Revised Study Protocol (10/29/2018)

Age-18 Follow-up of Home Visiting Intervention

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David L. Olds, Ph.D. [a]
Harriet Kitzman, R.N., Ph.D. [b]
Michael Knudtson, M.S. [a]
Robert Cole, Ph.D. [b]
Ted Miller, Ph.D [g]
Diana Fishbein, Ph.D. [h]
Elizabeth Anson, M.S. [b]
Joyce A. Smith, R.N., Ph.D. [b]
Kimberly Arcoleo, M.P.H. [b]
Ralph DiClemente, Ph.D. [d]
Gina Wingood, Sc,D, M.P.H. [e]
Angela M. Caliendo, M.D. PhD. [f]
Christian Hopfer, M.D. [c]
Evelyn Collins [b]

[a] University of Colorado Department of Pediatrics
[b] University of Rochester School of Nursing
[c] University of Colorado Department of Psychiatry
[d] Emory University, Rollins Public School of Health
[e] Columbia University, Mailman School of Public Health
[f] Brown University, Alpert Medical School
[g] Pacific Institute for Research and Evaluation
[h] Edna Bennett Pierce Prevention Research Center, Pennsylvania State University

Correspondence: David L. Olds, Ph.D.
University of Colorado Denver
13121 East 17th Avenue, MS8410
Aurora, CO 80045
phone: 303-724-2892; fax: 303-724-2901
e-mail: David.Olds@UCDenver.edu

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Abbreviations

T2 = Control Group
T4 = Nurse-visited Group
SE = Standard Error
LS = Least Square
ES = Effect Size (T4-T2 Mean Difference / pooled standard deviation)
AOR = adjusted odds ratio
AIR = adjusted incidence ratio
AHR = adjusted hazard ratio
CI = confidence interval
IR = incidence ratio
OR = odds ratio
SNAP=Supplemental Food and Nutrition Program
TANF=Temporary Assistance for Needy Families

STUDY OVERVIEW

This study is a longitudinal follow-up of 670 primarily African-American women and their 18-year-old firstborn children enrolled since 1990 in a randomized controlled trial (RCT) of prenatal and infancy home visiting by nurses. Nurses in this program are charged with improving pregnancy outcomes, child health and development, and maternal economic self-sufficiency.[1] This follow-up examines whether earlier program effects on maternal and child functioning [2-7] lead to less violent antisocial behavior, psychopathology, substance use and use-disorders, and risk for HIV; whether these effects are greater for those who carry genetic susceptibility to the environment and are at environmental risk; and whether program effects replicate those found with whites in an earlier trial.[8-10] Results from earlier phases of follow-up from this trial found that the Memphis program affected women's prenatal health, fertility, partner relations, and use of welfare; children's injuries, cognition, language, achievement, conduct, depression/anxiety, and use of substances through child age 12.[2-7] Program effects on maternal life-course were concentrated among mothers with higher psychological resources (better intellectual functioning, mental health, and sense of mastery), probably because higher-resource mothers could envision their success in the world of work, leading to better pregnancy planning and employment. Program effects on children were greater for those born to mothers with low psychological resources, because without help, low-resource mothers are especially challenged in the care of their children and their children function less well. Given the damaging effects of early stressors on developing neural circuitry, and given that many early neural developmental insults do not become fully evident until synaptic pruning is complete in late adolescence and early adulthood, there was reason to expect this early intervention would have enduring effects at youth age 18.

Hypotheses for Primary Grant

We specified hypotheses based upon the pattern of results found through child age 12, and separated them into primary and secondary hypotheses. Following the original formulation of hypotheses, we edited them to take into account results from the earlier Elmira trial[10] that were analyzed following the submission of the proposal for the current phase of follow-up in Memphis. We had originally hypothesized that program effects would be more pronounced for mothers and children living in the most disadvantaged neighborhoods in Memphis, but realized as these data were being gathered that virtually all of the participants in the Memphis trial lived in neighborhoods that were so disadvantaged that there was little meaningful variation among neighborhoods, and therefore removed this aspect of our hypotheses. We also found that it was impossible to consistently gather information from children's school records on outcomes like conduct grades from hundreds of schools, so substituted high school graduation as a secondary outcome. These refined hypotheses were specified prior to the completion of data gathering and any analysis of treatment-control differences. We specify the original hypotheses and then indicate the revised hypotheses for maternal and child outcomes. Compared to control-group counterparts:

Original Maternal Outcomes Hypotheses

1. **(Primary)** The program will continue to improve maternal life-course (fewer short inter-birth intervals, less use of welfare, more stable partner relations), especially for mothers with higher psychological resources.
2. **(Secondary)** The program will reduce maternal substance use disorders (SUDs) and depression, effects that will be more pronounced for a) mothers with low psychological resources, and b) those living in the most disadvantaged neighborhoods at registration.

Revised Maternal Outcome Hypotheses

1. **(Primary)** The program will continue to improve maternal life-course (reflected in total costs of welfare – SNAP, TANF, Medicaid), especially for mothers with higher psychological resources.
2. **(Secondary)** The program will reduce maternal substance use disorders (SUDs) and depression.

Original Child Outcomes Hypotheses

3. **(Primary)** The program will improve the health and development of firstborn children who will exhibit: a) superior cognitive, language, and academic functioning, and executive cognitive functioning (ECF); b) less depression and anxiety; c) fewer failed conduct grades and school disciplinary actions, d) less violent behavior and gang membership, and fewer arrests, juvenile detentions, and convictions - especially for crimes involving interpersonal violence.

4. **(Primary)** The program will reduce youth risk for HIV infection, including a) use of substances and SUDs; b) risky sexual behaviors; c) sexually transmitted infections (STIs) and d) pregnancies.
5. **(Primary)** Program effects on youth will be more pronounced for a) males, b) those born to low-resource mothers, and c) those living in the most disadvantaged neighborhoods at registration.

Revised Child Outcome Hypotheses

3. **(Primary)** The program will improve the health and development of firstborn children who will exhibit: a) superior cognitive, language, and academic functioning; b) less depression and anxiety; d) less gang membership, and fewer arrests, convictions, and self-reported antisocial behavior - especially for crimes involving interpersonal violence.
4. **(Primary)** The program will reduce youth risk for HIV infection, pregnancies, births, use of substances, and SUDs.
5. **(Secondary)** The program will improve firstborn children's executive cognitive functioning (ECF); and rates of high school graduation.
6. **(Primary)** Program effects on cognitive, language, and academic functioning, and executive cognitive functioning will be more pronounced among those born to low-resource mothers and on arrests and convictions among females.

Maternal and Child Outcomes (Not Revised)

7. **(Secondary)** Program effects on mothers and youth, in preliminary analyses, will be more pronounced for those with genetic vulnerabilities:
   a. Effects on youth depression and anxiety will be greater for those with low-activity genotypes (S/S, L_G/L_G, S/L_G) of the serotonin transporter gene (*SLC6A4*) promoter polymorphism, 5-HTTLPR, compared to those with high-activity genotypes (L_A/L_A); effects on these outcomes will be of intermediate magnitude for those with intermediate activity-level genotypes (S/L_A, L_A/L_G).
   b. Effects on youth violent antisocial behavior, SUDs, and risky sexual behavior will be more pronounced among males with the MAOA-LPR low activity alleles compared to males with MAOA-LPR high activity alleles, and among both males and females with 2 copies of the high-activity Val allele of the COMT Val158Met polymorphism compared to those with 2 copies of the low-activity met allele or heterozygotes.
   c. Effects on maternal SUDs will be concentrated among mothers with 2 copies of the Val158 alleles.
   d. Effects on child outcomes will be more pronounced among youth born to mothers with either 1) the S/S, S/L_G and "L_G/L_G" (low-activity) genotypes of 5-HTTLPR (conferring susceptibility for depression under adversity) or 2) 2 copies of the high activity COMT Val158 allele (conferring susceptibility to compromised ECF and SUDs under conditions of adversity).
8. **(Secondary)** Program effects on adolescent functioning will be explained by its improvement in prenatal health, early care of the child, maternal life-course, and earlier child academic and behavioral functioning.

Examination of Intervention Effects on Subsequent Children

With an administrative supplement, we addressed the following questions focused on subsequent children born within 5 years of the first child. Note that these questions were framed with no specific hypotheses about the degree to which particular subgroups would benefit from the intervention, given that intervention impact on pregnancy planning had been most pronounced on women with higher psychological resources.

1. To what degree does this program improve the health and development of subsequent children in terms of their a) language, academic, and executive cognitive functioning (ECF); b) depression and anxiety; c) failed conduct grades, d) violent behavior and gang membership, and e) arrests, juvenile detentions, and convictions, especially for violent crimes?
2. To what degree does this program reduce subsequent children's risk for HIV infection, including a) use and abuse of substances; b) risky sexual behaviors; c) sexually transmitted infections (STIs) and d) pregnancies?

3. To what degree are the program effects on subsequent children more pronounced for a) males, b) those born to high-resource mothers, and c) those living in the most disadvantaged neighborhoods at registration?
4. To what degree are program effects on subsequent children's functioning explained by its earlier impact on a) the timing and rates of subsequent births; b) families' use of welfare-related services; c) stability in partner relationships; d) improvements in neighborhood contexts; and e) antisocial behavior among the first-borns?

Aims of the Benefit-Cost Analysis

With an administrative supplement, we conducted a benefit-cost analysis of NFP in Memphis. The benefit-cost study was designed to:

1. **Estimate return on investment in Memphis NFP from the perspectives of government, society and individual participants.**

2. **Estimate the quality-adjusted life year (QALY) savings produced by the Memphis NFP**.

3. **Combine effectiveness estimates from Memphis NFP with those from other NFP evaluations and produce a combined estimate**.

4. **Develop a model that states can use to estimate the value of funding NFP programs**.-

5. **Compare the cost-effectiveness of the NFP to other commonly delivered childhood interventions**.

BACKGROUND AND SIGNIFICANCE

The Nurse-Family Partnership (NFP), the program examined in this trial, is different from most substance-abuse prevention efforts examined to date in that it focuses on improving early neuro-developmental, cognitive, and behavioral functioning of the child by improving prenatal health, reducing child abuse and neglect, and enhancing family economic self-sufficiency in the first two years of the child's life. These early alterations in biology, behavior, and family context are expected to shift the life-course trajectories of children living in highly disadvantaged families and neighborhoods away from psychopathology, SUDs, and risky sexual behaviors—all risks for HIV infection. Most substance-abuse preventive interventions have focused on school-age children in the pre-adolescent or adolescent age range, but Fishbein suggests that neuro-cognitive and socio-emotional risks rooted in early experience and biology can undermine the extent to which minority youth make use of conventional substance-use prevention efforts.[12]

Noting that adolescent SUDs are associated with childhood psychopathology and that treatment of childhood psychopathology can reduce subsequent SUDs, Kendall and Kessler[13] have recommended earlier treatment of childhood mental disorders. They question the value of preventive interventions on the grounds that many who need such interventions fail to participate because they have no sense of vulnerability to motivate participation. Low-income pregnant women bearing first babies, the target population served by the NFP, have profound senses of vulnerability during this specific time in their lives, however, that probably contributes to the high rates of participation in this prevention program.[1] Moreover, the program is now being replicated in hundreds of communities throughout the US.[14] Much of the policy impetus for the program, however, has been generated by the results of the Elmira trial (with a primarily white sample) on adolescent functioning through child age 15.[8-10] Replication of the Elmira findings, especially with different populations, is crucial. It also is important to gain a deeper understanding of its impact on adolescent SUDs, risk for HIV, psychopathology, and violence, and an understanding of those groups for whom the program does and does not work. In evaluating this proposal, it is important to appreciate the program's conceptual foundations. [1,15,16]

Epidemiologic and Developmental Foundations

Focus on Low-Income, Unmarried, and Teen Parents. The NFP registers low-income women having first births, and thus enrolls large portions of unmarried and adolescent mothers. These populations have higher rates of the problems the program was designed originally to address (e.g., poor birth outcomes, child abuse and neglect, and diminished parental economic self-sufficiency).[17,18]). Women bearing first children are particularly receptive to this service, and to the extent that they improve their prenatal health, care of their firstborns, and life-course they may apply those skills to subsequent children they choose to have.[1,19]

Program Content. Figure 1 shows the general conceptual model that has guided the nurses' work and how the program is thought to affect outcomes and moderate genetic vulnerabilities in the presence of stress. It is important to note that we assume that the program is operating in the context of high rates of neighborhood disadvantage and family poverty and stress, which are not shown explicitly in this figure. Moreover, given low rates of prenatal tobacco use in the Memphis sample, functional polymorphisms in GSTTI and DAT are not discussed in this proposal, even though they have been shown to intact with prenatal tobacco exposure to increase the risk for low birthweight and dysregulated child behavior.[20,21] Reduced exposures to prenatal toxicants, child abuse and neglect, dysregulated parenting, and untoward family environments are expected to shift the child's health and development toward greater behavioral regulation and interpersonal and cognitive competence, including reduced engagement with antisocial peers.

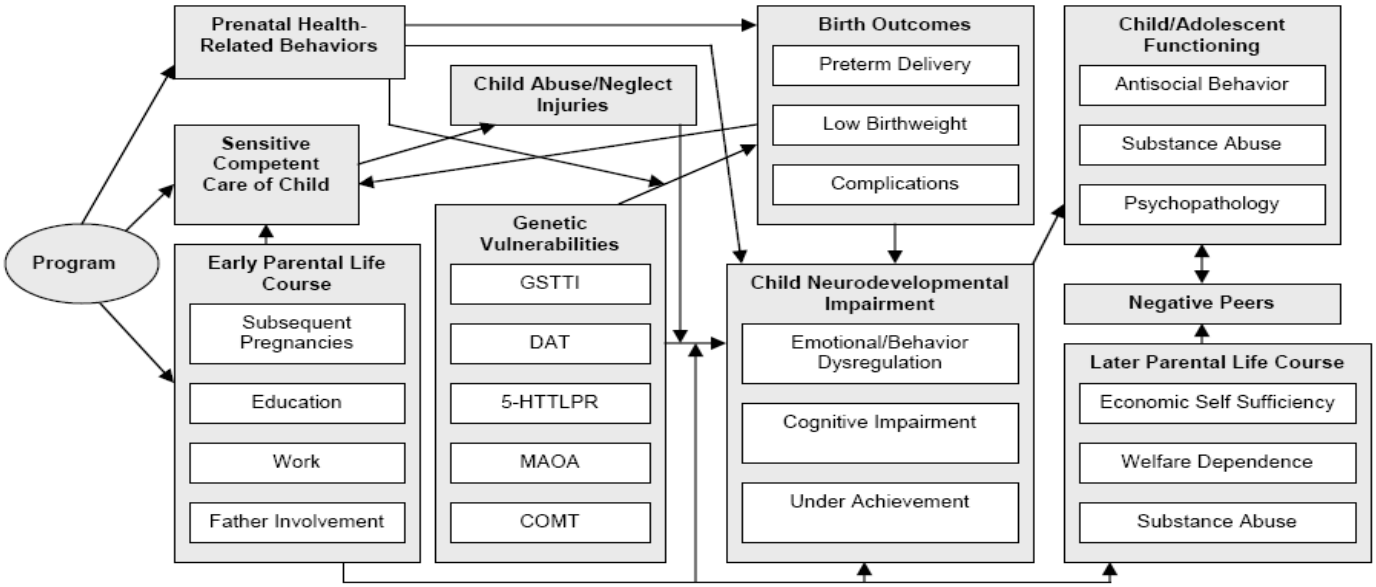


Figure 1. General Conceptual Model of Program Influences on Maternal and Child Health and Development

Evidence is accumulating that fetal and postnatal adversity, including prenatal exposures to alcohol and tobacco, produce sustained effects on cellular function and physiology (perinatal programming) which increase the risk for fetal growth restriction and subsequent behavioral and metabolic adaptations that, while increasing the likelihood that individuals will reach reproductive age, have maladaptive consequences for long-term behavioral health and chronic illness, including cardiovascular disease and diabetes.[22-25] The effects of these adversities on health and development are hypothesized to be mediated by their direct and indirect effects on the hypothalamic-pituitary-adrenal (HPA) axis: maternal adversity is thought to affect fetal growth through adrenal glucocorticoids; environmental adversity is thought to alter maternal physiology and behavior, which in turn programs HPA activity in the offspring. Thus, the perinatal period and the earliest years of the child's life are likely to be particularly important for the long-term health of humans and an opportune time for preventive intervention.

Nurse-Family Partnership nurses are charged with improving a) pregnancy outcomes by

improving women's prenatal health behaviors, b) the child's subsequent health and development by improving parents' early care of the child (especially reducing child maltreatment), and c) families' economic self-sufficiency by helping parents plan subsequent pregnancies and make informed choices about work, education, and partner relations. Their clinical strategies are informed by theories of human-ecology, attachment, and self-efficacy.[1,16].

Prenatal Health Behaviors. Prenatal tobacco and alcohol exposure increase the risk for fetal growth restriction,[26] preterm birth,[26], preterm birth,[26] and neurodevelopmental impairment (e.g., attention-deficit disorder, cognitive and language delays). [27-33] Children born with subtle neurological perturbations resulting from prenatal exposure to substances are more likely to be irritable and inconsolable,[34-36] making it more difficult for parents to care for them effectively. Improved prenatal health thus also helps parents become competent caregivers. The impacts of tobacco and alcohol exposure on birthweight and dysregulated behavior are moderated by genetic vulnerabilities.[20,21,37] Prenatal tobacco and alcohol use in the Memphis sample, however, were very low, although nurse-visited women, as hypothesized, did have lower rates of pregnancy-induced hypertension. Children exposed to hypertensive disorders of pregnancy and other obstetrical complications are at increased risk for violent aggression during adolescence.[38]

***Sensitive, Competent Care of the Child*.** Parents who empathize with and respond sensitively to their infants' cues are more likely to understand their competencies, leading to less maltreatment and unintentional injuries.[39] Competent early parenting is associated with better child behavioral regulation, language, and cognition.[39,40] Prolonged maltreatment can lead to chronically elevated stress hormones and low child serotonin levels,[41,42] which perturb this system and are implicated in stress-induced delays in neurodevelopment,[43] cognitive dysfunction,[43] dysregulated emotions,[43] and impulsive violence.[44] Early maltreatment is particularly damaging.[45,46] Later demanding, responsive, and positive parenting can provide some protection from the damaging effects of stressful environments and negative peer influences[47-49] on externalizing symptoms and substance use.[50-52] As outlined below, the Memphis program has produced a range of effects which strongly suggest that the nurses prevented child maltreatment and dysregulated caregiving in the first 2 years of life.

Early Parental Life Course. Closely spaced subsequent births undermine unmarried women's education and employment,[53] and limit their time and resources to nurture and protect their children. Married couples are more likely to achieve economic self-sufficiency, and their children are at lower risk for a host of problems.[54] Nurses promote fathers' involvement and help women make appropriate choices about the kinds of men they allow into their lives. The impact of father and partner involvement on child health depends upon the degree to which partners are antisocial.[55;56] Poverty early in life predicts compromised child educational achievement.[57] As noted below, the program has produced earlier effects on maternal life-course,[2-8] which we expect will endure in the next phase of follow-up, will affect women's susceptibility to depression and SUDs, and will contribute to enduring program effects on the child.

Modifiable Risks for Early-Onset Antisocial Behavior, Substance-Use Disorders, and Depression. Many of the prenatal and infancy risks addressed by this program are risks for early-onset antisocial behavior, substance use, and depression.[1-3,58-62] Prenatal tobacco and alcohol exposures, for example, are putative influences on children's disinhibited behaviors.[62] Children with early-onset conduct problems are more likely to have subtle neurodevelopmental deficits (such as problems with attention, impulsivity, and language) [34,38] that may contribute to, be caused by, or exacerbated by abusive and rejecting care early in life.[63;64] Moreover, childhood sexual abuse and physical trauma increase the likelihood of early substance use and risky sexual behaviors which increase the risk for HIV infection.[65;66] Frequent activation of the HPA system resulting from the chronic stress of abuse or neglect can produce high and prolonged glucocorticoid levels, which in turn can damage the developing hippocampus and other brain structures and impair attention, learning, and memory.[67] In studies with rodents, qualities of early care have been found to produce life-long effects on individuals' stress-reactivity independent of genetic background.[22] Thus, adolescents' impulse control, aggression, success in school, substance abuse, and risky sexual behavior are likely to be affected in part by the degree to which they were exposed to neurotoxic substances during pregnancy, or abused or neglected in their earliest years of life, even though these behaviors likely reflect, to some degree, genetic factors shared with their parents.[68]

In humans, aggressive and disinhibited behaviors that emerge prior to puberty are risks for adolescent SUDs,[69;70] antisocial behavior, and risky sexual behavior. Early onset antisocial behavior leads to more serious and violent offending that is distinguished from normative acting out in adolescence.[71;72] Children who develop Major Depressive Disorder (MDD) in childhood, compared to those who develop MDD later, are more likely to have perinatal insults, motor skill deficits, caretaker instability, and criminality, psychopathology and behavioral and socioemotional problems in their family of origin.[56] Youth who use substances perform poorly on neuropsychological tests measuring ECF, especially inattention, impulsivity, risky decision making, and verbal recognition memory.[73] There are indications from the literature on schizophrenia that errors in neuronal wiring during the earliest phases of brain development, while often manifest in early social, cognitive, and motor deficits, may not become fully evident in disabling disorder until synaptic pruning is complete – during late adolescence to young adulthood.[74] Early neuro-protective interventions may thus contribute to a range of functional benefits that are not fully evident until later stages of development.

Both conduct disorder (CD) and early substance use increase the risk for later SUDs and chronic antisocial behavior,[61;63;64;70;75-77]perhaps to some degree because these behaviors lead children into deviant peer groups and social contexts that reinforce their dysregulated behaviors. Moreover, children who begin using cannabis in adolescence (<17 years) are at greater risk for developing SUDs.[77] Adolescent substance use also is implicated in the development of adult antisocial behavior[78] and depression. Mood and anxiety disorders lead to adolescent substance-use problems to a greater extent in females than males.[79,80]

Integrity of ECF and its modulation of emotional responses to social stimuli may reflect key regulatory processes involved in drug abuse and related psychopathology. Impaired ECF compromises interpretation of social cues and undermines socially adaptive responses to stress.[81] The prefrontal cortex (PFC) is the primary neural regulatory mechanism sub-serving ECF;[81-83] its connections to the limbic system (e.g., the amygdala) modulate emotional responses to environmental and social stimuli.[12;81--87] Neural mechanisms underlying emotion contribute to impulse control and decision-making that may be modulated by the PFC and limbic system. These functions develop with distinct cognitive and emotional skills maturing at different times[88] that coincide with growth in the frontal lobe.[89-93] Because this neural circuitry is exquisitely sensitive to environmental influences, psychosocial stress due to factors such as abuse and neglect can impair the development of ECF and emotional regulation.[94-99] Prolonged stress exposures, as noted above, can cause chronically elevated stress hormones and perturbations in neurotransmitter activities that may delay the development of this circuitry and compromise cognitive, emotional, and behavioral regulation.[100;101] Given vulnerability of the PFC to stress, neurocognitive deficits may be more prevalent in low-income, high-crime neighborhoods, and families with significant dysfunction. Thus, developmentally relevant dimensions of ECF and emotional perception were examined at the 18-year follow-up, both as outcomes and mediators of outcomes, such as violence and SUDs.[102] Examining these outcomes is important given earlier program effects (discussed below) on hypertensive disorders of pregnancy, outcomes indicative of abuse and neglect (e.g., injury and death for preventable causes) and on children's cognition, achievement, and behavior.

Substance Use in Memphis Adolescents. In the Memphis City Schools in 2003, 30-day rates of cannabis use were 25.5% and 30-day rates of alcohol use were 34.4% among 11th graders.[103] Among 17-year-old substance users, 17% are estimated to have an SUD.[104] This means that there is substantial room for improvement and detection of possible program effects on substance use. The rate of SUDs should be about 6% in the current trial at child age 18; given reductions in early starting substance use at child age 12, there was a strong possibility that program effects would emerge in reduced SUDs by youth age 18 in the current trial.

Genetic Vulnerability to Compromised Mothering under Stress. Maternal behavior is a highly conserved set of capacities that is crucial for reproductive success.[105] Gene knockout studies and intervention trials with rodents show that perinatal experience is crucial in programming aspects of later maternal behavior;[105] this programming also appears to influence aspects of learning and memory. Many of the brain regions implicated in experimental interventions with rodents are the same as those implicated in mediating aspects of maternal behavior.[105] Findings with rodents suggest that maternal experience and behavior in the days following birth serves to "program" subsequent maternal behavior in

addition to establishing the offspring's level of HPA responsiveness to stress.[106-109] Extreme forms of maternal deprivation have been shown to have profoundly negative effects on the development of maternal behavior in adult non-human primates.[110] Rhesus monkey mothers who had been separated from their mothers at birth had lower levels of adequate caregiving among first-borns than they did among subsequent offspring.[110] The focus of the current intervention, which begins during the pregnancies of mothers with no previous live births, thus coincides with a period in maternal development in which caregiving is most vulnerable to intergenerational risks, current stress, and lack of support, and that may set the stage for future maternal behavior with subsequent offspring. As discussed below, polymorphisms in 5-HTTLPR and COMT val158met, given their putative role in the individual's regulation of stress[(e.g., 111-113)] and responsiveness to support (5-HTTLPR),[25] may play a role in moderating mothers' abilities to care competently for themselves and their children under conditions of extreme poverty, and teen- single-parenthood like those found in this sample, and may play a role in accounting for the intergenerational transmission of compromised parenting.[81;114-117]

Child Maltreatment, Adversity, and Genetic Vulnerability to Internalizing Problems, Behavioral Disinhibition, and Substance Use Disorders. Child abuse and neglect and early life adversity are non-specific factors that increase the risk for a host of later internalizing and externalizing problems (depression, post-traumatic stress disorder (PTSD), CD, antisocial personality disorder, as well as alcohol and substance use disorders)[118-121] but there are substantial differences in the degree to which individuals develop disorders in the context of these early adversities. Polymorphic variations in the 5-HTT and MAOA genes affect the individual's response to adversity, and thus may account for individual differences in the development of psychopathology in the context of prolonged and heightened adversity. Individuals with the short allele of the 5-HTTLPR polymorphism in the *SLC6A4* gene who experience maltreatment and life stress are at heightened risk for major depression, impulsivity, and substance use disorders in humans[111;122-124] and impulsivity and alcohol consumption in primates.[125;126] The literature does reveal inconsistencies, however, some of which may be explained by the age at which individuals experienced stress.[127;128] Social support may moderate the interaction of the low-expression variant of 5HTTLPR with the experience of child maltreatment in predicting depression.[129] While not entirely consistent,[130;131], the balance of evidence indicates that males with low-activity MAOA-LPR alleles and who experience child maltreatment are at greater risk for a variety of mental health problems, including attention deficit/hyperactivity and severe antisocial behavior, than are males with the high-activity MAOA-LPR alleles even if they experience child maltreatment. These gene x environment interactions are likely to increase individuals' risk for SUDs, unprotected sex during alcohol consumption, and HIV infection.[55;132;133]

Given other genetic and environmental moderating influences on development, the story is likely to be more complicated than revealed simply by polymorphisms in these two candidate genes and their interplay with environments.[134] COMT, for example, plays an important role in stress response, but the effect of COMT on the release of adrenocorticotrophin hormone (ACTH) may depend upon the presence of the low-expression variant of MAOA in the same individual.[135;136] Similarly, a recent study of the MAOA-LPR polymorphism and stress in females found that the interaction of stress with MAOA-LPR was supported by analyses that examined corresponding haplotypes as well as specific alleles, reinforcing the importance of the MAOA-system and these vulnerability alleles.[137] The evidence for the role of MAOA and 5-HTT in moderating stress reactivity was thus sufficiently compelling to warrant a disciplined examination of their possible role in accounting for individual differences in the impact of the NFP intervention.

The Role of 5-HTT in Moderating Stress Reactivity and Risk for Depression. The serotonin transporter gene (5-HTT) is involved in the reuptake of serotonin in brain synapses. A functional promoter polymorphism, 5-HTTLPR, consists of a varying number of copies of a 20-23 repeat sequence. Individuals with the short allele "S" (14 repeats) have less efficient transcription, which leads to deficient serotonin reuptake compared to those with the long allele (L) (16 repeats).[111] The lower activity 5-HTTLPR S allele has a significant but quantitatively small role in anxiety/dysphoria[138] and alcoholism;[139] 5-HTT has been identified as a stress resiliency gene, a role confirmed and expanded by neuroimaging studies. The S allele has been associated with greater activation of the amygdala in response to fearful stimuli[140;141] as well as uncoupling of the feedback circuit between the amygdala and the perigenual

cingulate that is responsible for the extinction of negative affect. This circuit accounts for 30% of the variance in anxious temperament.[142] Conversely, S allele carriers show greater coupling between the amygdala and ventromedial prefrontal cortex,[141] a fronto-limbic circuit that influences stress responses by the HPA Axis[143] and implicated in mood dysregulation and major depression. It has now been shown that 5-HTTLPR is functionally triallelic.[144] As noted below, at 12 years of age, nurse-visited children reported fewer internalizing disorders than did those in the control group. We planned to examine the extent to which these earlier program effects and those hypothesized depression and anxiety effects at age 18 were concentrated in those hypothesized to be particularly vulnerable to stress as a results of their carrying the 5-HTTLPR low activity alleles.

The Role of MAOA in Moderating Stress Reactivity and Risk for Impulsivity, Violence, and SUD. MAOA is on the X-chromosome and encodes the enzyme Monoamine Oxidase A (MAOA; EC 1.4.3.4), which metabolizes monoamines, including norepinephrine (NE), dopamine (DA), and serotonin (5-HT). A common functional variable number tandem repeat (VNTR) polymorphism in the promoter region of the monoamine oxidase A (MAOA) gene has been found to have five alleles containing 2, 3, 3.5, 4, and 5 copies of a 30-base pair (bp) tandem repeat that influences transcription. Enzyme expression is 2-10 times higher for the 3.5 and 4 repeats than for the 3 repeat.[145] The low activity variant has been of particular interest in explaining the high rates of aggression, delinquency, and substance use disorders found in males,[145;146] especially in the presence of early adversity.[132] Given that the MAOA gene is located on the X chromosome, there is greater statistical power to examine the relationship between early life adversity and the low-activity MAOA-LPR variant among males. There is less consistency in this relationship among females, perhaps because of lower statistical power due to the lower prevalence of the low-activity genotype among females, or perhaps because sex hormones such as testosterone interact with this MAOA genotype.[147] On the other hand, the MAOA gene appears to escape X-inactivation in females.[148] This conceivably results in higher brain MAOA expression for female high activity homozygotes than male high activity hemizygotes. Indeed, a recent study among American Indian females found that MAOA-LPR variant in combination with childhood sexual abuse increased the risk for alcohol use disorders (AUD) and especially AUD in combination with antisocial personality disorders.[137] In one study, the low-activity MAOA-LPR variant was associated with children's experience of abuse and neglect,[149] which emphasizes the importance of examining possible GE correlations in these types of studies. In the current study, there are indications that males in the intervention group are showing the greatest benefits in conduct at school and academic achievement. As noted below, we began preliminary analyses to examine whether these benefits for males are particularly pronounced for those with the low activity MAOA-LPR alleles, but the analysis requires more careful consideration of the validity of outcomes.

COMT Polymorphism and Response to Stress. Catechol-O-methyltransferase (COMT) plays an important role in the metabolism of CNS dopamine and norepinephrine in the prefrontal cortex. To date, there is no evidence to suggest a gene x environment interaction for COMT, but there is reason to believe that such interactions might exist. A common COMT polymorphism is responsible for a 3 to 4 fold variation in enzyme activity.[150] The frequency of the lower activity Met158 allele (COMT-L) is 0.22–0.38 in African-Americans and 0.44–0.53 in Caucasians. The higher activity Val158 allele (COMT-H) is related to compromised ECF,[112;151-153] drug abuse[154-156] and adult psychosis in adolescent cannabis users.[113] Moreover, recent evidence indicates that children with ADHD are more likely to develop childhood-onset CD if they have both the val/val genotype and have experienced prenatal adversity (reflected by low birthweight).[157] The Met158 allele, on the other hand, is linked with anxious temperaments, increased emotionality, and decreased pain threshold.[158-160] Thus, COMT genotype appears to play an important role in the balance between emotional resilience and vulnerability to stress. The putative increased vulnerability of Met158 allele carriers to stress may be more apparent in women because of sexually dimorphic effects in the COMT-anxiety association.[158;159] The limited number of women likely to carry the Met158 allele in this sample, however, prevents us from examining this subgroup as a moderator of treatment impact. As noted below, we have seen program effects on outcomes such as early starting substance use and compromised academic performance among children. We also see a trend for nurse-visited women to report lower use of substances at child age 9. We wish to see whether these effects are

more pronounced among those who carry 2 copies of the Val158 allele, and whether those with this genotype benefit the most from the intervention with respect to maternal and child SUDs at child age 18.

Differential Susceptibility Theory. Our original hypotheses about the role of specific functional classes of genes was based upon a diathesis-stress model which focused on vulnerability genes thought to affect internalizing and externalizing disorders under conditions of environmental adversity.[55,111,] In recent years, an alternative person-×-environment framework has been advanced which proposes that the same personal characteristics that make a child particularly vulnerable to adversity may also enable him or her to benefit more than others from a supportive environment.[161-163] This differential suceptibility theory postulates that some individuals are more developmentally responsive than others to the whole range of environmental experience. Empirical work aimed at examining this hypothesis is now emerging that exploits randomized controlled trials of parenting interventions to put this theory to test. RCT's reduce problems with gene x environment correlations that have plagued work in this area. Meta-analyses of randomized trials that have examined serotonin-sytem and dopaminergic-system genes -- "plasticity alleles" – as moderators of intervention impact indeed appear to play a role in increasing sensitivity to parenting interventions tested in trials.[164]

Adolescent Substance Use, Risky Sexual Behavior, and Risk for HIV. Neurobehavioral disinhibition reflects a latent trait characterized by behavioral under-control, affect dysregulation, and compromised ECF that increases youths' early-starting substance use and risk for SUD.[69;165] Elements of this trait, such as sensation seeking, increase individuals' tendencies to engage frequently in risky sexual behavior.[166] It is thus relevant that 49% of pregnant mothers enrolled in the current trial were <18 at registration. It is likely that compromised ECF mediates the relationship between the Val/Val genotype and risky sexual behavior, given that Val/Val undermines ECF and increases risk for polysubstance abuse.[156] Adolescent alcohol use increases risk for sexually transmitted diseases (STDs).[167;168]

While infrequently occurring (48 per 100,000), HIV infection is increased among low-income, African-American women living in the South, especially among substance users and those with STDs.[169;170] There is increased efficiency of transmission of HIV in the presence of co-infection with bacterial STDs or trichomoniasis.[171-173] Among sexually active 14–18-year-old females in Birmingham AL, 28.7% had at least one STD (either *N gonorrhoeae, C. trachomatis, or T vaginalis)* and 5.5% had two or more and infrequent parental monitoring predicted a 2-fold increase in infection.[174] In 2003, 55% of African-American 11th graders in Memphis City Schools had had sexual intercourse within 3 months of the interview; 73% had ever had intercourse, while 31% reported four or more sexual partners by the 11th grade.[103]

Given the health problems to be examined in the next phase of follow-up in this trial, it is important to emphasize that the NFP program reduced many of the prenatal, infant, and childhood factors discussed above that increase risk for violent antisocial behavior, psychopathology, SUDs and HIV infection.

PRELIMINARY STUDIES

Tested with a primarily white sample in the Elmira trial, the NFP program produced effects consistent with the program model, that on average tended to be greater for families at greater social disadvantage and where mothers were more psychologically vulnerable.[1-10] These effects were translated into cost savings.[175;176] The Memphis trial was designed to test the effects of the program with a large sample of very low-income African-Americans living in a major urban area, when the program was administered through a local health department, and the program developers had limited involvement in its implementation. In this trial, 1,138 low-income pregnant women (98% unmarried, 67% <19 years old, 92% African-American) were randomly assigned to experimental or comparison services; 742 were followed after delivery. The Memphis sample has resided in extraordinarily stressful neighborhoods and has endured extreme poverty. At registration, the mean level of neighborhood disorganization (assessed by census tract data at the block group and using the Lauritsen scale[177]) was 3.43 SD above the national mean, i.e., the average level of adversity in the sample neighborhoods was among the worst in the nation (in the top 1000th). 85% of the sample had incomes below the federal poverty guidelines. Design details are provided below and in the published articles. The differences in

neighborhood disorganization among participants in the 3 trials of the NFP is illustrated in Figure 2.

Given results in Elmira, we hypothesized that program effects on parenting and child outcomes would be greater for the group defined by mothers having fewer psychological resources (poorer mental health, intellectual functioning, and self-efficacy/mastery). We found support for this hypothesis [2-6] and that program effects on maternal life-course, especially in planning subsequent pregnancies, were concentrated among women with initially higher levels of psychological resources.[6] We interpreted this as a reflection of nurse-visited higher-resource women's ability to secure employment and manage care of their children simultaneously, providing high-resource mothers with motivation to plan future pregnancies; nurse-visited low-resource mothers had difficulty balancing these tasks and envisioning success in the world of work, so they had fewer reasons to plan future pregnancies, and instead focused their resources on care of their children. Details of earlier findings are provided below.

Maternal and Infant Outcomes

Prenatal Health, Care-Giving, and Injuries. Nurse-visited mothers, compared to control-group counterparts, exhibited superior prenatal health behaviors, fewer obstetric complications and infections, and better care of their children; their children had fewer health-care encounters for injuries/ingestions (Table 1). Program effects on care-giving and injuries were greater for mothers with low psychological resources. Figure 3 shows regressions of number of days children were hospitalized for injuries or ingestions from birth to age 2 on maternal psychological resources, fitted separately by treatment assignment. This figure emphasizes that the program effects on injuries and other child outcomes were concentrated on children born to mothers at greatest risk for compromised care-giving because of their limited psychological resources. Program impact on days hospitalized for injuries/ ingestions was limited to children with mothers in the lower half of the maternal psychological resource distribution (standardized to a mean of 100 and a standard deviation of 10). Table 1 shows that program effects on most child outcomes were greater for those born to the most vulnerable mothers. Discerning program impact on child abuse and neglect must be inferred from several sources of data (e.g., treatment-control differences in children's injuries revealed in their medical records, observations of infants' responses to their parents in laboratory observation paradigms), given that Tennessee child protection and child welfare records are not available prior to 2001, because of inadequacies in their earlier record keeping system. Moreover, such records under-estimate abuse[178] and are subject to surveillance bias.[179]

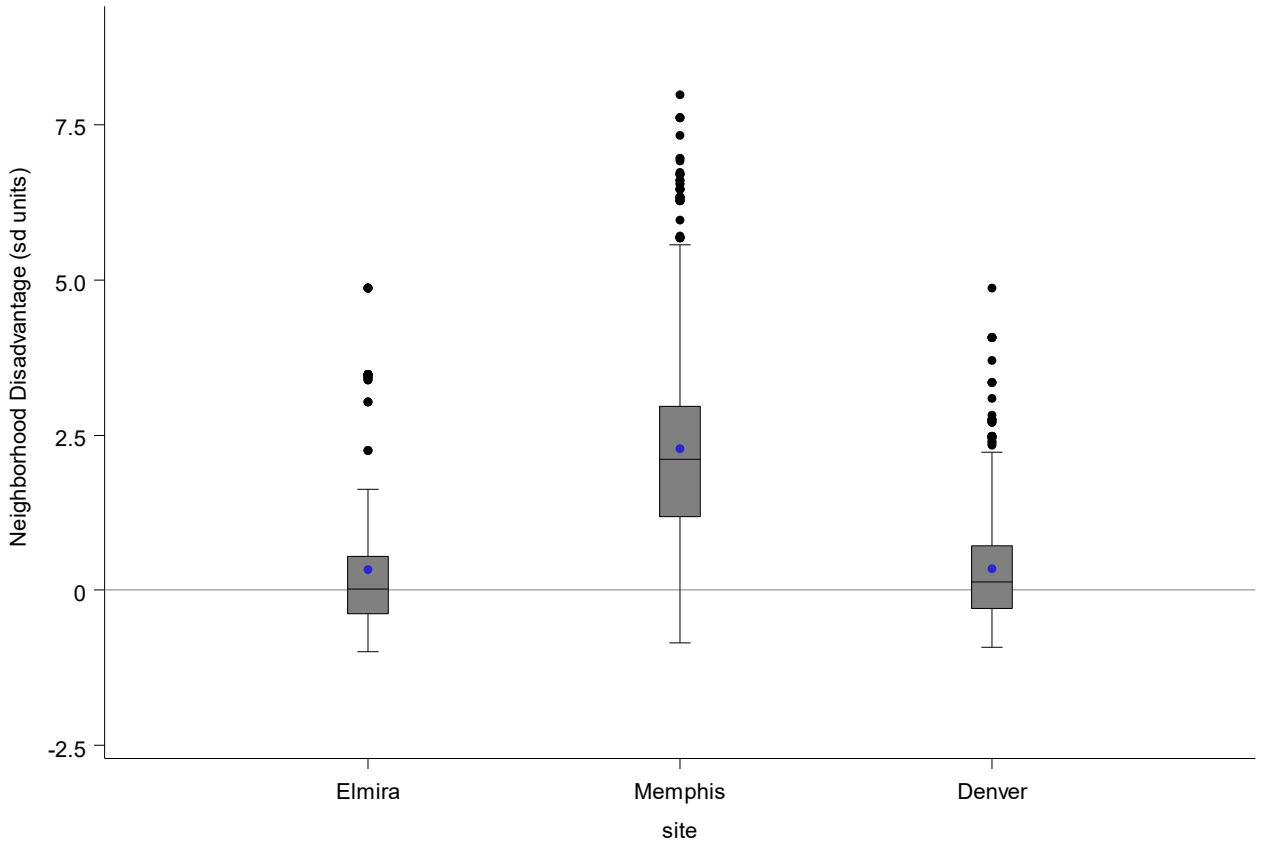


Figure 2. Box and whiskers plots of the distributions of neighborhood disadvantage scores at registration for participants in the Elmira, Memphis, and Denver trials of the NFP.

Maternal Life-Course. As shown in Table 1, the program also produced consistent effects on maternal life-course (e.g., increased stability of partner relationships; reduced fertility, use of food stamps, and welfare). Effects on fertility outcomes, like closely spaced subsequent births (<2 years), were more pronounced for higher-resource mothers. At child age 9, as a trend, nurse-visited mothers also reported using fewer different types of substances (p=.075).

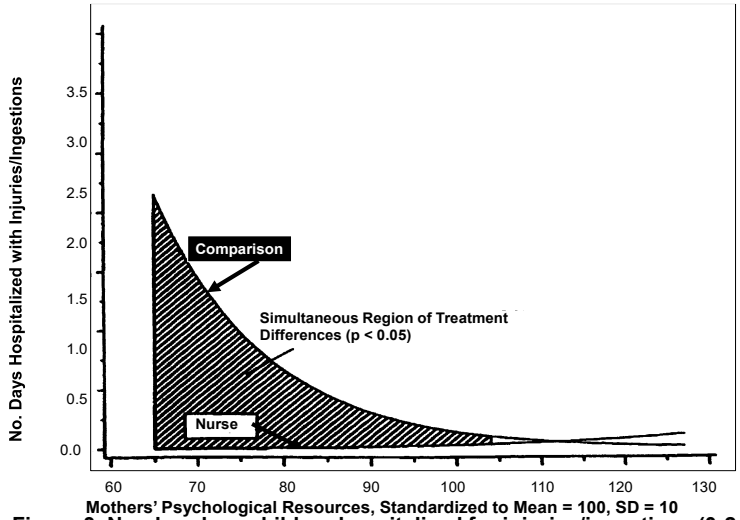
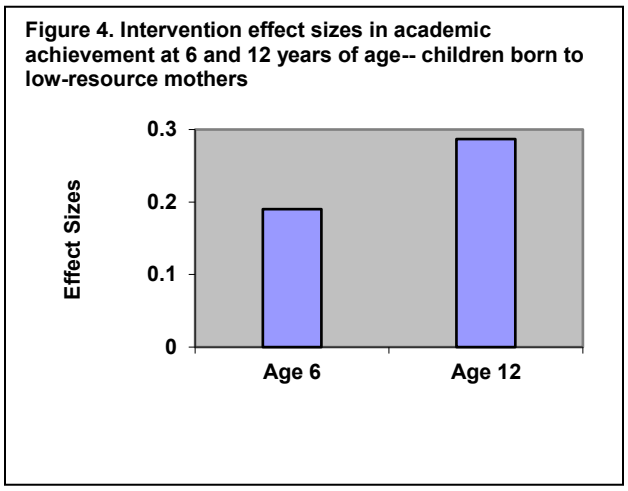


Figure 3. Number days children hospitalized for injuries/ingestions (0-2 yr) by maternal psychological resources and treatment condition -



Child Functioning in Elementary/Middle School

The program improved also child functioning from age 6 to 12, as can be seen in Table 1. Effects were greater for children born to low-resource mothers, given the particularly poor functioning of those in the control-group.

Cognition, Language, and Achievement. The program improved children's cognition and language at age 6. Between age 6 and 12, the program continued to improve children's academic achievement test scores, an effect limited to children born to mothers with low psychological resources. Importantly, program impact on achievement among children born to low-resource mothers increased in effect sizes from 6 to 12 years (see Table 1 and Figure 4) as cognitive demands of the tests increased. These effects were particularly strong for males and in math achievement and gave us reason to expect continued growth in impact as children matured.

Mental Health, Behavioral Regulation, Substance Use, and Death. Beginning at child age 6, program effects began to emerge on first born children's emotional and behavioral regulation. Nurse-visited children born to low-resource mothers revealed less dysregulated aggression and incoherence in response to the MacArthur Story Stems.[180] The program effect on coherence was particularly strong in the presence of high emotional arousal,[4] a pattern consistent with greater PFC moderation of limbic system reactions to stress. By age 12, nurse-visited children reported fewer internalizing disorders (borderline/clinical range) on the CBCL (Figure 5). [6] By age 12, nurse-visited children also reported substantially lower rates of 30-day tobacco, alcohol and marijuana use; fewer days of using the 3 substances, and using fewer different types of substances.[6] The program effect on early starting substance use was even greater when the counts of days of using substances or the counts of types of substances (indicators of greater severity) were used as the outcomes. We thus expected to find corresponding effects for SUDs for the 18-year-old youth at current next phase of follow-up.

Of particular note, there was a trend (p=.08) for nurse-visited firstborn children to die less frequently in the first 9 years of the child's life (10/498 vs. 1/222 live births);[7] 9 of the 10 control-group deaths were due to preventable causes (preterm delivery, Sudden Infant Death Syndrome, or injury); one death in the control group and the only death in the nurse-visited group were due to non-preventable causes (chromosomal anomalies, multiple congenital anomalies)[7] Two of the injury deaths in the control group were by firearm. By age 12, another nurse-visited child had died due to a brain tumor (not preventable). When viewed in light of earlier program effects on childhood injuries, these mortality data suggest that nurses helped parents reduce their children's exposure to serious, life-threatening adversities.

Table 1. Program effects on selected prenatal health, care-giving, injuries, maternal life-course, and child outcomes through child age 12

Variable	Sample	Comparison	Nurse	Comp vs. Nurse	
Prenatal Health after Enrollment		**Mean/Rate**	**Mean/Rate**	**p-value**	**Effect**
Pregnancy induced hypertension, %	Whole	20.0	13.0	.009	OR=0.65
Incidence of yeast infections after randomization	Whole	0.19	0.14	.05	IR=0.74
Sensitive, Competent Care of Child					
Beliefs associated with child abuse, Bavolek total score, 6-24 mo	Whole Low-Resource	100.5 102.5	98.7 100.2	.003 ≤.01	ES=-0.23 ES=-0.29
Emotional/cognitive stimulation (Home total score) 12 & 24 mo	Whole Low-Resource	30.9 30.3	32.3 31.5	.003 ≤.05	ES=0.24 ES=0.21
Child responsiveness, NCAST child total score, 6-24 mo	Whole Low-Resource	17.4 17.2	17.7 17.9	NS ≤.05	ES=-0.09 ES=-0.19
Injuries/Ingestions in Medical Record					
Incidence of encounters (all types)—Injuries/ingestions, 0-24 mo	Whole Low-Resource	0.56 0.67	0.43 0.41	.05 ≤.01	IR=0.77 IR=0.61
Incidence of hospitalizations—Injuries/ingestions, 0-24 mo	Whole Low-Resource	0.03 0.04	0.01 0.01	.01 <.10	IR=0.33 IR=0.25
Incidence of days hospitalized—Injuries/ingestions, 0-24 mo	Whole Low-Resource	0.18 0.26	0.04 0.02	.0003 ≤.01	IR=0.22 IR=0.08
Maternal Life-Course					
Count of Substances Used – child age 9	Whole	0.17	0.10	.075	IR=0.62

Count of closely spaced subsequent births – age 12	Whole	0.51	0.34	.019	IR=0.67
No. of Months with Partner, 6-12 years	Whole	57.89	68.11	.010	ES=-0.20
Food stamps use (avg. mos./yr), 0-12 years	Whole	7.19	6.54	.022	ES=0.13
AFDC/TANF use (avg. mos./yr), 0-12 years	Whole	5.30	4.69	.030	ES=0.12
Cognition, Language, & Achievement					
Mental Processing Composite (KABC) - age 6	Whole Low-Resource	90.24 87.64	92.34 90.49	.03 .03	ES=0.18 ES=0.25
Receptive vocabulary (PPVT) - age 6	Whole Low-Resource	82.13 79.08	84.32 81.75	.04 .07	ES=0.17 ES=0.21
Academic Achievement (reading + math) – age 6	Whole Low-Resource	91.17 88.69	91.65 91.07	.630 .084	ES=0.04 ES=0.19
Academic Achievement (reading + math) – age 12	Whole Low-Resource	87.94 85.66	89.23 88.77	.140 .009	ES=0.12 ES=0.29
Emotional/Behavioral Regulation, Mental Health, Substance Use, Death – First Born					
Dysregulated Aggression- MSSB - age 6	Whole Low-Resource	100.26 101.10	99.24 98.58	.26 .04	ES=-0.10 ES=-0.25
Incoherent Stories- MSSB - age 6	Whole Low-Resource	25.22 29.84	21.15 20.90	.07 .006	ES=-0.16 ES=-0.34
% Total Problems - Borderline/Clinical - CLCB - age 6	Whole	5.4	1.8	.04	OR=0.32
Count of Failed Conduct – males (grades 1-6)	Whole	0.10	0.06	.044	IR=0.56
Infant/Childhood Death 0-9 years	Whole	20.08/1000	4.5/1000	.080	OR=0.22
% used alcohol, cigarettes, or cannabis - age 12	Whole	5.2	1.6	.024	OR=0.29
No. days used substances-last 30 days - age 12	Whole	0.18	0.03	<.001	IR=0.17
Ever Sent to Juvenile Detention - age 12	Whole	9.4	7.2	.080	OR=0.52
% Internalizing Disorders (borderline/clinical – age12	Whole	31	22	.044	OR=0.63

Earlier program impacts on maternal mastery, partner stability, inter-birth intervals, and welfare use all helped mediate program effects on the socio-emotional health of the 6-year-olds, a pattern of results consistent with the theory shown in Figure 1. These findings need to be understood in the context of data on the life-course development of antisocial behavior. It is generally accepted that children who begin expressing antisocial behavior early in life (typically before puberty) are at heightened risk for violent, life-course persistent offending, and antisocial personality disorder.[63] Moreover, early dysregulated behavior is best predicted by interactions between neurodevelopmental problems and child maltreatment.[63] The more prevalent, but less serious adolescent-limited form of antisocial behavior[63;181] is thus less amenable to this intervention. This program is most likely to reduce early-onset, violent, persistent antisocial behavior.

The program effect on early substance use is particularly important, as early starters are at much greater risk for SUDs.[59] We conducted analyses in the control group that compared those who used any substance (n=20) by age 12 to the rest of the control group (also highly disadvantaged), and found that those who did had much poorer early functioning than those who abstained; space limitations prevent elaboration. The program reduced many of the earlier stressors and adverse outcomes associated with starting early. We also compared those in the control group who by age 12 had self-reported internalizing disorders (n=126) to those who did not and found that those with internalizing disorders also were at significantly greater risk than their counterparts without internalizing disorders (n=268). As with early starting substance use, the program affected many of the earlier stressors and child outcomes associated with age-12 internalizing disorders.

Implications for Later Psychopathology and SUDs. Program effects on children's academic, mental health, and behavioral functioning, including emergent use of substances through child age 12, led us to hypothesize that the program would continue to affect serious antisocial behavior in mid-adolescence, when risk-taking and antisocial behaviors reach their peak. Given that program impact on academic achievement is particularly strong for boys born to low-resource mothers and that boys born to low-resource mothers in the control group are declining in academic achievement over time, we expected that 12-year-old control-group children who used substances would be at much greater risk for

developing SUDs and becoming more violent and antisocial as they reach mid-adolescence. We expected that children's substance use and abuse would increase by age 18, but especially among control-group males, since they were expected to have fewer attachments to school and conventional life prospects due in part to increasing problems in school. These findings led us to expect greater differentiation of program effects by child gender at age 18. For boys, we expected that the program would reduce violent offending, involvement in the criminal justice system, and SUDs as these problems become more prevalent. Among females, we expect to see increasing program effects on depression/anxiety, SUDs, and general criminality.

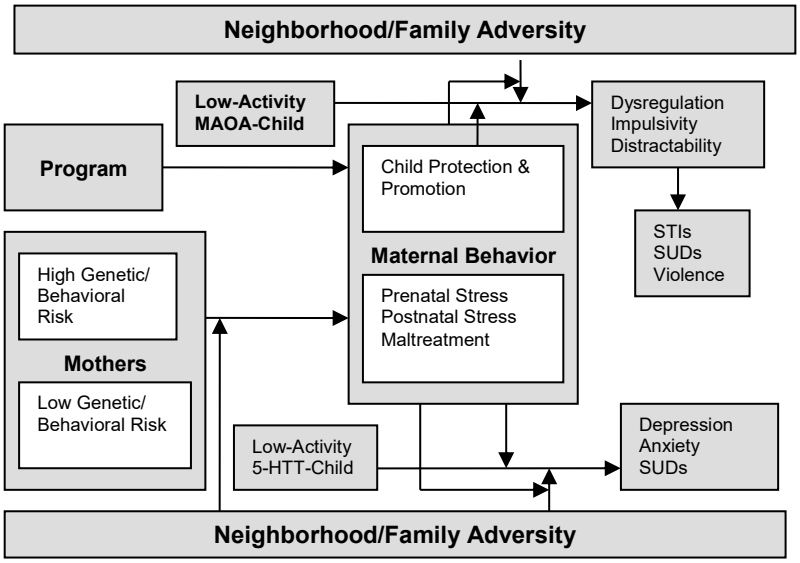
Hypothesized Greater Effect on Mothers Who Experience Stress and Are Genetically Susceptible

The degree of stress and support experienced by mothers in the period surrounding birth may have long-lasting effects on stress-reactivity in the offspring as well as long-lasting effects on maternal care-giving.[105-107;114] We therefore hypothesized that genetically-based individual differences in maternal susceptibility to environmental conditions would affect the degree to which care was compromised in the presence of environmental adversity and the degree to which the program is beneficial to particular mothers (Figure 5). The greater effect of the program on qualities of care-giving and children born to mothers with low psychological resources may reflect, at least in part, moderation of genetic vulnerabilities to stress (low activity alleles of 5-HTTLPR) and compromised ECF (COMT high activity alleles) under the significant levels of family- and neighborhood poverty found in the participants in the Memphis trial. Mothers with 2 copies of the low-activity variants of the 5-HTTLPR polymorphism giving birth for the first time, for example, may be particularly sensitive to developing internalizing disorders and compromised caregiving in response to environmental stressors, which may make this sub-group more responsive to the beneficial effects of the intervention. Mothers with two copies of the high-activity alleles of the COMT polymorphism, on the other hand, may be more susceptible to compromised ECF in the presence of stress, which in turn may make them more susceptible to impulsive behavior and substance abuse under conditions of stress, which creates a separate pathway through which maternal care may be compromised in environments characterized by stress, disorganization, and pressures to engage in substance use and other antisocial behaviors.

Hypothesized Program Impact on Genetically Susceptible Children

Program effects on children observed to date tend to be greater among those born to mothers who at registration lacked the resources to manage adversity in their lives (low psychological resources). Figure 5 shows more precisely how the program was hypothesized to moderate the interaction of stressful environmental conditions with the low activity variants of 5-HTTLPR and MAOA-LPR in the children. The nurses are thought to reduce stress on the developing child in two primary ways. The first involves the nurses' directly reducing child abuse and neglect. The second involves the nurses' activation of parents' instincts to protect their children from threats such as abusive boyfriends or gang activities in the neighborhood. We have only indirect evidence to support these hypothesized mechanisms centered on parental care, but the evidence summarized above (e.g., reduced injuries and deaths for preventable causes, reductions in parents' beliefs associated with child maltreatment) supports this characterization of program impact. By reducing child maltreatment and protecting their children from threatening environments, nurse-visited mothers are hypothesized to mitigate stressful environments that in the presence of the low activity MAOA-LPR variant in male

Figure 5. Hypothesized program moderation of gene-environment interactions that increase behavioral and emotional dysregulation



children increase risk for impulsivity and violence[132] and that in the presence of the low activity variants of 5-HTTLPR increase risk for depression.[111]

With improved behavioral regulation, language, and cognitive skills throughout their first 12 years of life, nurse-visited children experience greater success in school, which increases their motivation to find socially acceptable roles and avoid life styles that increase their susceptibility to SUDs, risky sexual behavior, pregnancy, HIV exposure, gang membership, and violence, effects that we hypothesize are more frequently occurring among children who are both genetically vulnerable and exposed to highly stressful environments, especially early in development. Moreover, to the extent that mothers have fewer closely spaced subsequent births, they have time and resources to protect those children they do have and to improve their economic conditions. While we expect program effects to be evident at both the main effect level and for those born to low-resource mothers, we think that the hypothesized genetic susceptibility factors will further elucidate those at risk and those who benefit the most from the intervention.

RESEARCH DESIGN AND METHODS

Sampling Design

Detailed descriptions of the research design and program can be found in our published reports. [2-9]

Original Sample Characteristics. We invited 1,290 women from the obstetrical clinic of the Regional Medical Center in Memphis to participate. We recruited women <29 weeks pregnant if they had no previous live births, no specific chronic illnesses thought to contribute to fetal growth retardation or preterm delivery, and at least 2 sociodemographic risks: a) unmarried, b) less than 12 years of education, c) unemployed. Eighty-eight percent (1138/1290) completed informed consent and were randomized to 1 of 4 treatment conditions described below. All low-income women in Memphis registered for prenatal care at this clinic, which meant that we enrolled nearly the entire population during the 1990–1991 enrollment period. The study was designed to follow 742 families in two treatment conditions after delivery. 92% of the women were African-American, 98% were unmarried, 67% were <19 years of age at registration, 85% came from households with incomes < federal poverty guidelines, and 9% smoked cigarettes. At randomization, there were no treatment differences in women's background characteristics.

Randomization. After the completion of informed consent and baseline interviews, identifying information on participants was entered into a computer program that randomized women to treatment conditions. The randomization methods were extensions of Soares and Wu.[182] The model on which we based the randomization included 5 classification factors: maternal race, chronological age (4 levels), gestational age at enrollment, employment status of head of household and geographic region of residence (4 regions).

Statistical Power in the Original Design. We conducted power calculations to determine the number and proportion of subjects to assign to treatment and control conditions while minimizing costs in the initial study period (prenatal through child age 2). This allowed disproportionate assignment of women to treatment and control conditions and a reduction in number of families followed into the postnatal phase of the trial. Given high rates of sample retention, the original power calculations hold.

Treatment Conditions

Treatment 1 - Transportation during Pregnancy. The 166 families in this treatment condition received free round-trip taxicab transportation for scheduled prenatal care appointments. This group did not receive any postpartum services or assessments.

Treatment 2 - Transportation during Pregnancy and Screening during Infancy. The 514 families in this group received: 1) free transportation for scheduled prenatal care; and 2) developmental screening and referral services for the child at the 6th, 12th, and 24th months of the child's life.

Treatment 3 - Transportation and Nurse-Visitation during Pregnancy Only. The 230 families in this treatment condition received: 1) free transportation for scheduled prenatal care; and 2) intensive nurse home-visitation services during pregnancy and one postpartum visit in the hospital before discharge and one postpartum visit in the home. This group did not receive any postpartum services or assessments.

Treatment 4 - Transportation and Nurse-Visitation during Pregnancy and Infancy. The 228 families in this condition received: 1) free transportation for scheduled prenatal care; 2) intensive nurse home-visitation services during pregnancy and through the child's second birthday; and 3) developmental screening and referral services for the child at the 6th, 12th, and 24th months of the child's life.

Program Plan and Implementation

NFP nurses were charged with 1) improving the outcomes of pregnancy by helping women improve their prenatal health; 2) improving children's subsequent health and development by helping mothers and other caregivers provide more competent care of their babies; and 3) improving women's own health and development by helping them develop self-care practices, plan subsequent pregnancies, complete their educations, and find work. The program guidelines included specific activities to support women's protection of their personal health, including eating balanced diets, avoiding use of substances, exercise, hygiene, advocating for themselves with providers of office-based care, and guidance on risky behavior and social relationships.[1] The program guidelines provided extensive support to mothers and other caregivers in their efforts to care well for their children, including promoting "back to sleep" and safe bedding, reducing hazards in the home, regulated and responsive care of the child.[1,16]

The home-visitation program was carried out by the Memphis/Shelby County Health Department during a nursing shortage, which contributed to staff turnover during the conduct of the trial. Program designers were minimally involved in program implementation. These features of program implementation, along with registration of nearly the entire population, make this nearly an effectiveness trial on the efficacy/effectiveness spectrum.

Research Activities for Current Phase of Follow Up

The 18-year follow-up study consisted of a longitudinal follow-up of women and firstborn youth who had not declined participation or died before the first child turned 18. A supplement to this grant allowed us to examine the health and development of subsequent children born within the first five years following birth of the first child. The functioning of subsequent children follows the exact same measurement plan followed for firstborn children with the exception of examining high school graduation. For the postnatal phase of the trial, we followed families assigned to treatments 2 (n=514) and 4 (n=228) for primary assessments. As shown in Table 2, which provides the CONSORT information for mothers and first-born children, we have been remarkably successful in retaining the sample through the most recent follow-up. At child age 18, we completed assessments on 618 mothers and 629 youth, for completion rates of 83% of the mothers and 85% of the children originally randomized, and 90% of the mothers and 92% of the children who had not died prior to the 18-year assessment. These assessments do not include an additional 16 cases where the biological mother was not the custodial parent and an interview was conducted with the child's guardian. We discuss CONSORT information for subsequent children in the results section below. Obtaining high rates of sample retention is crucial in ensuring accurate estimates of intervention impact, as simulation analyses of the 12 year follow-up of this trial have indicated that if the sample recruitment efforts had been shut down at 70 or 80% of the originally enrolled participants, the rates of type II errors would have increased. [183]

We compared background characteristics among mothers and study children by treatment status for those eligible, but not seen with those eligible and seen this phase (see Tables S1 and S2 in appendix). Those not seen tended to more likely be non-African American, have low household poverty and lower scores on a measure of maternal beliefs associated with child abuse. However, there was no evidence for attrition related bias by treatment status. We have previously noted that at randomization there were differences between control and nurse-visited in household poverty and maternal beliefs associated with child abuse. We therefore have retained these as covariates as described in the statistical models section below.

In the process of tracing the sample for the 18-year follow-up, we uncovered a pattern of maternal and child mortality in which mothers and children in the control group appeared to have died more frequently than those visited by nurses, so we reviewed National Death Index records to ascertain patterns of maternal and child mortality over the first two decades following birth of the first child. The intervention-control difference in child mortality had been evident, as a trend, by child age 9, but given the infrequency of death for women and children in the age-ranges covered by this trial, we had not

hypothesized intervention effects on mortality. We present below the results of the mortality analysis through the current phase of follow-up.

Table 2. Sample Recruitment, randomization, attrition, and completed assessments at previous phases of the trial

Eligible Subjects Invited to Participate	1290				
Number Refused	151				
Number Randomized	1138				
Treatment Group Assignment	**1**	**2**	**3**	**4**	**Total (TX 2 & 4)**
Number Allocated to Each Treatment	**166**	**514**	**230**	**228**	**742**
Miscarriages (first born)	6	19	6	8	27
Stillbirths (first born)	0	5	3	2	7
Child deaths before age 18		11		2	8
Maternal Deaths before age 18		15		3	18
Mother declined before age 18		14		11	26
Lost to follow up (no current address) - mother		8		6	14
Passive refusal (have current address) - mother		20		5	25
Completed Mother 18 year assessment		**426**		**192**	**618**
Completed Other Custody assessment (for child behavior)		11		5	16
Lost to follow up (no current address) - child		20		9	29
Passive refusal (have current address) - child		9		2	11
Completed First Child 18 year assessment		**435**		**194**	**629**

Given the study hypotheses, planned assessments were based upon interviews; neuropsychological, cognitive, and academic achievement tests; urine samples to assess STI's and substance use; saliva to gather DNA; and official records families' use of welfare-related services (Supplemental Nutritional Assistance Program – SNAP, Temporary Assistance for Needy Families - TANF, and Medicaid), families' involvement with child welfare, and school records.

Assessment of Hypothesized Outcomes

In choosing outcome measures for this phase of the trial, we strived to achieve a balance between those that had clear clinical and public health relevance, such as SUDs and neuropsychological functions
presumed to reflect more closely underlying neurobiological substrates.[184;185] For the 18-year follow-up, we relied upon maternal interview, child interview, child testing, and reviews of state and school administrative records. We had planned to obtain teacher reports of child behavior and conduct grades, but found it simply unfeasible to do so. We assessed youth's STI's and substance use with urine assays and collected buccal swabs and saliva for DNA. The entire assessment took an average of 3.0 hours. For both mothers and youth, we used audio computer-assisted self-interview (ACASI) methods for sensitive portions of the interview; other sections were completed by direct interview. A copy of the instrument employed at the year-18 follow-up is included in the Appendix. All assessment procedures were pre-tested and refined with 20 pilot cases. Almost all of the measures employed in this follow-up were standardized and have acceptable validity and reliability with low-income minorities. We have forgone reporting specific validity and reliability indices to save space. Tables 3 and 4 display major constructs and sources of data in our measurement design.

Maternal Life-Course and Health

***Subsequent Pregnancy*.** We assessed number, timing, and outcome of subsequent pregnancies, including number of therapeutic abortions, live births, low-birth-weight newborns, and intervals between births. Our primary outcomes consisted of 2 variables: 1) the count of closely spaced subsequent births (within 2 years of one another); and 2) the number of subsequent child days (density of other children in the household) over the 18-year period following the birth of the first child. The second outcome consists of the sum of numbers of days between births of each subsequent child and

the first child's 18th birthday. The subsequent pregnancy variables were dropped as outcomes for this phase of the trial

Use of Welfare Services. We interviewed women to assess their use of TANF, food stamps, Medicaid, WIC, supplemental social security income, and subsidized child care, and abstracted Tennessee records of TANF, food stamps, and Medicaid use. Given that over 90% of the women live in Tennessee, Tennessee records provided reasonable estimates and were further supplemented by reported use of these services for periods the mother reported being outside of Tennessee. Delays in obtaining these administrative data delayed the final analysis of this report. Our primary outcomes are total government costs of women's use of SNAP, TANF/AFDC, and Medicaid over the 18-year period following birth of the first child.

Table 3. Outcome Domains and Sources of Data for Assessment of Maternal Life-Course and Health

Outcome Domain	In-person Interview	Admin Record	Biological Assay
Subsequent pregnancies	X		
Use of welfare services	X	X	
Substance Use and SUDs	X		
Relationship with partner	X		
Domestic Violence	X		
Maternal Depression	X		
Susceptibility Genes			X

Substance Use and SUDs. We obtained diagnoses of abuse and dependence on alcohol and 9 drugs or drug classes with the *Composite International Diagnostic Interview (CIDI)-Substance Abuse Module (CIDI-SAM)*, a structured, 30-to-60-minute interview designed for trained, lay interviewers. It is a descendent of the NIMH Diagnostic Interview Schedule. CIDI's reliability and validity[186;187] made it the main assessment for DSM-IV Substance Field Trials and for the National Comorbidity Study.[188] Its validity has been documented in substance-dependent, conduct-disordered adolescents.[189] We used an ACASI version for making DSM-IV Abuse/Dependence diagnoses. We also assessed women's frequency of using substances with questions from the Drug Use Screening Inventory,[190] which assesses substance use based on measures of quantity and frequency of use of cigarettes, alcohol, and illegal substances. It also includes questions on severity of problems created in 10 domains of functioning.[190] Our primary outcome consisted of whether or not the mother abused or was dependent on any of the substances after she was randomized into her treatment condition.

Relationship with Current Partner. We interviewed mothers regarding their current partners, lengths of their relationships, whether they were married or cohabiting, whether he is the father of index or subsequent children, his employment, education, criminal involvement, and quality of relationships with their children. We also assessed the degree to which mothers are committed to their partners, have effective communication, and experience conflict.[191] The primary outcome is the duration of their relationship counted in months.

Domestic Violence. We administered Straus's Conflict Tactics Scales used in earlier phases of this trial to obtain information on the degree to which mothers experienced violence from any of their partners during the 6-month period preceding the interview.[192] These data have not yet been compiled into analysis variables.

Maternal Depression and Anxiety. We administered the Beck Depression Inventory (BDI-II) to measure depression severity.[193] Women also completed the Beck Anxiety Inventory (BAI), a 21-item self-report check-list developed to distinguish anxiety symptoms from depression.[194] Our primary outcomes were whether or not they crossed the borderline or clinical cut points on these inventories.

Vulnerability Genes. We gathered saliva using Oragene technology to obtain DNA for genotyping. Our description of gathering and processing DNA and conducting genetic analyses is provided below.

Other Maternal Measures. While not the focus of specific hypotheses, we gathered information on a variety of maternal characteristics that will be useful in interpreting the results of our primary analyses and that are needed for an economic analysis, which we will conduct with support from a separate application. They include measures of maternal employment by interview; the degree to which

the father of the child (if not the current partner) is involved in the life of the firstborn child; and mothers' involvement with the criminal justice system.

Child Assessments

As shown in Table 4, we evaluated the first-born children using *tests* of intellectual functioning, language, neurocognitive skills, and academic achievement; *interviews*; and *abstractions* of electronic school records and state foster care data. Moreover, we conducted direct assessments of adolescents' physical health, focusing on the presence of STDs use of substances through urinalysis, blood pressure, and weights and heights. We gathered DNA for genotyping, using Oragene (described below). Gathering these data will be integrated into an overall physical health assessment that includes measures of obesity, and hypertension. Youth were provided counseling for STI's and substance use; those with identified STI's were asked to return to the study physician to obtain confidential, one-dose treatment for detected pathogens.

Table 4. Constructs, Variables, and Source of Data for Assessments of Youth

Outcome Domain	In-Person Interview	Direct Assess	Admin Records	Parent Report
Cognitive and Language Abilities		X		
Executive Functions (risky decision making, impulsivity, facial recognition, verbal working memory)		X		
Behavior Problems/Mental Disorders (Depression/Anxiety)	X			
Substance Use and Disorders	X	X		
Sexual Behavior/Pregnancies	X	X		
Sexually Transmitted Infections		X		
High School Graduation	X		X	
Violent Criminality and Gang Membership	X			
Arrests, Convictions, and Juvenile Detention	X			X
Foster Care Placements			X	X
Violence Exposure (home, school, and community) – DID WE RETAIN THIS?	X			
Vulnerability Genes (MAOA, 5-HTT, COMT)		X		

Cognitive and Language Abilities. We conducted tests of intellectual and language ability to trace trajectories in these functions over time and to sort out program impact on ECF from general intelligence and language. We chose 2 tests that could be conducted by non-clinicians: the 4th edition of the Peabody Picture Vocabulary Test–III (PPVT), which we administered to firstborn children at age 6; and the Matrices subtest from the Kaufman Brief Intelligence Test (KBIT–2). The Matrices is a non-verbal, visual problem-solving test with both concrete and abstract tasks. The KBIT is a brief version of the IQ measure also used with firstborn children at age 6.[195]

Risky Decision Making. We administered a version of the *Cambridge Decision Making Task (CDMT)* adapted for adolescents[87] The CDMT was developed to dissect cognitive components of sensitivity to consequences and risk taking[196] and consistently activates the orbital portion of the prefrontal cortex in neuroimaging.[87;196] This region also modulates emotional responses to environmental and social stimuli.[197-199] Subjects were instructed to earn as many points as possible given a choice between various bet amounts associated with specific probabilities of winning. The larger reward is always associated with the least likely outcome, thus capturing the conflict inherent in risk-taking.

Sustained Attention. We measured youths' capacity for sustained attention using the Leiter-R Sustained Attention Test.[200]

Facial Recognition. We administered the *Facial Recognition Task.*[201] It measures the ability to identify emotional expressions in people's faces, which involves circuitry between the PFC and limbic system (particularly amygdala), and which is vulnerable to stress. The ability to recognize facial expressions properly is impaired in youth and adults with externalizing disorders, such as CD, violence, and drug abuse.[202-206] Our primary outcome was the total number of correctly identified facial expressions.

Verbal Working Memory. Verbal working memory is an important component of executive functioning eroded in children with the Val/Val COMT genotype.[153] We assessed verbal working memory with the forward and backward recall of number sequences from the Wechsler Adult Intelligence Scale.

Academic Achievement. We administered the math subtest of the Peabody Individual Achievement Test-R-Norm-Updated (PIAT R-NU), which we also had administered at age 12. The PIAT has age-referenced norms. We had intended to abstract children's grade point averages in reading and math, but encountered difficulties in obtaining school records, so dropped this part of the assessment plan.

Behavior Problems and Mental Disorders. We administered the Youth Self Report (YSR) of the Child Behavior Checklist 11-18,[207] as we have done at ages 2, 6, and 12, using the computerized method. The CBCL generates two broadband syndromes: internalizing problems and externalizing problems, as well as a total-problems scale. The newest version also includes a method of generating a DSM profile. Our primary outcome was internalizing problems. The YSR was augmented with corresponding reports from parents. (We had planned to gather CBCL data from teachers, but ran into difficulties in obtaining school records and teacher reports, so this part of our measurement design was discarded.) We created both quantitative scores and dichotomous outcomes that reflected whether children fell into the clinical or borderline range of the internalizing problems scale.

Substance Use and SUDs. We diagnosed Abuse and Dependence on alcohol and nine other drugs or drug classes with the *CIDI-SAM,* discussed above, producing a SUD outcome comprised of the age the child began abusing or became dependent on any of the substances. We also assessed the frequency of cigarette, alcohol, and illegal drug use (cannabis, cocaine, crack, heroin, amphetamines, hallucinogens) using the Adolescent Version of the Drug Use Screening Inventory, which provides information on both the frequency of drug use during the past 30 days as well as information on the severity of disturbance that goes beyond categorical diagnoses.[208,209] We assayed urine samples to screen for cotinine, PCP, benzodiazepines, cocaine, amphetamines, THC, opiates, and barbiturates. We decided against using alcohol metabolites, given their limited sensitivity in sporadic users.[210] We derived a variable consisting of whether or not the child reported using any illegal substances in the past 30 days or had a positive lab test.

Sexual Behaviors. We assessed reports of specific sexual behaviors for adolescents in the ACASI section of the interview. We assessed age of first sexual experience (oral, vaginal, and anal sex), number of lifetime male and female partners, and the number of partners in the last three months. Retrospective recall of sexual behaviors is stable for intervals as long as 3 months.[211;212] Given that many adolescents engage in sexual behavior on infrequent or episodic bases,[213] we chose an assessment interval of 3 months to maximize our ability to detect sexual behavior without compromising reliability. Information will be elicited over the past 3 months on: number of different sexual partners, detailed questions on the incidence of protected and unprotected oral, vaginal, and anal sex. Additional questions addressed the number of treated sexually transmitted infections (STI) over the lifetime, whether the respondent ever had sex for money, drugs, or food. Participants estimated the number of occasions in which they engaged in protected and unprotected vaginal and anal intercourse using a format developed by St. Lawrence.[214]

Risk for HIV Infection. We created an HIV risk score taking into account the following factors: gender, type of intercourse (vaginal, anal), number of partners, and the probability of sexual transmission of HIV within the Memphis/Shelby County community. The HIV risk transmission index score was created using a modified Bernoulli process model (Pinkerton and Abramson, 1998). [215] The probability of HIV acquisition was calculated as follows:

Probability of HIV acquisition =

π [1-(1- α UVI)^{n} (1- α PVI)^{n} (1- α UAI)^{n} (1- α PAI)^{n}]

- "π" represents the prevalence of HIV within a population. Prevalence of HIV in Shelby County in 2012 was estimated at a rate of 655.6 for African American and 139.3 for Caucasian per 100,000 (Shelby County Health Department, 2012). Mother's race at intake was used for child's race.

- "n" represents the number of acts performed over a three month period

- "α" represents the probability of HIV transmission per sexual act. Sexual acts are

noted as unprotected vaginal intercourse (UVI), protected vaginal intercourse (PVI), unprotected anal intercourse (UAI), and protected anal intercourse (PAI). Based on the gender of the participant and their partner, sexual acts are further noted as insertive or receptive intercourse. Risk of transmission for each sexual act was provided by CDC.
http://www.cdc.gov/hiv/policies/law/risk.html

Sexually Transmitted Infections. We obtained urine specimens to ascertain the presence of the following treatable STDs: *N gonorrhoeae, C. trachomatis, and T vaginalis.* State-of-the-art nucleic acid amplification technology was used for STD testing. Specifically, Becton-Dickinson's proprietary DNA amplification technology, called Strand Displacement Amplification (SDA), tested for chlamydia and gonorrhea and polymerase chain reaction (PCR) tested for trichomonas. DNA urine tests for chlamydia, gonorrhea, and trichomonas are highly sensitive and specific.[216;217] Use of the SDA/PCR assays are preferable to traditional tissue culture diagnostic methods because they are non-invasive (urine samples versus cervical/urethral swab) and can effectively be collected in non-clinical settings.[218]

Adolescents were provided urine collection containers and escorted to a private, secure room in which to produce the specimen. Memphis-based staff were trained by personnel from Dr. Caliendo's laboratory in these procedures. Site study staff decanted the urine specimens to centrifuge tubes labeled with unique, anonymous, subject-sample identifiers and stored the specimens in refrigerators. Subject-sample ID linkage was maintained in confidential logs on site that were kept in secure, locked storage. The samples were packed in International Air Transportation Association-approved bio-specimen boxes and shipped via Federal Express overnight delivery to Dr. Caliendo's laboratory. The laboratory processed the specimens and sent the results to the Rochester data processing center.

Youth who tested positive for an STD pathogen (chlamydia, gonorrhea, or trichomonas) were offered directly observed treatment, single session (DOT-SS) therapeutic regimen. We treated infected adolescents at no charge with the following antimicrobials,[219] each of which constitutes a single session therapeutic regimen: N. Gonorrhea – Ciprofloxacin (Cipro™); C. Trachomatis–Azithromcyin (Zithromax™); T. Vaginalis–Metronidazole (Flagyl™). Chlamydia and gonorrhea are reportable infections and were reported by clinic staff to the TN State Department of Health. Our rationale for basing treatment on these DNA amplification tests is: 1) the test has been extensively evaluated in several research settings and shown to have superior sensitivity and specificity to existing diagnostic methods; 2) it is clinically and ethically contradictory to offer retesting with less sensitive methods; 3) STD experts are increasingly concerned about the importance of trichomonas as an STD, increasing the importance of highly accurate diagnosis.[220-222] A provider with Planned Parenthood administered medication, reviewed symptoms, and provided standard STD counseling. These standard activities treat the index STD. Other types of STD-related care (e.g., HIV counseling/testing; syphilis screening) were not study outcomes and were conducted at the discretion of the participant's clinician. Despite appropriate medical care, there is high recurrence of STDs (nearly 40%).[223;224]

Study staff cannot request identifying information about the adolescents' sex partners. However, in the Parental Consent and Adolescent Assent, we explicitly stipulated that per state statutes, we were required to notify the County Health Department of all reportable STDs. The County Health Department was legally responsible for and had a mechanism in place to initiate partner tracing for reportable STDs and provide treatment to partners. However, as part of this study, we instructed adolescents treated for STDs to refer their sexual partners for evaluation, testing, and treatment at a local health department, clinic, or physician's office. To facilitate this process, study staff provided adolescents with a brochure containing the phone numbers and contact information for the local health department or STD clinics.

Pregnancies. We assessed the number and outcomes of pregnancies (miscarriage, therapeutic abortion, still birth, live birth) for both males and females, focusing on the timing and number of pregnancies. The primary outcomes are the count of pregnancies and timing of first pregnancy.

High School Graduation and GEDs. We obtained permission to review children's school records to assess high school graduation. We had hoped to assess conduct grades, disciplinary actions, and school attendance records but found that such records were incomplete and extraordinarily difficult to obtain from the many different school systems that the children attended. We therefore settled for official records of high school graduation and GEDs. We conducted these reviews after all youth would

have graduated from high school had they been on track for graduation (the youngest child being age 20 at review). We employed self-reports of high school graduation and GED completion and validated self-reports with official records in all but 10 cases. Our primary outcome was whether the child had graduated from high school.

Violent Criminality and Gang Membership. Following the National Youth Survey,[225] we interviewed youth to assess whether they had engaged in any of the following categories of criminal behavior over the life-course: felony assault, felony theft, robbery. We aggregated their responses into a scale of interpersonal violent offending over the life-course that included self-report of these types of behaviors plus having been convicted of a violent offense. We additionally derived a variable for whether or not the child reported being a member of gang prior to age 18.

Arrests, Convictions, and Juvenile Detention. We assess by maternal, other custody and youth interview the number of times the youth were arrested, convicted, and sent to juvenile detention, and the offenses that led to the arrests. Using a life history calendar, the dates of arrests and the reasons. The primary outcomes consisted of the count of arrests and convictions as wells as counts of arrests and convictions for violent offenses.

Foster Care Placements. We obtained approval to review child welfare records after 2001. Abstraction of records after this date will improve validity (earlier records are incomplete) and reduce surveillance bias on families' involvement with child welfare, as families will have ended program participation years earlier.[179] We finally just received a file with these data, but were unable to process and understand at the time of this submission.

Susceptibility Genes. As with the mothers, we gathered saliva using Oragene technology to obtain DNA. Our description of gathering and processing DNA and conducting genetic analyses is provided below.

Contextual Factors

We assessed the children's social contexts in their neighborhoods.

Neighborhood. We employed block-level Census data (e.g., % poverty, unemployment, female-headed households, households receiving public assistance) to create variables that characterize neighborhood adversity.[226-228] We coded the block-group data from the census tract that corresponds to each of the neighborhoods in which the children lived at time of their 18-year assessment, at mothers' registration in the trial, and at each of the earlier times they completed intervening assessments.

Genotyping MAOA, 5-HTT, and COMT

The Laboratory of Neurogenetics at NIAAA conducted genotyping of the 3 genes hypothesized to interact with child abuse and neglect and life stress. Participant mothers and youth provided saliva, which was processed using Oragene[229] and sent to NIAAA. At the NIAAA lab, genomic DNA was extracted and concentrations normalized. Genotyping for 5-HTT was done by methods described in Hu et al.[144] and MAOA-LPR by methods describe in Ducci et al.[230] MAOA-LPR was done only for youth. Genotyping of the COMT Val158Met polymorphism was done in conjunction with genotyping for 186 ancestry-informative markers (AIMS) using a large-scale addictions array tool for identifying vulnerability genes in addiction and psychiatric disorders. The addictions array is a tool developed within the Laboratory of Neurogenetics and has been validated in preliminary analyses using four distinct ethnic populations; Finnish Caucasians, African Americans, Han Chinese and Native Americans. Accuracy as determined by duplication was found to be >99.99 for all populations. Using the program Structure2.0[3] the AIMS were able to differentiate all four ethnic groups and to quantify the relative degrees of admixture. Analyses were performed by the Illumina GoldenGate assay protocols, using a TECAN liquid handling robot, using Sentrix 96-sample format arrays. Imaging was performed using an Illumina 500GX Beadstation and genotype data analyzed using Beadstudio 2.0 software (Illumina). Use of this array allowed for determination of the COMT polymorphism and AIMs genotyping at the lowest possible cost per sample.[231]

In the analyses reported below, we examined AIMS allele frequencies by treatment condition and gender to ensure that the estimation of treatment effect by genotype subclasses are not confounded by differences in population admixtures. The same AIMs were also genotyped in 1051 individuals from the 51 worldwide populations represented in the HGDP-CEPH Human Genome Diversity Cell Line Panel (http://www.cephb.fr/HGDP-CEPH-Panel). Ancestry factor scores were generated for each study subject

by running *Structure 2.2* (http://pritch.bsd.uchicago.edu/software.html). AIMs genotype data for each subject were analyzed individually along with the data for the 51 CEPH populations to identify population substructure and compute individual ethnic factor scores. The mean (SE) African ancestry score was 0.76 (0.01) (median, 0.83) for mothers and youth. A subset of 34 youth had > 0.54 European ancestry (EA) (median = 0.93). When these were removed from the dataset, the African ancestry score of the resulting AA youth was mean (SE), 0.82 (0.00) (median = 0.83).

Promoter Region of the Serotonin Transporter (5-HTTLPR). The promoter region of the serotonin transporter gene (*SLC6A4*) was used to characterize genetic vulnerability to depression and to test whether 5-HTT gene variation moderates the influence of child maltreatment and life stress on depression. The promoter activity of the 5-HTT gene, located on 17q11.2, is modified by sequence elements within the proximal 5' regulatory region, designated the 5-HTT gene-linked polymorphic region (5-HTTLPR). The short ("S") allele in 5-HTTLPR is associated with lower transcriptional efficiency of the promoter compared with the long ("L") allele. An additional functional allele has been discovered in the HTTLPR locus: an A to G substitution in the first of the 2 extra repeats defining the L allele.[144] This polymorphism accounts for more of the inter-individual variation in 5-HTT expression.[144] The 3 alleles are S, L_A and L_G; their frequencies are given in Table 5. The L_G and S alleles are functionally equivalent: both cause reduction of expression. On a functional basis, S and L_G can be grouped for genetic analyses, yielding 3 genotypes, low/low, low/high and high/high. Frequencies of these genotypes are approximately 1:2:1 in African-Americans and Caucasians. Those individuals with either S/S, S/L_G, or L_G/L_G genotypes were grouped for analysis to reflect the vulnerable segment of the sample. Details of the methods used for genotyping are given in Hu et al.[144]

Table 5. Distribution of HTTLPR Genotype and Allele Frequencies in Several Populations

		Frequency of Genotype						Freq. of Allele		
Population	**N**	SS	SL_A	SL_G	L_AL_A	L_AL_G	L_GL_G	S	L_A	L_G
U.S. whites group 1	297	.16	.33	.09	.26	.14	.03	.37	.49	.14
U.S. whites group 2	286	.12	.37	.08	.22	.18	.02	.35	.50	.15
African-American	**624**	**.07**	**.25**	**.12**	**.27**	**.23**	**.06**	**.25**	**.51**	**.24**
From: Hu, et al., (2006). *American Journal of Human Genetics,78*:819.										

Monoamine Oxidase A (MAOA). A well-characterized variable number tandem repeat (VNTR) polymorphism exists at the promoter of the *MAOA* gene, which affects expression.[145] The polymorphism (MAOA-LPR), located 1.2 kb upstream of the MAOA coding sequence, consists of a 30-bp repeated sequence present in 3, 3.5, 4, or 5 copies. The polymorphism displays significant variations in allele frequencies across ethnic groups. The polymorphism has been shown to affect transcriptional activity of the MAOA gene promoter by gene fusion and transfection experiments involving 3 different cell types. Alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2-10 times more efficiently than those with 3 or 5 copies of the repeat, suggesting an optimal length for the regulatory region. Transcription efficiency is not yet known for the 2 and 5 copy repeats. Primer sequences and PCR conditions are described in Ducci et al.[230] Table 6 shows frequencies for these alleles in African-Americans; note that alleles with 3 (low activity) and 4 (high activity) copies are much more frequently occurring. Alleles were grouped as either low or high activity for analysis. Those with 2- and 5-copy repeats were grouped together and treated as a separate class in the analysis presented below.

Table 6. Allele frequencies for the MAOA-VNTR among African-American males and females (courtesy of F. Ducci, 2007)

		Allele frequencies				
Population	N	2	3	3.5	4	5
Males	620	0.05	0.50	0.001	0.45	0.003
Females	340	0.07	0.47	0	0.45	0.004

Catechol-O-Methyltransferase (COMT). Catechol-O-Methyltransferase (COMT) is largely responsible for metabolism of DA and NE in human pre-frontal cortex. A common COMT Val158Met polymorphism is responsible for a 3 to 4 fold variation in enzyme activity,[150] Table 7 shows the allele

frequencies and genotypes for the COMT polymorphism among African-American and white control subjects in a population-based study of breast cancer in North Carolina.

Table 7. COMT Allele frequencies and genotypes for whites and blacks in North Carolina

		Genotype			Allele Frequency	
Population	N	COMT-H/H	COMT-H/L	COMT-L/L	COMT-H	COMT-L
African-Americans	263	0.42	0.45	0.13	0.65	0.35
Whites	379	0.22	0.50	0.28	0.47	0.53

Statistical Models and Methods of Analysis

The primary analyses made use of general linear model methods and their extensions. The focus was on full model specification to account for all sources of variation, and a full examination of interactions among model factors. The primary classification factors for examination in our models, as determined by our hypotheses and earlier work, include treatments (Control vs. Nurse Visited - T), maternal psychological resources (low versus high – P), and sex of child (S). Standard covariates included an index of household poverty, maternal beliefs associated with child abuse, and for child outcomes, age of the child at the 18-year interview. Genetic analyses included the gene as an additional classification factor and were interacted with treatment status only (see more information below). We employed pared-down versions of full model specification when we had infrequently occurring outcomes (e.g. convictions for interpersonal violence). In general the approach involved beginning with a fully specified model and continuing to eliminate non-significant interactions unless a specific a prior hypothesis forced the interaction term(s) into the model.

Continuous variables were run with a general linear model; dichotomous variables with binomial error distributions; low frequency count variables with negative binomial distributions. For outcomes measured over the life course, the above models were extended to mixed or generalized mixed models to account for correlated data (random effects for time with unstructured variance terms). Subsequent children analyses were also run with mixed or generalized mixed models to account for correlation within the same family. We were interested in the treatment effects for subsequent children alone, as opposed to an overall family effect that would include the first born children.

We employed Cox proportional hazard models [232] for outcomes with a survival component. We present in the tables adjusted hazard rates at age 18 since the vast majority of the sample was interviewed after their 18th birthday but rapidly drops off after this date. The methods used for the mortality analyses can be found elsewhere.[11]

We examined mediation in models with simultaneous equations, testing the significance of direct and indirect effects and their equality using methods outlined by Mackinnon. [233] We investigated models where the intervention had a significant effect through child age 2 on outcomes significantly different at this phase in the low psychological resource group.

While missing data in this trial were remarkably low, especially at this 18-year follow-up, we were sensitive to the potential pitfalls of only analyzing cases with complete data. We have a paper in the pipeline that indicates that at child age 12 estimates of treatment-control differences would have been reduced dramatically had we discontinued sample recruitment at levels retention often is considered acceptable for studies like this (70-80%), and that these reductions in treatment effects are not simply a reflection of statistical power or differences in measured baseline characteristics.[183] There are likely differences in life-course trajectories not explained by measured baseline characteristics. We have complete data on all relevant background characteristics. Our primary strategy has been to minimize attrition to greatest extent possible. We will consider comparing our analyses to the same analyses employing multiple imputation.[234] For the multiple imputations, we generally would use a Markov Chain Monte Carlo method to impute enough data to have a monotone missing data pattern. Once we have a monotone missing data pattern, we would employ imputation approaches appropriate for the type of data (continuous, dichotomous, or low frequency count data). We will perform sensitivity analyses to ensure that results are similar under various assumptions. In general, given very low attrition, such approaches are not warranted.

Examination of Hardy-Weinberg Equilibrium. We calculated allele frequencies for each polymorphism examined in this study (5-HTTLPR, MAOA-LPR, COMT Val158Met) to determine whether

the sample is in HWE. Given the relatively small sample sizes involved in these calculations, we relied upon absolute deviations from HWE in addition to formal statistical significance in making determinations as to whether the polymorphisms are in HWE.[236]

Inclusion of Gene Activity Classification Factors. Some of our models included classification factors for functional classifications (activity variants) of the polymorphisms hypothesized to moderate program impact in this trial (5-HTTLPR, MAOA-LPR, and COMT Val158Met); we were not interested in genotypes per se, but rather functional classes that group genotypes by activity level (low – L , high - H or intermediate - I). In the case of 5-HTTLPR, L_G and S alleles are both low-activity variants that lead to low expression; from the analysis standpoint, the low-activity genotypes (L_G/L_G, S/S, and L_G/S) were grouped into the low-activity class; the high activity genotypes (L_A/L_A,) into a high-activity class; and the remaining genotypes (L_A/L_G and L_A/S) grouped into an intermediate class. We used a similar approach with MAOA-LPR and COMT Val158Met. In the case of the X-linked MAOA-LPR, we grouped males into high and low expression allele groups and excluded females from analyses. In the COMT Val158Met analyses, we excluded non-African ancestry participants.

Tests of Hypotheses

Maternal Outcome Hypotheses

Hypothesis 1 (primary): The program will continue to improve maternal life-course reflected in total costs for welfare (SNAP, AFDC/TANF, and Medicaid), especially for mothers with high psychological resources. We tested Hypothesis 1 by examining the primary maternal life-course outcome (public expenditures for SNAP, AFDC/TANF and Medicaid) in our primary model, estimating public expenditures for these benefits over time, which included a factor for T and P, the interaction between these classification factors (T x P), and a set of covariates. For the pubic benefit expenditure outcome, we analyzed the data in mixed models that included, in addition to the core model terms, women as levels of a random factor, a fixed repeated measures classification factor for time (first-born child age) of assessment, and all interactions of time with the other fixed classification factors. We examined the treatment–control difference summing across levels of maternal psychological resources, and conducted planned contrasts for women in the high-resource group.

Hypothesis 2 (secondary). The program will reduce maternal SUDs and depression. We examined SUDs and depression by examining planned contrasts within the classification structure specified for Hypothesis 1, using generalized linear models, logistic for depression and SUD.

Child Outcome Hypotheses

Hypothesis 3a–d (primary): The program will improve the health and development of firstborn children who will exhibit: a) superior cognitive, language, and academic functioning; b) less depression and anxiety; c) less gang membership, and fewer arrests, convictions, and self-reported antisocial behavior - especially for crimes involving interpersonal violence**.** We will examine this hypothesis in the model used to test hypotheses 1 and 2, after adding child sex (S) as a classification factor. We will test hypotheses 3a–d by examining each of child outcome in the saturated TxPxS (2x2x2) model, including covariates. In our first-level analysis, we will examine treatment–control differences averaging across levels of maternal psychological resources and child sex. Outcomes that have essentially normal distributions (e.g., cognitive and academic outcomes) will be examined in the general linear model. Those that have low-frequency count distributions (e.g., counts of failed conduct grades) will be examined in the generalized model. For very sparsely distributed outcomes, we may need to drop certain model terms, such as 3-way interactions or nonsignificant covariates to increase model stability. We will retain model terms with highest levels of significance and those central to the hypothesis. Finally, we will examine outcomes that have binomial distributions in the fully specified logistic modelSome outcomes, such as standardized math scores, will have multiple measures for each child at different ages, and the model will include additional repeated measures factors for child age.

Hypothesis 4 a–c (primary): The program will reduce youth risk for a) HIV infection, b) pregnancies, births, c) use of substances, and SUDs**.** We will employ nearly identical analytic methods for testing hypothesis 4 as we employ for testing hypothesis 3. The primary outcome(s) for HIV risk will consist of indices that we will create to quantify HIV risk exposure.

Hypothesis 5 (secondary): The program will improve firstborn children's executive cognitive functioning (ECF); and rates of high school graduation. We will employ nearly identical analytic methods

for testing hypothesis 5 as we employ for testing hypothesis 3.. In analysis of executive cognitive functions, we will control statistically for KBIT matrices scores and PPVT to discern the impact of the program on executive functions independent of general intelligence and language.

Hypothesis 6 (primary): Program effects on cognitive, language, and academic functioning, and executive cognitive functioning will be more pronounced a) among those born to low-resource mothers and b) on arrests and convictions among females**.** We will test the hypothesized conditional effects in the core model (TxPxS with covariates). Planned contrasts for children will focus the treatment contrast on children born to low-resource mothers for cognitive, language, and academic functioning, and executive cognitive functioning outcomes. Planned contrasts for arrest and conviction will focus the treatment contrast on females.

Hypothesis 7* (secondary)*: Program effects on mothers and children will be more pronounced for those with genetic vulnerabilities: *a) Effects on youth depression and anxiety will be greater for those with the low-activity 5-HTTLPR genotypes (S/S, L_G/L_G, S/L_G) compared to those with the high-activity genotypes (L_A/L_A); effects on these outcomes will be of intermediate magnitude for those with intermediate activity genotypes (S/L_A).* We will test this hypothesis by adding a 3-level 5-HTT genetic vulnerability factor to the statistical model and examining treatment–control differences within levels of genetic risk. *b) Effects on youth violent antisocial behavior, SUDS, and risky sexual behavior, including STIs and pregnancies, will be more pronounced among males with the MAOA-LPR low-activity alleles and among both males and females with the Val/Val (H/H) COMT genotype.* We will repeat the analysis of child outcomes, substituting first a factor that classifies the sample into groups of MAOA alleles that confer high versus low activity, focusing the treatment contrast on males within the low-MAOA category; we will repeat this analysis for both males and females, substituting the COMT genotype as the genetic vulnerability factor, focusing the treatment contrast on the high-activity subgroup (Val/Val). *c) Effects on maternal SUDs will be concentrated among those mothers with the Val/Val COMT genotype.* In testing this hypothesis, we again will add the COMT genotype (H/H, H/L, LL) to our standard model and repeat the analysis of maternal SUDs, focusing on our planned treatment contrast on the H/H subgroup. *d) Effects on child outcomes will be more pronounced among children born to mothers with either: 1) the low-activity 5-HTTLPR genotypes; or 2) 2 copies of the high-activity COMT Val158 alleles (COMT-H).* In testing this hypothesis, we again will add the 5-HTTLPR genetic risk factor to our standard models and repeat the analysis of child outcomes, with planned contrasts focusing on treatment–control differences within the low-activity 5-HTTLPR subgroup defined by mothers' having either high- low- or intermediate activity classifications. Given limited statistical power to examine treatment contrasts within any one of these subgroups alone, we also will create a maternal genetic risk factor based upon whether mothers possess any one of these risk genotypes and then re-run the analysis of treatment-control differences focusing on planned comparisons within the high genetic risk factor defined by mothers possessing either one of these 2 risk genotypes.

Hypothesis 8(Secondary): Program effects on adolescent functioning will be explained by its improvement in prenatal health, early care of the child, maternal life-course, and earlier child functioning. Tests of mediation will follow the theoretical model of Figure 1 and use the methods described above. To illustrate, we have hypothesized that nurse visitation will have an indirect effect on adolescent academic performance through its effect on maternal-life course. To test one aspect of this hypothesis, we will regress academic performance on treatment condition and density of subsequent children born to the mother; we will also regress density of subsequent children on intervention condition. If the paths from intervention to density and from density to academic performance are both significant, we will have met the joint significance test criterion. We will next calculate the indirect effect, based on these same two path coefficients, and compare the resultant z' to Mackinnon's table of critical values. If the z' is equal to or higher than the appropriate critical value, we will conclude that density of subsequent children mediates the effect of nurse visitation on academic outcomes.

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