/ethnic groups.

Table 4.5 shows models examining whether attractiveness moderates the effects of stress process variables (i.e., SES, social support and SLEs) on depression. Models 1 and 2 show no support for attractiveness moderation on the effects of childhood SES on depression ($p = .24$ and .82 for parental education and household income, respectively). Model 3 indicated a significant negative interaction between social support and attractiveness ($\Delta\chi^2 = 19.4$, $df = 1$, $p < .001$). Similarly, Model 4 indicated a highly significant positive interaction between SLEs and attractiveness ($\Delta\chi^2 = 21.6$, $df = 1$, $p < .001$). Model 5 tests the robustness of the 2 significant interactions in a combined model, finding the SLEs × attractiveness interaction to remain highly significant ($p < .001$), while the social support × attractiveness effect became nonsignificant ($p = .13$). Model 6 describes a sensitivity analysis in which Model 5 was reran using the CES-D 3 item subscale as the outcome. Results are highly robust across the 2 CES-D specifications, with parameters involving attractiveness all maintaining their direction, significance and magnitude, with the exception of SLEs × attractiveness, which showed even larger effects and significance in the sensitivity analysis. The interactive effects of attractiveness and SLEs are shown in Figure 4.2, which illustrates that, contrary to theoretical expectations, the depressogenic effects of SLEs are approximately twice as large among the most attractive as compared to the least attractive

individuals.

Results also proved robust in various additional sensitivity analyses. First, to increase the normality of the outcome distribution and ensure significant results were not driven by outliers, the CES-D was square root transformed and the final mixed model reran for both the 9 and 3 item CES-D measures. As shown in Appendix 4.2, results were highly robust with the attractiveness × age interaction significant at $p < .01$ and the SLEs × attractiveness interaction significant at $p < 0.001$, for both CES-D specifications. Next, to improve measurement of the various multiple indicator latent variables, an SEM of the 3 item CES-D specification was fit, with results, shown in Appendix 4.3, indicating comparable coefficient values and significance for all parameters of interest.

Finally, to explicitly account for measurement error in the evaluation of attractiveness, estimates of the reliability of the attractiveness measure were calculated and included in the SEM to specify the proportion of measure's variance that was due to error. The reliability of the attractiveness measure was calculated using the Wiley and Wiley (1970) parameterization of the Heise (1969) quasi-simplex reliability model. The Heise model is an SEM that provides reliability estimates for a single measure observed three or more times, and is superior to traditional test-retest reliability in that it allows change in the unobserved, "true" score. Analysis of the three waves of attractiveness data indicated reliability of the attractiveness measure to equal 0.534. Thus, in the final SEM, 46.6% (= (1 - 0.534) × 100) of the variance of the attractiveness repeated measures was specified as residual variance. As described in Appendix 4.4, results of this analysis further supported the attractiveness findings, with the attractiveness × age interaction significant at $p < .01$ and the SLEs × attractiveness interaction significant at $p < 0.01$.

Discussion

Although a pervasive aspect of social reality and a central preoccupation of contemporary culture, physical attractiveness remains an understudied topic in social science research. This is unfortunate because, as recent economic research on wage premiums has demonstrated (e.g., Biddle and Hamermesh 1998; Hamermesh 2006), the influence of physical attractiveness on outcomes of interest to social scientists can be considerable. Yet, despite evidence that attractiveness can be influential on such distal and socially constructed outcomes as earnings, research has been slow to investigate more proximate, fundamental influences of attractiveness, such as mental health. The current study has addressed this limitation, investigating the influence of attractiveness on early life depression using Add Health, a large, nationally representative, longitudinal dataset with minority over-representation. Given the notable superiority of the Add Health data over the small, non-representative samples formerly analyzed[55], the current study represents a substantial advance toward a more definitive understanding of the influence of attractiveness on depression in early life.

Several major findings emerge from this analysis. First, there is a considerable, highly significant, effect of attractiveness on depression. Second, the strength of effect of attractiveness on depression varies across the age range examined, linearly increasing from virtually no influence at age 12 to a substantial effect at age 28. Third, no robust evidence was found of cumulative disadvantage between attractiveness and social determinants of depression. To the contrary, the influence of SLEs was found to be greater among more

[55] The sample analyzed here is over 10 times larger than the cumulative sample of the most recent meta-analysis of the association of attractiveness to "mental health" (Langlois et al. 2000).

versus less attractive individuals. Overall, these results support socialization and social expectancy perspectives positing that attractiveness exerts an affective influence (Langlois et al. 2000; Darley and Fazio 1980) and developmental perspectives indicating adolescence as a key period for the solidification of adult identity and the internalization of social expectations (Loevinger 1976). Finally, results suggest that rather than promoting resilience to additional sources of adversity, attractiveness actually engenders greater sensitivity to SLEs, indicating the need for novel theoretical perspectives explaining the apparent resilience of unattractive individuals.

The most fundamental finding of the current study is that attractiveness does indeed exhibit a substantial association to depression, at least in early life. While this finding is resonant with theoretical expectations, it runs contrary to many previous empirical analyses (e.g., McGovern et al. 1996; Noles et al. 1985). While various factors may have contributed to this disparity in results, statistical power is apt to be a primary issue. Given the moderate size of the attractiveness effect reported here, coupled with the dramatic differences in sample sizes between current (N = 36536) and previous (N = 1100 (McGovern et al. 1996); N = 224 (Noles et al. 1985)) studies, it is likely that former examinations were simply underpowered to reliably detect the effect. Additionally, age variation in the strength of the attractiveness effect may also help explain heterogeneity in effect estimates, as many previous studies have focused on pre-adult life stages in which, according to the present results, the effect of attractiveness has yet to reach its maximal level (e.g., Noles et al. 1985). In any case, it is reassuring that the estimates produced here are largely consistent with meta-analysis results from Langlois and colleagues (2000)—the current best estimate in the literature.

While the present analysis cannot definitively elucidate *why* attractiveness matters to depression, careful reasoning suggests that this is apt to result from internalizing pervasive differences in social treatment. Leaving aside the potential issue of reverse causality (more on this below), there are two primary plausible mechanisms, 1) there are intrinsic differences, independent of environment, in the neurobiology of attractive and homely individuals that cause differences in affect, or 2) the observed differences in affect stem from systematic environmental differences between attractive and unattractive individuals.

Explanations in the vein of the first possibility include the idea that unattractiveness is correlated with inherently, perhaps genetic, poorer affect-related neurological function. There is, however, currently no research establishing such a link, and further, there are reasons to suspect it is not so. The most compelling evidence arguing against an intrinsic relationship between attractiveness and depression come from studies that examine affective changes brought on by appearance enhancing medical/dental procedures. For instance, research has shown that individuals who receive orthodontic treatment generally reap a significant benefit in psychological well-being (see Kiyak 2008 for review). Such findings argue against the possibility of an intrinsic link because appearance enhancing dental and medical procedures obviously do not change underlying neurophysiology, only superficial appearance. A second possible explanation of an intrinsic link could be an unobserved third variable influencing both depression and attractiveness, such as general physical health. That is, it is often been shown that poor health exerts a depressogenic influence (e.g., Berkman et al. 1986). Further, it is not unreasonable to think that poor health may be perceived as physically unattractive—indeed there is a substantial evolutionary literature positing that attractiveness is, in essence, a signal denoting underlying health (e.g., Rhodes 2006). However, physical health does not

appear to be driving the current findings, as sensitivity analyses indicate that controlling for self-rated health does not substantively change reported results.

In contrast to the lack of support for intrinsic explanations, a careful consideration of the literature yields several converging sources of support for the effects of attractiveness being socially mediated. First, as discussed above, it has been decisively shown that people are perceived differently based on their attractiveness, not only in terms of social desirability, but also in such apparently unrelated areas as competence, intelligence and personal integrity (Langlois 2000; Feingold 1992; and Eagly 1991). Further, it has been shown that these differences in perception translate into treatment differences, with attractive individuals benefiting from a pervasive social premium (Langlois 2000). Finally, while it is difficult to definitively establish that the these treatment differentials are internalized as differences in self-esteem, such a process seems eminently plausible, particularly given knowledge of socialization patterns by race/ethnicity and childhood SES (e.g., Lareau 2003; Cross 1995, 1991). That is, if, as is generally agreed to be the case in sociology, societal perceptions based on race and class are internalized by social actors, it stands to reason that the same would hold true for the equally visible status of attractiveness. Finally, it is but a small and noncontroversial step to conclude that differences in self-esteem will translate into affective differences (Brown et al. 1990; Baumeister 2003).

Theoretical expectations were also upheld regarding developmental variations in attractiveness. Specifically, the finding that the influence of attractiveness increases as individuals age from early adolescence to young adulthood is consistent with expectations from both socialization and pubertal development perspectives. From the socialization perspective, adolescence is a period in which many adult roles become solidified—it is a life

stage in which individuals become increasingly aware of social class gradients (Aries and Seider 2007; Ostrove and Cole 2003) and racial/ethnic differences (Fisher et al. 2000; Phinney and Chavira 1992). Thus, individuals come to understand the stratified nature of society, and begin to evaluate others according to these norms, during adolescence. Attractiveness, along with social background characteristics, is likely to be among the primary dimensions along which adolescents come to see social desirability during this period.

Here, the pubertal development explanation dovetails with the socialization perspective, in that puberty may be the mechanism driving the adolescents' increasing awareness of attractiveness. Clearly, puberty is a time in which youths experience burgeoning sexual awareness, which transforms how they perceive their peers and changes the goals and calculus of social interaction (Udry and Billy 1987; Udry 1988). Quite suddenly, during puberty, attractiveness develops a new dimension as social currency—what was formerly merely a playmate becomes the object of ardent desire. Further, given substantial, cross-individual consistency in attractiveness ratings (Rhodes 2006), this desirability is not evenly distributed; for some the transition to puberty brings the amorous attention of many, and for others it generates disinterest, or worse, disdain. This phenomenon almost certainly translates into popularity gradients (Kennedy 1990; Becker and Luthar 2007), which are, in turn, apt to have affective repercussions (e.g., Oldenburg and Kerns 1997).

More research is needed to determine exactly how well the pubertal explanation explains the increase in the influence of attractiveness during adolescence. A promising avenue for such an extension would be to introduce measures of pubertal development,

operationalized as either hormonal levels or Tanner developmental stages, to the current model, and assess how well this process mediate the observed effects (see Angold et al.1998 for a similar approach to explaining the emergence of the gender gap). More generally, further research is needed to more exactly describe longitudinal variation in the influence of attractiveness on depression. In the current study, I have found that a model of linear increase from ages 12- 28 had superior fit compared to models assuming a static level or quadratic change. However, given that these are only three functional forms out of a larger set of possibilities and both the pubertal development and socialization explanations suggest that the increase in effect size likely plateaus prior to 28, a more detailed examination is called for. Thus, future research on samples with denser repeated observations throughout adolescence could be used to test piecewise models that empirically determine the optimal plateau point. Furthermore, even if the current functional form is robust and it is found that the effect does, in fact, increase more or less linearly from ages 12 to 28, surely the effect does not continue to increase indefinitely. Longitudinal data covering a longer period of the life course will be necessary to extend current knowledge into later life stages.

Surprisingly, no support was found of cumulative disadvantage between attractiveness and established social determinants of depression. In fact, the opposite was found for SLEs—that is, as illustrated in Figure 4.2, attractive individuals were shown to be *more* sensitive to the effects of SLEs. Furthermore, given its strong statistical significance ($p = 0.0001$) and robustness in sensitivity analysis, this finding is unlikely to be a false positive. So, what then is to be made of the finding that being unattractive, rather than weakening individuals' capacity to cope with additional adversity, actually toughens them, making them more resilient to additional stressors? Clearly, any explanation at this point is post hoc and

speculative; however, some precedent for this finding can be found in the literature on self-esteem and depression. In particular, research into the *buffering hypothesis* has yielded some results consistent with the current finding (see Baumeister et al. 2003 for review). The buffering hypothesis posits that the influence of self-esteem operates, at least in part, through moderating the effects of life stress (Brown and Harris 1978). Thus, the hypothesis may, in essence, be considered a cumulative disadvantage perspective, in that it is expected that two depressogenic factors, namely low self-esteem and life stress, will have interactively detrimental effects. And though some studies have found support for this hypothesis (e.g., DeLongis et al. 1988), other studies have found the opposite—that is, they have found that the affective benefits of high self-esteem are primarily reaped at low levels of life stress, with individuals of both high and low self-esteem experiencing comparable levels of depression under high life stress conditions (e.g., Whisman and Kwon 1993).

Given that self-esteem is held to be a primary mechanism through which attractiveness influences affect, research finding individuals with high self-esteem to be more vulnerable to life stress is quite relevant and may describe the same phenomenon reported in the present study. However, former research is less useful in providing a narrative for understanding this finding, pointing to the need for a novel theoretical perspective. One potential explanation in this regard is that the continual psychosocial buffeting endured by the unattractive develops their capacity to cope with adversity. According to this logic, as the homely come to accept social adversity as a matter of course, they adopt a more defensive, "hunkered down" existential stance and thus, are less unbalanced by the occurrence of stressful event. The converse of this argument would therefore suggest that the attractive, accustomed to a favorable breeze blowing at their back, are less prepared for the

psychological blow of a stressful event, and thus, experience a greater degree of disruption. While this explanation is certainly plausible, it is, of course, strictly speculative at this point. Further research will be needed to more fully understand this unexpected finding.

The current analysis offers the first systematic examination of social and developmental interactions in the influence of attractiveness on depression in early life. However, the study is nonetheless limited in several respects. First, the measure of attractiveness used here is less than ideal. While the measure has the strength of being based on a dynamic viewing of the individual, rather than a single image (Rubenstein 2005), it suffers from the weakness of being based on a single individual's rating. As research has shown that each individual's attractiveness criteria typically include both an individual-specific, subjective element as well as an "objective", universal component (Honekopp 2006), having only a single rater for each observation likely introduces significant non-systematic measurement error. Future data collection efforts aimed at elucidating the effects of attractiveness would do well to video a portion of the interview; thus, enabling the possibility of multiple raters.

Another limitation of the current study concerns that perennial difficulty of observational research—causality. Specifically, the current study cannot definitively establish that the direction of the associations of attractiveness to depression flow in the hypothesized direction. That is, it may be the case that a portion of the association reported here is a result of depression diminishing the attractiveness of subjects. But while the threat to inference posed by reverse causality cannot be definitively ruled out, a careful consideration of the implications of the two competing conceptual models of causality give reasons to suspect that the primary direction is attractiveness to depression.

Specifically, the two potential models of causality—attractiveness→depression versus depression→attractiveness—imply different mediating steps. The key difference here is that one would imagine that the effect of depression on attractiveness is relatively immediate, while, as described in length above, the influence of attractiveness on depression is likely to be a gradual process. That is, to speculate a bit, depression seems apt to influence attractiveness by endowing an unpleasant quality to the personality and facial expression, and/or an inattention to hygiene, dress and style. In all of these instances the influence of depression on attractiveness would be fairly immediate. This immediacy suggested by the depression→attractiveness model contrasts with the model implied by the attractiveness→depression and with the results shown in the current analysis. This is because the attractiveness→depression model implies a socialization process through which the gradients in social treatment gradually become internalized. Thus, in contrast to the immediacy of depression→attractiveness model, the attractiveness→depression model implies a developmental process in which the effect of attractiveness on depression gradually manifests in adolescence, as individuals mature psychosocially and appearance-based differences in social treatment accumulate. Seen from this theoretical perspective, the developmental interaction observed in the current study offers some support for the attractiveness→depression model, as it demonstrates that the association of attractiveness to depression manifests gradually in adolescence as per the internalization model. However, this evidence is not definitive and future research should pay particular attention to causality. It is important to note though, that data allowing a definitive test of causality, such as large scale experimental or quasi-experimental studies, are unlikely to become available on this topic in the foreseeable future, leaving researchers to grapple with the topic using a combination of

conceptual leverage and clever analysis of observational data.

Despite these limitations, the present study improves our understanding of the role of attractiveness in early life depression. Specifically, results show that unattractive individuals experience significantly higher levels of depression than their more attractive peers, and that this gap increases across adolescence and young adulthood. Furthermore, findings indicate that depressogenic effects of SLEs are greater among attractive versus unattractive individuals, suggesting that unattractiveness engenders some degree of psychosocial resilience. In sum, these findings demonstrate the importance of physical attractiveness as a important, under-appreciated risk factor for depression. More generally, the study adds to the burgeoning literature showing that physical attractiveness is a central predictor for a variety of social processes ranging from earnings to mental health (e.g., Hamermesh and Biddle 1994; Langlois 2000), and highlights the socially contingent nature of the influence of physical attractiveness. Hopefully, future research will continue to examine the implications of physical attractiveness, addressing the limits of our knowledge of a pervasive facet of social life that has been unfortunately neglected in sociological research.

Table 4.1. Descriptive statistics of analysis variables

Variable	Mean	SD	Min	Max
CES-D 9 item	0.618	0.474	0	3
CES-D 3 item	0.476	0.599	0	3
Physical Attractiveness	3.542	0.839	1	5
Age	20.000	4.899	12	28
Gender (Female=1)	0.505	0.500	0	1
White	0.505	0.500	0	1
Black	0.225	0.417	0	1
Asian	0.071	0.256	0	1
Hispanic	0.170	0.375	0	1
Other Race	0.030	0.171	0	1
Parental Education (mean)	5.751	1.830	1	9
Household Income (thousands)	46.207	51.671	1	999
Social Support	4.035	0.580	1	5
Stressful Life Events Index	2.053	2.413	0	25

Table 4.2: CES-D descriptive statistics by attractiveness rating

	CES-D 9 item			CES-D 3 item		
Attractiveness rating	Mean	SD	N	Mean	SD	N
1 (Lowest)	0.640	0.506	794	0.518	0.648	794
2	0.707	0.501	2364	0.539	0.634	2362
3	0.632	0.474	22698	0.477	0.599	22694
4	0.592	0.465	17828	0.460	0.589	17828
5 (Highest)	0.601	0.481	6755	0.486	0.606	6755

Table 4.3: Examining developmental variation in the effect of attractiveness on depression

	Model 1	Model 2	Model 3	Model 4
Attractiveness	-0.016***	-0.019***	-0.009	-0.022*
	(0.000)	(0.000)	(0.081)	(0.017)
Age		0.029***	0.035***	0.018
		(0.000)	(0.000)	(0.098)
Age Squared		-0.003***	-0.003***	-0.002**
		(0.000)	(0.000)	(0.004)
Attractiveness x Age			-0.002*	0.003
			(0.015)	(0.269)
Attractiveness x Age Sq				-0.000
				(0.085)
Intercept	0.675***	0.669***	0.631***	0.679***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD	0.301***	0.308***	0.308***	0.307***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.366***	0.356***	0.356***	0.356***
	(0.000)	(0.000)	(0.000)	(0.000)
N	50439	50439	50439	50439
Log likelihood	-30766.0	-30018.3	-30015.3	-30013.8

P-values in parentheses

* p<0.05, ** p<0.01, *** p<0.001

Table 4.4: Testing gender and racial/ethnic differences in the effects of attractiveness on depression

	Model 1	Model 2	Model 3
Attractiveness	-0.001	-0.001	-0.004
	(0.785)	(0.888)	(0.514)
Age	0.032***	0.032***	0.032***
	(0.000)	(0.000)	(0.000)
Age Squared	-0.003***	-0.003***	-0.003***
	(0.000)	(0.000)	(0.000)
Age x Attractiveness	-0.002*	-0.002*	-0.002*
	(0.017)	(0.017)	(0.014)
Female	0.150***	0.154***	0.150***
	(0.000)	(0.000)	(0.000)
Black	0.047***	0.047***	0.036
	(0.000)	(0.000)	(0.143)
Asian	0.160***	0.160***	0.127**
	(0.000)	(0.000)	(0.004)
Hispanic	0.059***	0.059***	0.020
	(0.000)	(0.000)	(0.465)
Other Race	0.027	0.027	0.038
	(0.108)	(0.109)	(0.500)
Parental Education (mean)	-0.019***	-0.019***	-0.019***
	(0.000)	(0.000)	(0.000)
Household Income	-0.017***	-0.017***	-0.017***
	(0.000)	(0.000)	(0.000)
Social Support	-0.224***	-0.224***	-0.224***
	(0.000)	(0.000)	(0.000)
SLEs	0.035***	0.035***	0.035***
	(0.000)	(0.000)	(0.000)
Female x Attractiveness		-0.001	
		(0.835)	
Black x Attractiveness			0.003
			(0.638)
Hispanic x Attractiveness			0.011
			(0.144)
Asian x Attractiveness			0.009
			(0.445)
Other Race x Attractiveness			-0.003
			(0.831)
Intercept	0.490***	0.488***	0.499***
	(0.000)	(0.000)	(0.000)
Random intercept SD	0.239***	0.239***	0.239***
	(0.000)	(0.000)	(0.000)
Residual SD	0.351***	0.351***	0.351***
	(0.000)	(0.000)	(0.000)
N	36536	36536	36536
Log likelihood	-19146.3	-19146.3	-19145.0

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Table 4.5: Testing stress process moderation of the effects of attractiveness on depression

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Attractiveness	-0.001	-0.001	-0.001	-0.003	-0.002	0.014
	(0.853)	(0.784)	(0.873)	(0.588)	(0.654)	(0.065)
Age	0.032***	0.032***	0.032***	0.031***	0.031***	0.052***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Age Squared	-0.003***	-0.003***	-0.003***	-0.003***	-0.003***	-0.004***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Age x Attractiveness	-0.002*	-0.002*	-0.002*	-0.002*	-0.002*	-0.002*
	(0.015)	(0.017)	(0.014)	(0.043)	(0.037)	(0.020)
Female	0.150***	0.150***	0.150***	0.150***	0.150***	0.203***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Black	0.047***	0.047***	0.047***	0.047***	0.047***	0.035***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Asian	0.160***	0.160***	0.159***	0.159***	0.159***	0.111***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Hispanic	0.059***	0.059***	0.059***	0.059***	0.059***	0.045***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Other Race	0.027	0.027	0.027	0.027	0.027	0.046*
	(0.108)	(0.108)	(0.110)	(0.113)	(0.113)	(0.029)
Parental Education (mean)	-0.013*	-0.019***	-0.019***	-0.019***	-0.019***	-0.016***
	(0.015)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Household Income	-0.017***	-0.018	-0.017***	-0.017***	-0.017***	-0.014**
	(0.000)	(0.130)	(0.000)	(0.000)	(0.000)	(0.006)
Social Support	-0.224***	-0.224***	-0.182***	-0.224***	-0.198***	-0.197***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
SLEs	0.035***	0.035***	0.035***	0.018***	0.020***	0.024***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education x Attractiveness	-0.002					
	(0.255)					
Income x Attractiveness		0.000				
		(0.942)				
Social Support x Attractiveness			-0.012**		-0.007	-0.004
			(0.010)		(0.130)	(0.552)
SLEs x Attractiveness				0.005***	0.004***	0.006***
				(0.000)	(0.000)	(0.000)
Intercept	0.489***	0.490***	0.489***	0.496***	0.494***	0.207***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD	0.239***	0.239***	0.239***	0.239***	0.239***	0.270***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.351***	0.351***	0.351***	0.351***	0.351***	0.486***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
N	36536	36536	36536	36536	36536	36531
Log likelihood	-19145.6	-19146.3	-19142.9	-19136.6	-19135.5	-29588.1

P-values in parentheses

* p<0.05, ** p<0.01, *** p<0.001

Figure 4.1. Variation in Depression Trajectories by Level of Attractiveness

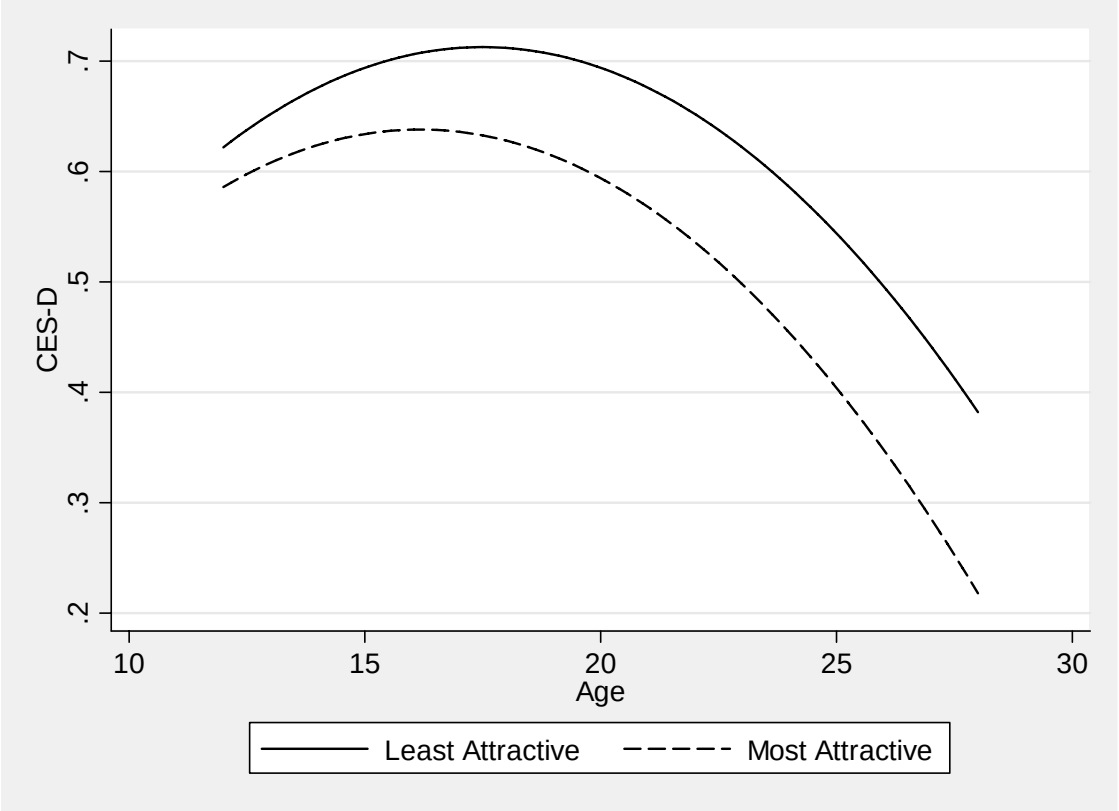
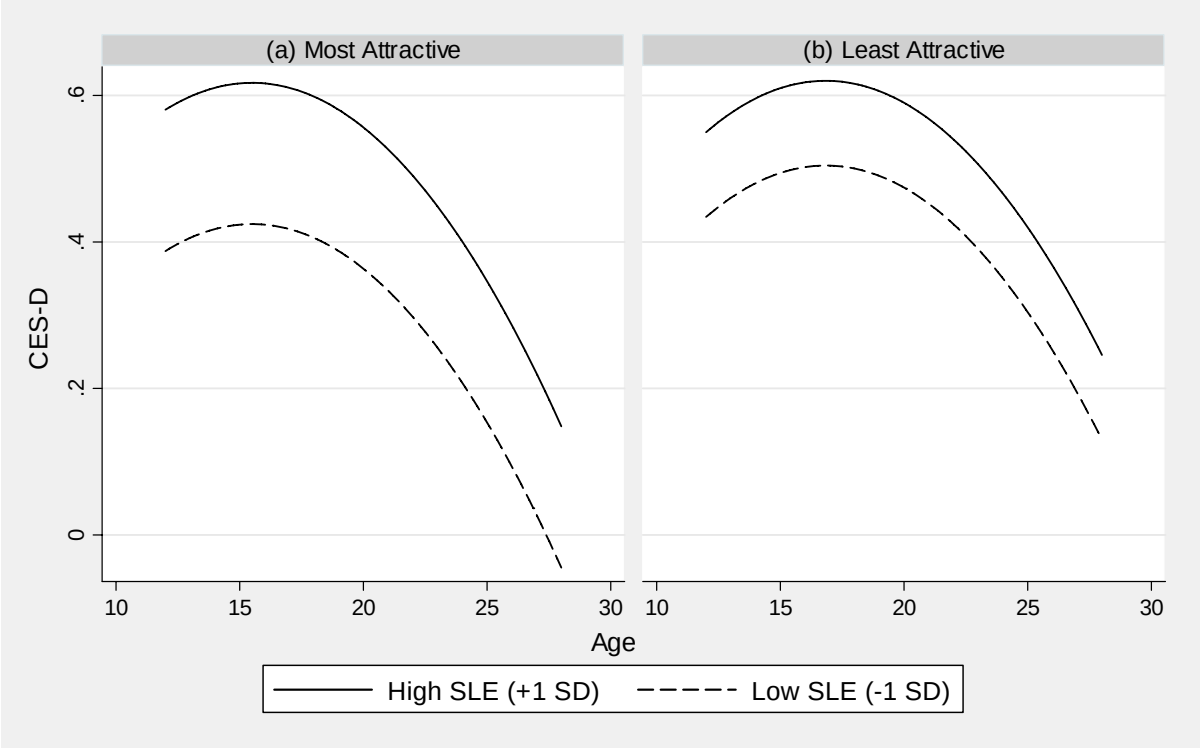


Figure 4.2. Mediating Effects of Attractiveness on the Influence of SLEs on Depression Trajectories



Chapter 5: Conclusion

The sociological perspective on mental health has made tremendous contributions to the study of depression over the past three decades. More than any other approach, the sociological perspective has convincingly shown the importance of structural factors in generating and perpetuating mental health disparities. Among the various theories of social influence on depression, Pearlin's stress process model (1981; 1989) stands out for both its longevity and comprehensiveness. The basic logic of the stress process model is that the social location of individuals influences stress exposure and vulnerability that, in turn, produce physical and psychological responses. But while research from the stress process perspective, and complementary approaches such as Link and Phelan's fundamental causes theory (1995), have made notable contributions to our understanding of depression, this success has, in a sense, jeopardized the future relevance of the perspective as an active research frontier in mental health. That is, in maturing and establishing effective models of social influence on depression, many of the primary goals of the approach have been largely satisfied, suggesting that future research conducted from a strictly structural perspective will likely meet with only incremental gains.

This is not to suggest, however, that the sociological study of depression has reached an impasse. Rather, it implies that significant future advances in understanding the function of social determinants will likely be driven by investigating their interactive effects with sources of individual differences not typically examined by social scientists, such as genetic

variation. This observation is indicated by research showing that even with high quality data and exhaustive, well-specified models, conventional social psychological approaches still fall short of providing comprehensive models of depression (Costello et al. 2002). One primary reason for this shortcoming is individual variation in sensitivity to social factors, with individuals differing markedly in their ability to take advantage of protective factors and in their vulnerability to social adversity (Monroe and Simons 1991; Zuckerman 1999). And though some of this variation may eventually be explained by improved measurement and modeling of social influences, there is a growing recognition that, as posited by the diathesis-stress model, much of it is likely due to constitutional differences.

Clearly then, the diathesis-stress model, and the related GxE approach, hold great promise to improve understanding of depression. These emerging perspectives are, however, characterized by serious theoretical shortcomings of their own. Chief among these limitations is a relatively weak conceptualization of the social environment. Research to date from the GxE perspective has largely been focused on proximate environmental factors, such as SLEs, and neglect of more distal, fundamental, structural causes. While in practice GxE researchers have generally lacked conceptual rigor in separating proximate and distal environmental risks, with some creating composite measures aggregating the two (e.g., Eley et al. 2004), Moffitt et al. (2005) have explicitly called for a focus proximate environmental factors, and the exclusion of distal ones, in their seminal GxE research guidelines. This guideline, though warranted in many cases, threatens to marginalize the role of distal, structural causes of depression such as childhood poverty. As Pearlin (1989) noted almost two decades ago, research focusing strictly on the effect of proximate stressors on mental health miss the vital sociological insight that exposure to stress, as well the presence of buffering psychological resources, is significantly influenced by one's structural position.

Thus, there is the potential for productive synthesis in combining well-developed sociological models of depression with emerging perspectives from psychology and behavior genetics. Within this synthesis, an approach exploring the role of established social predictors as moderators of the influence of constitutional factors holds particular promise. This strategy takes advantage of recent technological developments allowing inexpensive genotyping, as well as importing understudied factors such as physical attractiveness, to enhance the explanatory power of sociological models. Through combining the well-theorized, nuanced conceptualization of the social environment offered by sociology with individual differences perspective embodied in GxE studies, there is the potential to build more comprehensive predictive models of mental health and to advance the relevance of sociological perspectives in contemporary discourse on mental health.

Advancing such a synthesis is, however, likely to be a halting and difficult process. At its best, it represents the integration of two academic worldviews that not only have a degree of institutionalized wariness toward one another (Adkins and Vaisey 2009), but also markedly different methodological approaches stemming from fundamentally different epistemological positions. This epistemological divide derives from basic differences in the source of theoretical expectations between the social sciences and molecular genetics. Specifically, whether acknowledged or not, the research agenda in the social sciences typically originates in the experience of the individual in society. For instance, observing depression in individuals who have experienced an unusual degree of misfortune, or noting health disparity between racial groups with different mean levels of social and economic power, serves to motivate the development of intuitive theories of the causes of these phenomena. This tendency has lead to an social science research culture focused on hypothesis-testing, as we (or society, more generally) typically have specific, intuitive ideas

to test regarding the function of the social world in which we operate.

This approach contrasts sharply with the logic guiding the research agenda in molecular genetics. In molecular genetics, scientists are essentially observing a world that operates by a set of laws that are largely unknown and totally foreign to our direct experience. In this context, intuition is basically useless—there is no hunch derived from personal experience that can suggest the importance of a given 1000 nucleotide segment of DNA. Thus, molecular geneticists lack the intuitive framework that social scientists have regarding their topic of study, and therefore, must systematically build their understanding of molecular function based entirely on empirical studies. This difference has led to two divergent perspectives on the optimal approach to advance science, with molecular genomics embracing data mining approaches in massive genome-wide analyses which explanatorily consider several hundreds of thousands of genetic polymorphisms, while social scientists focus on (comparatively) narrowly scoped hypothesis-testing to avoid the oft-disparaged "fishing expedition". Reconciling these two distinct epistemologies and research cultures represents a substantial challenge, but will be absolutely essential in order to reap the benefits of combining the theoretical leverage offered by social science perspectives with the empirical approaches necessary to examine the massive, poorly understood data of the human genome.

The current project moves toward this lofty goal by extending previous research in several, specific respects. First, it systematically examines GxE between multiple candidate gene polymorphism and multiple environmental risks on depression. Second, it moves beyond the atemporality characterizing most genetic studies to consider age variation in the effects of candidate genes on depression. Third, it adopts a comprehensive approach to investigating genetic effects, systematically testing thousands of combinations of allelic

specifications and environmental risks, while explicitly adjusting significance criteria using FDR—an advanced statistical genetics technique accounting for multiple testing. Finally, the study is the first to examine the direct and interactive influences of physical attractiveness on depression using a large, nationally representative sample.

Findings from chapter 2 suggest several potential gene-environment interactions. The most promising associations detected were for interactions between the *MAOA* VNTR promoter polymorphism and social support among females. Specifically, while on average both genders showed highly significant protective effects for social support, females with the rare 2R *MAOA* allele showed no effects of social support on depression. Similarly, females with high activity 3.5R or 4R *MAOA* alleles showed diminished gains from social support compared to those with low activity alleles (i.e., primarily 3R homozygotes).

MAOA has long been considered a top candidate gene for psychiatric conditions as the enzyme it encodes is involved in the degradation of neurotransmitters, primarily serotonin and norepinephrine (Bach et al. 1988), and inhibitors of the enzyme have been found effective in the treatment of depression (Murphy et al. 1994). However, studies of main genetic effects for *MAOA* have failed to provide robust support for a significant association to affective disorders (e.g., Furlong et al. 1999). And while the combination of functional evidence and inconsistent candidate gene results indicates *MAOA* as promising GxE candidate for depression, very little empirical work in this vein has been conducted, with only two methodologically limited, small sample analyses published to date (Eley et al. 2004; Cicchetti et al. 2007).

This dearth in *MAOA* GxE research considered in tandem with the various advantages of the current study over former research (e.g., larger sample and longitudinal, repeated measures) suggest that the current results are worth following up in future research.

However, this effort should be tempered by a recognition that the current results were not entirely robust. Specifically, the *MAOA* 2R finding failed to replicate in sensitivity analyses examining a 3 item depression measure in both mixed model and SEM frameworks. Similarly, the 3.5/4R finding failed to replicate in an SEM analysis of the 3 item outcome. While results from all of these sensitivity analyses were in the directions indicated by the primary analyses, and approached the conventional $p < .05$ significance threshold, they are still best viewed with a degree of skepticism, particularly when considering the magnitude of multiple testing in this analysis.

Results from Chapter 3 were more compelling, demonstrating robust evidence of age moderation of genetic influence on depression. Specifically, promising associations were detected for interactions between the *DRD4* dopamine receptor gene and age trajectories in the full sample, and the *MAOA* VNTR promoter polymorphism and trajectories among males. Regarding *DRD4*, individuals with the 5R allele were found to exhibit a roughly reversed trajectory compared to the normative inverted-U pattern. Thus, individuals with any 5R alleles were shown to have relatively low depression levels through late adolescence, before experiencing increases in early adulthood. This pattern suggests that carriers of the *DRD4* 5R allele navigate their high school years with relative psychological ease compared to others, but begin to experience elevated psychological distress as they transition into adult roles. Interpreting the molecular mechanism underpinning this finding is problematized by the fact that there is very little is known about the 5R allele. Given its relatively low allele frequency (2.76% of the full sample), it has not been well-characterized in functional studies; thus, its gene expression profile is poorly understood.

One potential explanation of the *DRD4* 5R finding stems from association studies

linking *DRD4* to substance abuse. The *DRD4* 5R allele[56] has shown evidence of association to abuse of various substances, including alcohol (e.g., Muramatsu et al. 1996) and heroin (e.g., Li et al. 1997). And while these findings remain controversial (see Lusher et al. 2001), their potential relevance to the current *DRD4* finding becomes apparent when considering the life course context of substance abuse. Specifically, social control factors limiting access and abuse of substances, such as parental monitoring and legal obstacles, while relatively strong in adolescence, loosen in young adulthood as individuals leave their parents' homes and can legally purchase alcohol. Given that the upswing in depression for *DRD4* 5R carriers observed here closely corresponds to the transition to adulthood, and that substance abuse and depression are highly correlated and frequently clinically comorbid (e.g., Grant and Harford 1995), it seems possible that loosening social control is a key explanatory factor of the elevated distress levels observed among 5R carriers in young adulthood.

An association between the *MAOA* 3.5R allele and depression trajectory components in the male sample was also found in the analysis presented in chapter 3. Specifically, males with the 3.5R genotype were found to have more curvilinear depression trajectories than the normative pattern, with higher peaks in late adolescence and sharper declines in early adulthood. Substantively, this indicates that males with the 3.5 genotype have a particularly distressful time during high school and the subsequent transition to adulthood, but converge with their peers in early adulthood. This age variation in the influence of *MAOA* may explain inconsistencies in former *MAOA*-depression association results, which have shown both elevated depression levels among male carriers of the 3.5R and other long *MAOA* alleles (Du et al. 2005; Yu et al. 2005), and also no significant association (Kunugi et al. 1999). Moreover, the current results may shed light on results from a recent meta-analysis of six

[56] In some cases coded together with other "long" alleles.

MAOA-depression association studies, which found a strong trend toward increased depression among carriers of the 3.5R and other long *MAOA* alleles falling just short of statistical significance (OR = 0.86; 95% CI: 0.74–1.01).[57] Interestingly, this meta-analysis found strong evidence of heterogeneity in effect sizes across studies. Results of the current study offer a potential explanation for this heterogeneity, suggesting that age differences across samples may be driving effect differences.

Finally, several major findings emerged from the analysis presented in chapter 4. First, a considerable, highly significant, effect of attractiveness on depression was found. Second, the strength of this effect was shown to vary across the age range examined, linearly increasing from virtually no influence at age 12 to a substantial effect at age 28. Third, no robust evidence was found of cumulative disadvantage between attractiveness and social determinants of depression. On the contrary, the influence of SLEs was indicated to be greater among more versus less attractive individuals. Overall, these results support socialization and social expectancy perspectives positing that attractiveness exerts an affective influence (Langlois et al. 2000; Darley and Fazio 1980; Zebrowitz 1997) and developmental perspectives indicating adolescence as a key period for the solidification of adult identity and the internalization of social expectations (Loevinger 1976). Further, results suggest that rather than promoting resilience to additional sources of adversity, attractiveness actually engenders greater sensitivity to SLEs, indicating the need for novel theoretical perspectives explaining the apparent resilience of less attractive individuals.

Expectations were upheld regarding developmental variations in attractiveness. Specifically, the finding that the influence of attractiveness increases as individuals age from early adolescence to young adulthood is consistent with expectations from both socialization

[57] Reverse coded –i.e., *MAOA* 3.5 and 4 coded 0 and other *MAOA* alleles coded 1.

and pubertal development perspectives. From the socialization perspective, adolescence is a life stage in which individuals become increasingly aware of social class gradients (Aries and Seider 2007; Ostrove and Cole 2003) and racial/ethnic differences (Fisher et al. 2000; Phinney and Chavira 1992). Thus, individuals come to understand the stratified nature of society, and begin to evaluate others according to these norms, during adolescence. Attractiveness, along with social background characteristics, is likely to be among the primary dimensions along which adolescents come to see social desirability during this period. Here, the pubertal development explanation dovetails with the socialization perspective, in that puberty may be the mechanism driving the adolescents' increasing awareness of attractiveness. Clearly, puberty is a time in which youths experience burgeoning sexual awareness, which transforms how they perceive their peers and changes the goals and calculus of social interaction (Udry and Billy 1987; Udry 1988). Thus, during puberty, attractiveness develops a new dimension as social currency. Further, given substantial reliability in attractiveness ratings (Rhodes 2006), this social currency is not evenly distributed—for some the transition to puberty brings the amorous attention of many, and for others it generates disinterest and disdain. This phenomenon almost certainly translates into popularity gradients (Kennedy 1990; Becker and Luther 2007), which are, in turn, apt to have affective repercussions (e.g., Oldenberg and Kerns 1997).

Contrary to expectations, no support was found of cumulative disadvantage between attractiveness and established social determinants of depression. In fact, the opposite was found for SLEs—that is, attractive individuals were shown to be *more* sensitive to the effects of SLEs. Furthermore, given its strong statistical significance ($p = 0.0001$) and robustness in sensitivity analysis, this finding is unlikely to be a false discovery. So, what then is to be made of the finding that being unattractive, rather than weakening individuals' capacity to

cope with additional adversity, actually toughens them, making them more resilient to additional stressors? Clearly, any explanation at this point is post hoc and speculative; however, some precedent for this finding can be found in the literature on self-esteem and depression. In particular, research into the *buffering hypothesis* has yielded some results consistent with the current finding (see Baumeister et al. 2003 for review). The buffering hypothesis posits that the influence of self-esteem operates, at least in part, through moderating the effects of life stress (Brown and Harris 1978). Thus, the hypothesis may, in essence, be considered a cumulative disadvantage perspective, in that it is expected that two depressogenic factors, namely low self-esteem and life stress, will have interactively detrimental effects. And though some studies have found support for this hypothesis (e.g., Lazarus 1988), other studies have found the opposite—that is, they have found that the affective benefits of high self-esteem are primarily reaped at low levels of life stress, with individuals of both high and low self-esteem experiencing comparable levels of depression under high life stress conditions (e.g., Whisman and Kwon 1993).

Given that self-esteem is held to be a primary mechanism through which attractiveness influences affect, research finding individuals with high self-esteem to be more vulnerable to life stress is quite relevant and may describe the same phenomenon reported in the present study. However, former research is less useful in providing a narrative for understanding this finding, pointing to the need for a novel theoretical perspective. One potential explanation in this regard is that the continual psychosocial buffeting endured by the unattractive develops their capacity to cope with adversity. According to this logic, as the homely come to accept social adversity as a matter of course, they develop a "thicker skin" and thus, are less unbalanced by the occurrence of stressful event. Conversely, this argument suggests that the attractive, accustomed to a favorable breeze blowing at their back, are less

prepared for the psychological blow of a stressful event, and thus, experience a greater degree of disruption. While this explanation is certainly plausible, it is, of course, strictly speculative at this point. Further research will be needed to more fully understand this unexpected finding.

The current studies offer a considerable advance in understanding the etiology of depression in early life. However, the study is nevertheless limited in several respects. First, additional waves of data would allow an extension of our understanding of how depressive symptoms develop over a longer period of the life course. The present investigation was limited to ages 12-26 based on three waves of data that are currently available from the Add Health study. Fortunately, the fourth wave of data collection for Add Health is now underway (http://www.cpc.unc.edu/projects/addhealth/design_focus/wave4) and will allow an elaboration of the models presented here to include participants in their late 20's and early 30's.

Another shortcoming of the study was the conceptualization of stress being limited to SLEs. It has been demonstrated that other aspects of the stress process, such as chronic stressors, are also important components of the stress-depression relationship (e.g., Pearlin 1989). Future research could improve upon the current analyses through more exhaustive models integrating chronic stressors as predictors and moderators.

In addition to expanding the conceptualization of environmental risks, future research could also benefit from increasing coverage of genetic variation. While candidate genes studies are apt to remain important in GxE studies into the near future, there is a progressive movement in genetics toward more exploratory analyses examining genetic variation across the genome. These genome-wide association studies (GWAS) typically include over 500K genetic markers, and while still relatively uncommon in behavioral research, the rapidly

decreasing cost of genotyping guarantees that such data will soon come available for longitudinal, behavioral surveys. This development will represent a paradigm shift in GxE studies, allowing analysis of social moderation on an unprecedented scale. However, it will also pose challenges to social scientists as they join statistical geneticist in grappling with how to best analyze such massively wide data. While the FDR techniques employed here represent vanguard techniques for addressing the issues of multiple testing inherent to GWAS, this area will certainly remain an active research frontier into the foreseeable future.

Regarding the investigation of the influence of physical attractiveness on depression, while the current analysis represents a dramatic advance from former research in terms of data quality and modeling sophistication, it is limited by a suboptimal measure of physical attractiveness. That is, although the measure has the strength of being based on a dynamic viewing of the individual, rather than a single image (Rubenstein 2006), it suffers from the weakness of being based on a single individual's rating. As research has shown that each individual's attractiveness criteria typically include both an individual-specific, subjective element as well as an "objective", universal component (Honekopp 2006), having only a single rater for each observation likely introduces significant non-systematic measurement error. Future data collection efforts aimed at elucidating the effects of attractiveness would do well to video a portion of the interview; thus, enabling the possibility of multiple raters.

Despite these limitations, the present study improves our understanding of the process of early life depression and advances a framework for future research in the area. Specifically, results show possible GxE between *MAOA* and social support among females and temporal variation in the effects of *MAOA* among males. Additionally, a developmentally and socially contingent role was found for physical attractiveness, with the influence physical attractiveness increasing across early life and more pronounced at low

levels of SLEs. Beyond any given substantive result, however, this study makes strides toward establishing a flexible approach for the study of social moderation of genetic and other sources of individual differences. It is my hope that future research will continue to develop this perspective to improve our understanding of how structural factors interact with constitutional differences to influence mental health across the life course.

Appendices

Appendix 2.1. List of Items in Stressful Life Events Index

Wave I, II, and III items	**Wave I and II items only**
Death of a parent	Was expelled from school
Suicide attempt resulting in injury	Suffered a serious injury
Friend committed suicide	Father received welfare
Relative committed suicide	Mother received welfare
Saw violence	Was raped
Threatened by a knife or gun	Ran away from home
Was shot	Nonromantic sexual relationship ended
Was stabbed	Suffered verbal abuse in a romantic relationship
Was jumped	Suffered physical abuse in a romantic relationship
Threatened someone with a knife or gun	Suffered verbal abuse in a nonromantic sexual relationship
Shot/stabbed someone	Suffered physical abuse in a nonromantic sexual relationship
Was injured in a physical fight	
Hurt someone in a physical fight	**Wave III items only**
Unwanted pregnancy	Evicted from residence, cutoff service
Abortion, still birth, or miscarriage	Entered full time active military duty
Had a child adopted	Discharged from the armed forces
Death of a child	Cohabitation dissolution
Romantic relationship ended	Received welfare
Had sex for money	Involuntarily dropped from welfare
Contracted a STD	Marriage dissolution
Skipped necessary medical care	Baby had major health problems at birth
Juvenile conviction	Death of a romantic partner
Adult conviction	Death of a spouse
Served time in jail	

Appendix 2.2. Social Support Scale

1.	How much do you feel that adults care about you?
2.	How much do you feel that your teachers care about you?
3.	How much do you feel that your parents care about you?
4.	How much do you feel that people in your family understand you?
5.	How much do you feel that your family pays attention to you?

Appendix 2.3. Parameter estimates (*p*-values) of linear mixed models among females: Effects of stress process and *MAOA* 2R × SLEs on 4 specifications of depression

	9 item avg	9 item factor	3 item avg	3 item factor
MAOA 2R/2R	0.141	0.100	0.201	0.099
	(0.662)	(0.699)	(0.620)	(0.746)
MAOA 2R/2R * SLE	0.621*	0.689**	1.447***	1.056***
	(0.024)	(0.003)	(0.000)	(0.000)
Hispanic	0.035	0.017	0.037	0.020
	(0.319)	(0.548)	(0.386)	(0.541)
Black	0.003	0.002	-0.013	-0.014
	(0.918)	(0.952)	(0.725)	(0.630)
Asian	0.206***	0.107**	0.128*	0.083
	(0.000)	(0.008)	(0.037)	(0.073)
American Indian	0.100	0.100	0.161	0.110
	(0.193)	(0.099)	(0.085)	(0.118)
Other Race	-0.216	-0.156	-0.192	-0.139
	(0.128)	(0.162)	(0.266)	(0.286)
Age	0.011	0.026**	0.033*	0.030**
	(0.292)	(0.003)	(0.019)	(0.005)
Age Squared	-0.002**	-0.002**	-0.003***	-0.002**
	(0.002)	(0.004)	(0.001)	(0.004)
Social Support	-0.267***	-0.188***	-0.244***	-0.186***
	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education (mean)	-0.030***	-0.019***	-0.024**	-0.017**
	(0.000)	(0.001)	(0.007)	(0.009)
Household income (logged thousands)	-0.003	-0.007	-0.014	-0.014
	(0.856)	(0.564)	(0.470)	(0.332)
SLE	0.059***	0.051***	0.081***	0.060***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.674***	0.363***	0.474***	0.329***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Household level)	0.179***	0.135***	0.201***	0.155***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.147***	0.109***	0.154***	0.113***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.378***	0.314***	0.510***	0.385***
	(0.000)	(0.000)	(0.000)	(0.000)
N	2904	2904	2904	2904
Log restricted likelihood	-1683.194	-1099.207	-2454.485	-1638.725

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 2.4. Parameter estimates (*p*-values) of linear mixed models among females: Effects of stress process and *MAOA* 2R × SLEs on square root transformed CES-D

	9 item avg	3 item avg
MAOA no 2R	-0.053	0.018
	(0.336)	(0.815)
MAOA no 2R * Support	-0.280**	-0.242
	(0.004)	(0.077)
Hispanic	0.020	0.025
	(0.410)	(0.460)
Black	-0.001	-0.006
	(0.965)	(0.849)
Asian	0.131***	0.110*
	(0.000)	(0.028)
American Indian	0.046	0.096
	(0.384)	(0.204)
Other Race	-0.141	-0.189
	(0.151)	(0.178)
Age	0.011	0.023*
	(0.140)	(0.041)
Age Squared	-0.002***	-0.003***
	(0.000)	(0.000)
Social Support	0.094	0.051
	(0.321)	(0.704)
Parental Education (mean)	-0.023***	-0.021**
	(0.000)	(0.004)
Household income (logged thousands)	-0.003	-0.017
	(0.773)	(0.290)
SLE	0.037***	0.055***
	(0.000)	(0.000)
Intercept	0.806***	0.503***
	(0.000)	(0.000)
Random intercept SD (Household level)	0.124***	0.159***
	(0.000)	(0.000)
Random intercept SD (Individual level)	0.105***	0.143***
	(0.000)	(0.000)
Residual SD	0.260***	0.400***
	(0.000)	(0.000)
N	2904	2904
Log restricted likelihood	-608.1	-1787.5

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 2.5. Parameter estimates of structural equation model among females: Effects of *MAOA* 2R × social support

Parameter	Estimate	SE	z value	p value
Measurement models				
Depression (factor loadings constrained equal across repeated measures)				
Item 1 (could not shake off the blues)	1.000	-	-	-
Item 2 (were depressed)	1.181	0.032	36.467	0.000
Item 3 (were sad)	0.968	0.033	29.670	0.000
Parental education				
Biological mother	1.000	-	-	-
Biological father	1.104	0.292	3.775	0.000
Resident mother (non-biological)	1.386	0.350	3.959	0.000
Resident father (non-biological)	1.152	0.313	3.681	0.000
Social support				
Item 1 (adults care about you, wave I)	1.000	-	-	-
Item 2 (teachers care about you, wave I)	1.099	0.123	8.938	0.000
Item 3 (parents care about you, wave I)	0.801	0.078	10.218	0.000
Item 4 (family understands you, wave I)	1.803	0.163	11.050	0.000
Item 5 (family pays attention to you, wave I)	1.637	0.155	10.589	0.000
Item 6 (adults care about you, wave II)	1.109	0.125	8.890	0.000
Item 7 (teachers care about you, wave II)	1.182	0.154	7.700	0.000
Item 8 (parents care about you, wave II)	0.723	0.088	8.261	0.000
Item 9 (family pays attention to you, wave II)	1.566	0.186	8.435	0.000
Item 10 (family pays attention to you, wave II)	1.485	0.169	8.783	0.000
Structural effects				
Social support --> depression trajectory intercept	-0.082	0.177	-0.461	0.645
Parental education --> depression trajectory intercept	-0.039	0.018	-2.169	0.030
Hispanic --> depression trajectory intercept	0.044	0.037	1.196	0.232
Black --> depression trajectory intercept	0.013	0.039	0.327	0.744
Asian --> depression trajectory intercept	0.098	0.054	1.801	0.072
Other race --> depression trajectory intercept	0.067	0.078	0.853	0.394
Household income --> depression trajectory intercept	-0.010	0.017	-0.579	0.562
MAOA no 2R --> depression trajectory intercept	0.048	0.072	0.675	0.500
MAOA no 2R × social support --> depression trajectory intercept	-0.330	0.180	-1.838	0.066
SLEs --> depression repeated measures	0.091	0.023	3.953	0.000
Latent variable residual variance				
Within-household intercept	0.046	0.008	5.718	0.000
Log likelihood		-28416.552		

Appendix 2.6. Parameter estimates (*p*-values) of linear mixed models among females: Effects of stress process and *MAOA* 3R × social support on 4 specifications of depression

	9 item avg	9 item factor	3 item avg	3 item factor
MAOA 3R/3R	-0.019	-0.012	-0.015	-0.010
	(0.532)	(0.608)	(0.686)	(0.716)
MAOA 3R/3R * Support	-0.121*	-0.096*	-0.149*	-0.104*
	(0.014)	(0.013)	(0.014)	(0.022)
Hispanic	0.032	0.014	0.033	0.017
	(0.356)	(0.605)	(0.441)	(0.601)
Black	0.012	0.008	-0.002	-0.006
	(0.710)	(0.739)	(0.952)	(0.827)
Asian	0.216***	0.114**	0.139*	0.091
	(0.000)	(0.004)	(0.025)	(0.053)
American Indian	0.101	0.101	0.163	0.112
	(0.186)	(0.094)	(0.081)	(0.113)
Other Race	-0.214	-0.155	-0.189	-0.137
	(0.130)	(0.165)	(0.274)	(0.294)
Age	0.011	0.025**	0.033*	0.029**
	(0.308)	(0.004)	(0.021)	(0.006)
Age Squared	-0.002**	-0.002**	-0.003***	-0.002**
	(0.002)	(0.004)	(0.001)	(0.005)
Social Support	-0.245***	-0.171***	-0.217***	-0.167***
	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education (mean)	-0.030***	-0.019***	-0.025**	-0.018**
	(0.000)	(0.001)	(0.006)	(0.008)
Household income (logged thousands)	-0.004	-0.008	-0.015	-0.015
	(0.803)	(0.525)	(0.443)	(0.311)
SLE	0.059***	0.051***	0.081***	0.061***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.676***	0.364***	0.476***	0.330***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Household level)	0.176***	0.132***	0.196***	0.152***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.148***	0.110***	0.157***	0.114***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.379***	0.315***	0.512***	0.386***
	(0.000)	(0.000)	(0.000)	(0.000)
N	2904	2904	2904	2904
Log restricted likelihood	-1687.439	-1105.883	-2465.277	-1649.010

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 2.7. Parameter estimates (*p*-values) of linear mixed models among females: Effects of stress process and *MAOA* 3.5/4R × SLEs on square root transformed CES-D

	9 item sum	3 item sum
MAOA no 3.5 or 4R	-0.024	-0.026
	(0.244)	(0.368)
MAOA no 3.5 or 4R * Support	-0.075*	-0.093*
	(0.022)	(0.048)
Hispanic	0.018	0.023
	(0.464)	(0.510)
Black	0.007	-0.006
	(0.763)	(0.842)
Asian	0.141***	0.120*
	(0.000)	(0.017)
American Indian	0.047	0.097
	(0.376)	(0.199)
Other Race	-0.141	-0.188
	(0.153)	(0.181)
Age	0.011	0.022*
	(0.148)	(0.043)
Age Squared	-0.002***	-0.003***
	(0.000)	(0.000)
Social Support	-0.165***	-0.167***
	(0.000)	(0.000)
Parental Education (mean)	-0.023***	-0.021**
	(0.000)	(0.004)
Household income (logged thousands)	-0.005	-0.020
	(0.677)	(0.217)
SLE	0.037***	0.055***
	(0.000)	(0.000)
Intercept	0.756***	0.525***
	(0.000)	(0.000)
Random intercept SD (Household level)	0.122***	0.157***
	(0.000)	(0.000)
Random intercept SD (Individual level)	0.108***	0.144***
	(0.000)	(0.000)
Residual SD	0.260***	0.400***
	(0.000)	(0.000)
N	2904	2904
Log restricted likelihood	-611.2	-1789.0

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 2.8. Parameter estimates of structural equation model among females: Effects of *MAOA* 3.5/4R × social support

Parameter	Estimate	SE	z value	p value
Measurement models				
Depression (factor loadings constrained equal across repeated measures)				
Item 1 (could not shake off the blues)	1.000	-	-	-
Item 2 (were depressed)	1.182	0.032	36.460	0.000
Item 3 (were sad)	0.968	0.033	29.663	0.000
Parental education				
Biological mother	1.000	-	-	-
Biological father	1.095	0.288	3.806	0.000
Resident mother (non-biological)	1.378	0.346	3.985	0.000
Resident father (non-biological)	1.143	0.307	3.717	0.000
Social support				
Item 1 (adults care about you, wave I)	1.000	-	-	-
Item 2 (teachers care about you, wave I)	1.100	0.123	8.933	0.000
Item 3 (parents care about you, wave I)	0.800	0.078	10.217	0.000
Item 4 (family understands you, wave I)	1.799	0.163	11.034	0.000
Item 5 (family pays attention to you, wave I)	1.633	0.154	10.576	0.000
Item 6 (adults care about you, wave II)	1.116	0.124	8.990	0.000
Item 7 (teachers care about you, wave II)	1.186	0.154	7.720	0.000
Item 8 (parents care about you, wave II)	0.727	0.087	8.317	0.000
Item 9 (family pays attention to you, wave II)	1.564	0.185	8.444	0.000
Item 10 (family pays attention to you, wave II)	1.484	0.168	8.816	0.000
Structural effects				
Social support --> depression trajectory intercept	-0.373	0.055	-6.840	0.000
Parental education --> depression trajectory intercept	-0.038	0.017	-2.155	0.031
Hispanic --> depression trajectory intercept	0.042	0.036	1.142	0.254
Black --> depression trajectory intercept	0.006	0.037	0.172	0.863
Asian --> depression trajectory intercept	0.107	0.055	1.956	0.050
Other race --> depression trajectory intercept	0.064	0.078	0.819	0.413
Household income --> depression trajectory intercept	-0.013	0.017	-0.765	0.444
MAOA no 3.5/4R --> depression trajectory intercept	-0.020	0.033	-0.604	0.546
MAOA no 3.5/4R × social support --> depression trajectory intercept	-0.132	0.089	-1.482	0.138
SLEs --> depression repeated measures	0.092	0.023	3.981	0.000
Latent variable residual variance				
Within-household intercept	0.046	0.008	5.712	0.000
Log likelihood		-28416.704		

Appendix 2.9. Parameter estimates (*p*-values) of linear mixed models among full sample: Effects of stress process and DAT1 8R × parental education on 4 specifications of depression

	9 item avg	9 item factor	3 item avg	3 item factor
DAT1 8R/8R	0.218	0.208	0.360	0.286
	(0.335)	(0.245)	(0.197)	(0.175)
DAT1 8R/8R * Parental education	-0.124	-0.168*	-0.275**	-0.207**
	(0.149)	(0.013)	(0.009)	(0.010)
Female	0.120***	0.104***	0.161***	0.119***
	(0.000)	(0.000)	(0.000)	(0.000)
Hispanic	0.031	0.019	0.039	0.022
	(0.222)	(0.344)	(0.205)	(0.352)
Black	0.060**	0.043*	0.044	0.033
	(0.008)	(0.016)	(0.110)	(0.113)
Asian	0.159***	0.085**	0.099*	0.069*
	(0.000)	(0.002)	(0.022)	(0.035)
American Indian	0.022	0.035	0.079	0.041
	(0.684)	(0.422)	(0.242)	(0.422)
Other Race	-0.008	-0.022	-0.040	-0.035
	(0.928)	(0.772)	(0.729)	(0.686)
Age	0.018*	0.031***	0.042***	0.038***
	(0.011)	(0.000)	(0.000)	(0.000)
Age Squared	-0.002***	-0.002***	-0.003***	-0.002***
	(0.000)	(0.000)	(0.000)	(0.000)
Social Support	-0.225***	-0.158***	-0.203***	-0.155***
	(0.000)	(0.000)	(0.000)	(0.000)
Parental Education (mean)	-0.028***	-0.016***	-0.019**	-0.014**
	(0.000)	(0.000)	(0.003)	(0.004)
Household income (logged thousands)	-0.006	-0.007	-0.012	-0.011
	(0.618)	(0.474)	(0.408)	(0.303)
SLE	0.036***	0.029***	0.043***	0.031***
	(0.000)	(0.000)	(0.000)	(0.000)
Intercept	0.520***	0.230***	0.265***	0.167***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Household level)	0.166***	0.124***	0.187***	0.142***
	(0.000)	(0.000)	(0.000)	(0.000)
Random intercept SD (Individual level)	0.179***	0.135***	0.194***	0.147***
	(0.000)	(0.000)	(0.000)	(0.000)
Residual SD	0.345***	0.288***	0.476***	0.359***
	(0.000)	(0.000)	(0.000)	(0.000)
N	5636	5636	5635	5635
Log restricted likelihood	-2878.753	-1752.809	-4467.471	-2887.725

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 3.1. Parameter estimates (*p*-values) of linear mixed models among full sample: Effects of *DRD4* 5R on square root transformed depression trajectories

	9 item avg	3 item avg
DRD4 no 5R	-0.280**	-0.394**
	(0.004)	(0.009)
DRD4 no 5R * Age	0.095**	0.142**
	(0.001)	(0.001)
DRD4 no 5R * Age Sq	-0.006***	-0.009***
	(0.000)	(0.001)
Female	0.073***	0.128***
	(0.000)	(0.000)
Hispanic	0.019	0.030
	(0.294)	(0.239)
Black	0.045**	0.037
	(0.006)	(0.112)
Asian	0.120***	0.100**
	(0.000)	(0.006)
American Indian	0.008	0.048
	(0.831)	(0.392)
Other Race	0.003	-0.043
	(0.959)	(0.652)
Age	-0.081**	-0.105**
	(0.003)	(0.014)
Age Squared	0.004*	0.006*
	(0.016)	(0.033)
Social Support	-0.161***	-0.167***
	(0.000)	(0.000)
Parental Education (mean)	-0.022***	-0.017**
	(0.000)	(0.002)
Household income (logged thousands)	-0.006	-0.017
	(0.488)	(0.154)
SLE	0.024***	0.029***
	(0.000)	(0.000)
Intercept	0.934***	0.725***
	(0.000)	(0.000)
Random intercept SD (Household level)	0.120***	0.163***
	(0.000)	(0.000)
Random intercept SD (Individual level)	0.131***	0.163***
	(0.000)	(0.000)
Residual SD	0.243***	0.387***
	(0.000)	(0.000)
N	5627	5626
Log restricted likelihood	-954.0	-3349.3

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 3.2. Parameter estimates of structural equation model among full sample: Effects of *DRD4* 5R on depression trajectories

Parameter	Estimate	SE	z value	p value
Measurement models				
Depression (factor loadings constrained equal across repeated measures)				
Item 1 (could not shake off the blues)	1.00	-	-	-
Item 2 (were depressed)	1.206	0.06	18.74	0.00
Item 3 (were sad)	1.01	0.04	27.20	0.00
Parental education				
Biological mother	1.00	-	-	-
Biological father	0.944	0.24	4.01	0.00
Resident mother (non-biological)	1.243	0.25	4.91	0.00
Resident father (non-biological)	1.198	0.29	4.17	0.00
Social support				
Item 1 (adults care about you, wave I)	1.00	-	-	-
Item 2 (teachers care about you, wave I)	1.139	0.08	13.79	0.00
Item 3 (parents care about you, wave I)	0.723	0.05	15.11	0.00
Item 4 (family understands you, wave I)	1.517	0.11	14.18	0.00
Item 5 (family pays attention to you, wave I)	1.406	0.10	14.67	0.00
Item 6 (adults care about you, wave II)	0.959	0.08	11.65	0.00
Item 7 (teachers care about you, wave II)	1.092	0.10	10.76	0.00
Item 8 (parents care about you, wave II)	0.555	0.05	10.21	0.00
Item 9 (family pays attention to you, wave II)	1.257	0.13	9.82	0.00
Item 10 (family pays attention to you, wave II)	1.181	0.11	10.44	0.00
Structural effects				
Social support --> depression trajectory intercept	-0.265	0.03	-7.91	0.00
Parental education --> depression trajectory intercept	-0.035	0.01	-2.61	0.01
Female --> depression trajectory intercept	0.153	0.02	8.39	0.00
Hispanic --> depression trajectory intercept	0.032	0.05	0.65	0.51
Black --> depression trajectory intercept	0.056	0.03	1.66	0.10
Asian --> depression trajectory intercept	0.091	0.05	1.80	0.07
Other race --> depression trajectory intercept	0.046	0.07	0.67	0.50
Household income --> depression trajectory intercept	-0.007	0.01	-0.51	0.61
DRD4 No 5R --> depression trajectory intercept	0.047	0.10	0.45	0.65
DRD4 No 5R --> depression trajectory linear slope	0.031	0.01	2.25	0.02
DRD4 No 5R --> depression trajectory quadratic slope	-0.004	0.00	-2.97	0.00
SLEs --> depression repeated measures	0.047	0.01	4.30	0.00
Latent variable residual variance				
Within-household intercept	0.033	0.00	7.73	0.00
Between-household intercept	0.026	0.01	3.87	0.00
Log likelihood		-55140.86		

Appendix 3.3. Parameter estimates (*p*-values) of linear mixed models among males: Effects of *MAOA* 3.5R on square root transformed depression trajectories

	9 item avg	3 item avg
MAOA 3.5R	-0.263	-0.269
	(0.107)	(0.298)
MAOA 3.5R * Age	0.136*	0.164
	(0.013)	(0.068)
MAOA 3.5R * Age Sq	-0.012**	-0.017*
	(0.004)	(0.020)
Hispanic	0.033	0.055
	(0.196)	(0.132)
Black	0.088***	0.087**
	(0.000)	(0.008)
Asian	0.118**	0.113*
	(0.001)	(0.021)
American Indian	-0.029	-0.006
	(0.610)	(0.936)
Other Race	0.137	0.148
	(0.142)	(0.264)
Age	0.011	0.039***
	(0.115)	(0.000)
Age Squared	-0.001**	-0.003***
	(0.002)	(0.000)
Social Support	-0.140***	-0.142***
	(0.000)	(0.000)
Parental Education (mean)	-0.019***	-0.011
	(0.000)	(0.146)
Household income (logged thousands)	-0.005	-0.010
	(0.692)	(0.571)
SLE	0.018***	0.019***
	(0.000)	(0.000)
Intercept	0.643***	0.289***
	(0.000)	(0.000)
Random intercept SD (Household level)	0.130***	0.201***
	(0.000)	(0.000)
Random intercept SD (Individual level)	0.133***	0.128***
	(0.000)	(0.000)
Residual SD	0.223***	0.370***
	(0.000)	(0.000)
N	2701	2700
Log restricted likelihood	-325.4	-1530.1

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 3.4. Parameter estimates of structural equation model among males: Effects of *MAOA* 3.5R on depression trajectories

Parameter	Estimate	SE	z value	p value
Measurement models				
Depression (factor loadings constrained equal across repeated measures)				
Item 1 (could not shake off the blues)	1.00	-	-	-
Item 2 (were depressed)	1.24	0.06	22.36	0.00
Item 3 (were sad)	1.07	0.05	22.04	0.00
Parental education				
Biological mother	1.00	-	-	-
Biological father	0.75	0.36	2.12	0.03
Resident mother (non-biological)	1.10	0.30	3.71	0.00
Resident father (non-biological)	1.26	0.49	2.57	0.01
Social support				
Item 1 (adults care about you, wave I)	1.00	-	-	-
Item 2 (teachers care about you, wave I)	1.20	0.11	11.08	0.00
Item 3 (parents care about you, wave I)	0.66	0.06	12.07	0.00
Item 4 (family understands you, wave I)	1.27	0.12	10.37	0.00
Item 5 (family pays attention to you, wave I)	1.22	0.11	11.23	0.00
Item 6 (adults care about you, wave II)	0.82	0.11	7.60	0.00
Item 7 (teachers care about you, wave II)	1.01	0.13	7.70	0.00
Item 8 (parents care about you, wave II)	0.41	0.05	7.56	0.00
Item 9 (family pays attention to you, wave II)	1.00	0.16	6.27	0.00
Item 10 (family pays attention to you, wave II)	0.93	0.13	6.95	0.00
Structural effects				
Social support --> depression trajectory intercept	-0.15	0.03	-5.16	0.00
Parental education --> depression trajectory intercept	-0.02	0.01	-1.28	0.20
Hispanic --> depression trajectory intercept	0.03	0.04	0.75	0.46
Black --> depression trajectory intercept	0.09	0.03	2.47	0.01
Asian --> depression trajectory intercept	0.08	0.05	1.70	0.09
Other race --> depression trajectory intercept	0.03	0.06	0.47	0.64
Household income --> depression trajectory intercept	-0.01	0.02	-0.29	0.77
MAOA 3.5R --> depression trajectory intercept	-0.20	0.08	-2.65	0.01
MAOA 3.5R --> depression trajectory linear slope	0.12	0.04	2.69	0.01
MAOA 3.5R --> depression trajectory quadratic slope	-0.01	0.00	-3.51	0.00
SLEs --> depression repeated measures	0.03	0.01	2.90	0.00
Latent variable residual variance				
Within-household intercept	0.02	0.00	6.54	0.00
Between-household intercept	0.04	0.01	6.19	0.00
Log likelihood		-26600.80		

Appendix 4.1: Interviewer effects on attractiveness rating, by race and gender interviewer-subject combinations

	Rater							
	Female	Male	White	Black	Asian	Hispanic	Other race	All
Female rating Female	0.145***							-0.005
	(0.000)							(0.837)
Female rating Male	0.020							-0.128***
	(0.302)							(0.000)
Male rating Male		-0.204***						-0.260***
		(0.000)						(0.000)
Male rating Female		0.056*						-
		(0.023)						-
White rating White			0.068***					0.032
			(0.000)					(0.058)
White rating Non-white			0.028					-
			(0.123)					-
Black rating Black				-0.095***				-0.074**
				(0.000)				(0.005)
Black rating Non-black				-0.047*				-0.024
				(0.028)				(0.311)
Asian rating Asian					-0.442*			-0.463*
					(0.021)			(0.015)
Asian rating Non-Asian					-0.695**			-0.687**
					(0.008)			(0.009)
Hispanic rating Hispanic						0.035		0.040
						(0.403)		(0.349)
Hispanic rating Non-Hispanic						-0.081		-0.073
						(0.076)		(0.116)
"Other" race rating "Other"							0.278	0.255
							(0.228)	(0.267)
"Other" race rating Non-"Other"							0.115*	0.119*
							(0.020)	(0.019)
Intercept	3.425***	3.513***	3.456***	3.508***	3.495***	3.494***	3.491***	3.566***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
R^2	0.006	0.006	0.001	0.001	0.001	0.000	0.000	0.014

Appendix 4.2. Parameter estimates (*p*-values) of linear mixed models: Effects of physical attractiveness on square root transformed depression trajectories

	9 item avg	3 item avg
Attractiveness	-0.002	0.014*
	(0.679)	(0.022)
Age	0.023***	0.043***
	(0.000)	(0.000)
Age Squared	-0.002***	-0.003***
	(0.000)	(0.000)
Age x Attractiveness	-0.001**	-0.003**
	(0.01)	(0.002)
Female	0.096***	0.162***
	(0.000)	(0.000)
Black	0.034***	0.029***
	(0.000)	(0.000)
Asian	0.117***	0.107***
	(0.000)	(0.000)
Hispanic	0.041***	0.038***
	(0.000)	(0.000)
Other Race	0.017	0.042*
	(0.152)	(0.029)
Parental Education (mean)	-0.014***	-0.013***
	(0.000)	(0.000)
Household Income (logged thousands)	-0.012***	-0.013***
	(0.000)	(0.006)
Social Support	-0.127***	-0.148***
	(0.000)	(0.000)
SLEs	0.012***	0.018***
	(0.000)	(0.000)
Parental Education x Attractiveness		
Income x Attractiveness		
Social Support x Attractiveness	-0.008*	-0.004
	(0.016)	(0.421)
SLEs x Attractiveness	0.003***	0.004***
	(0.000)	(0.001)
Intercept	0.638***	0.276***
	(0.000)	(0.000)
Random intercept SD	0.171***	0.225***
	(0.000)	(0.000)
Residual SD	0.249***	0.390***
	(0.000)	(0.000)
N	36536	36531
Log likelihood	-6665.1	-21838.7

P-values in parentheses
* p<0.05, ** p<0.01, *** p<0.001

Appendix 4.3. Parameter estimates of structural equation model: Effects of physical attractiveness on depression trajectories

Parameter	Estimate	SE	z value	p value
Measurement models				
Depression (factor loadings constrained equal across repeated measures)				
Item 1 (could not shake off the blues)	1.000	-	-	-
Item 2 (were depressed)	1.241	0.008	151.038	0.000
Item 3 (were sad)	1.014	0.007	142.748	0.000
Parental education				
Biological mother	1.000	-	-	-
Biological father	1.041	0.043	24.336	0.000
Resident mother (non-biological)	1.270	0.049	25.911	0.000
Resident father (non-biological)	1.283	0.049	25.944	0.000
Social support				
Item 1 (adults care about you, wave I)	1.000	-	-	-
Item 2 (teachers care about you, wave I)	1.071	0.025	42.785	0.000
Item 3 (parents care about you, wave I)	0.667	0.015	44.850	0.000
Item 4 (family understands you, wave I)	1.539	0.029	53.367	0.000
Item 5 (family pays attention to you, wave I)	1.392	0.026	54.252	0.000
Item 6 (adults care about you, wave II)	1.061	0.020	52.393	0.000
Item 7 (teachers care about you, wave II)	1.092	0.023	47.440	0.000
Item 8 (parents care about you, wave II)	0.659	0.013	49.023	0.000
Item 9 (family pays attention to you, wave II)	1.507	0.028	54.170	0.000
Item 10 (family pays attention to you, wave II)	1.429	0.026	55.260	0.000
Depression growth factor means/intercepts				
Intercept	0.000	-	-	-
Linear slope	0.039	0.004	10.488	0.000
Quadratic slope	-0.004	0.000	-18.587	0.000
Structural effects				
Social support --> depression trajectory intercept	-0.279	0.008	-34.239	0.000
Parental education --> depression trajectory intercept	-0.027	0.003	-8.858	0.000
Female --> depression trajectory intercept	0.186	0.005	33.867	0.000
Hispanic --> depression trajectory intercept	0.042	0.008	5.317	0.000
Black --> depression trajectory intercept	0.032	0.007	4.552	0.000
Asian --> depression trajectory intercept	0.089	0.011	8.305	0.000
Other race --> depression trajectory intercept	0.041	0.016	2.503	0.012
Household income --> depression trajectory intercept	-0.014	0.004	-3.448	0.001
Attractiveness --> depression repeated measures	0.005	0.005	0.947	0.344
Attractiveness × age --> depression repeated measures	-0.002	0.001	-2.069	0.039
Attractiveness × SLEs --> depression repeated measures	0.004	0.001	3.178	0.001
SLEs --> depression repeated measures	0.027	0.004	6.823	0.000
Latent variable residual variance				
Depression trajectory intercept	0.059	0.002	35.539	0.000
Fit indices				
CFI		0.821		
TLI		0.821		
RMSEA		0.020		
Log likelihood		-724233.535		

Appendix 4.4. Parameter estimates of structural equation model: Effects of physical attractiveness, modeled with explicit measurement error, on depression trajectories

Parameter	Estimate	SE	z value	p value
Measurement models				
Depression (factor loadings constrained equal across repeated measures)				
Item 1 (could not shake off the blues)	1.000	-	-	-
Item 2 (were depressed)	1.241	0.008	151.040	0.000
Item 3 (were sad)	1.014	0.007	142.748	0.000
Parental education				
Biological mother	1.000	-	-	-
Biological father	1.041	0.043	24.337	0.000
Resident mother (non-biological)	1.270	0.049	25.914	0.000
Resident father (non-biological)	1.283	0.049	25.946	0.000
Social support				
Item 1 (adults care about you, wave I)	1.000	-	-	-
Item 2 (teachers care about you, wave I)	1.071	0.025	42.785	0.000
Item 3 (parents care about you, wave I)	0.667	0.015	44.850	0.000
Item 4 (family understands you, wave I)	1.539	0.029	53.367	0.000
Item 5 (family pays attention to you, wave I)	1.392	0.026	54.252	0.000
Item 6 (adults care about you, wave II)	1.061	0.020	52.393	0.000
Item 7 (teachers care about you, wave II)	1.092	0.023	47.440	0.000
Item 8 (parents care about you, wave II)	0.659	0.013	49.023	0.000
Item 9 (family pays attention to you, wave II)	1.507	0.028	54.170	0.000
Item 10 (family pays attention to you, wave II)	1.429	0.026	55.260	0.000
Depression growth factor means/intercepts				
Intercept	0.000	-	-	-
Linear slope	0.033	0.002	13.951	0.000
Quadratic slope	-0.004	0.000	-18.524	0.000
Structural effects				
Social support --> depression trajectory intercept	-0.279	0.008	-34.240	0.000
Parental education --> depression trajectory intercept	-0.027	0.003	-8.918	0.000
Female --> depression trajectory intercept	0.186	0.005	33.899	0.000
Hispanic --> depression trajectory intercept	0.042	0.008	5.340	0.000
Black --> depression trajectory intercept	0.033	0.007	4.598	0.000
Asian --> depression trajectory intercept	0.089	0.011	8.309	0.000
Other race --> depression trajectory intercept	0.041	0.016	2.508	0.012
Household income --> depression trajectory intercept	-0.014	0.004	-3.281	0.001
Attractivness --> depression repeated measures	0.009	0.010	0.844	0.399
Attractivness × age --> depression repeated measures	-0.004	0.002	-2.116	0.034
Attractivness × SLEs --> depression repeated measures	0.004	0.001	3.164	0.002
SLEs --> depression repeated measures	0.027	0.004	6.838	0.000
Latent variable residual variance				
Depression trajectory intercept	0.059	0.002	35.539	0.000
Fit indices				
CFI		0.793		
TLI		0.792		
RMSEA		0.021		
Log likelihood		-739294.379		

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