

A Prospective Cohort Study of Influences on Externalizing Behaviors Across Childhood: Results From a Nurse Home Visiting Randomized Controlled Trial

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Objective: This study investigated genetic and environmental influences on behavior in a cohort of 600 children followed prenatally to 18 years.

Method: A randomized controlled trial of prenatal/infancy nurse home visits (NHV) was conducted in 600 predominantly African American mothers and their firstborn children from Memphis, TN. Mothers were assessed in pregnancy for mental health (MH), self-efficacy, and mastery. Mothers reported longitudinally on smoking and alcohol/drug use. The functional polymorphisms *SLC6A4* 5-HTTLPR, *FKBP5* rs1360780 and *DRD2/ANKK1* rs1800497 were genotyped together with 186 ancestry informative markers. Composite externalizing disorders (ED) continuous total scores from the mother-report Achenbach Child Behavior Checklist were included as dependent variables in regression analyses for time points 2, 6, 12, and 18 years.

Results: Behaviors at younger ages strongly predicted later behaviors ($p < .0001$). Children whose mothers had high self-efficacy and had received NHV were better behaved at age 2 years. Poorer maternal MH adversely influenced ED up to 12 years, but at age 18 years, maternal

mastery exerted a strong, positive effect ($p = .0001$). Maternal smoking was associated with worse ED at 6 and 18 years. Main and interactive effects of genetic polymorphisms varied across childhood: *FKBP5* rs1360780 up to age 6, 5-HTTLPR from 6 to 12, and *DRD2/ANKK1* rs1800497 from 2 to 18 years.

Conclusion: Our study suggests that maternal MH and resilience measured in pregnancy have long-lasting effects on child behavior. Maternal smoking across childhood and genetic factors also play a role. NHV had a positive effect on early behavior. Our findings have implications for prevention of pathological behaviors in adulthood.

Clinical trial registration information—Age-17 Follow-Up of Home Visiting Intervention; <http://clinicaltrials.gov/>; NCT00708695.

Key words: Achenbach Child Behavior Checklist, nurse home visiting, 5-HTTLPR, FKBP5, DRD2/ANKK1

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Both genetic and environmental factors influence the development of externalizing behaviors, such as aggression and antisocial behavior, across childhood and adolescence. Externalizing behaviors in children as young as age 3 years persist and have been associated with increased risk of psychopathology, including alcoholism and drug addiction, in adulthood.^{1,2} Studies have shown that externalizing behaviors are highly heritable (55–65%).^{3–5} Variation in genes implicated in dopaminergic, serotonergic, and neuroendocrine systems appears to increase risk for development of externalizing behaviors.³

The environment in which a child is reared, particularly that provided by the primary caregiver, most often the mother, also has implications for behavioral development. For example, maternal stress during pregnancy is associated with emotional problems in childhood,⁶ and early-life maternal psychopathology can result in long-lasting

behavioral problems.^{2,7} Many studies have shown that children of mothers with depression have increased rates of antisocial behavior, depression, and high emotionality^{8–10} and are often exposed to harsh discipline and poor nurturing.¹¹ Results of a few studies suggest that the psychopathology trajectory can be altered by means of prenatal/early childhood educational home-visiting interventions; for example, a paraprofessional-delivered home visitation intervention program for American Indian teenage mothers resulted in improved parenting skills and fewer externalizing and internalizing child behavior problems at 3 years.¹² A longitudinal nurse home visitation (NHV) study in predominantly white impoverished mothers in Elmira, NY, showed that adolescents in the NHV group had fewer arrests and convictions, consumed less alcohol, and smoked less than controls, but there were no differences in other behavioral problems.^{13,14}

The current study was undertaken within a predominantly African American (AA) sample of primarily low-income unmarried women living in Memphis, TN, who, together with their firstborn children, had been followed from pregnancy through their child's 18th birthday.¹⁵



Supplemental material cited in this article is available online.

During pregnancy, mothers had been randomly assigned to a control group or to prenatal and infancy NHV, the aim of which was to improve pregnancy outcomes, children's health and development, and mothers' health and life course. The current study was limited to the 600 firstborn children who were interviewed at the 18-year assessment and provided DNA, together with their mothers, who had been assessed during pregnancy for mental health, measures of resilience (self-efficacy and mastery), and longitudinally for smoking and for alcohol and drug use. All these maternal measures are hypothesized to influence externalizing behaviors in children. Mothers also provided DNA. Three common functional polymorphisms in genes implicated in the dopaminergic, serotonergic, and neuroendocrine systems were genotyped in the children and their mothers. All 3 polymorphisms predict emotional dysregulation and behavioral disorders. The *DRD2/ANKK1* Glu713Lys rs1800497 polymorphism has been associated with increased ventral striatal activation during reward processing¹⁶; 5-HTTLPR, the promoter polymorphism in the serotonin transporter gene *SLC6A4*, has been widely implicated in stress sensitivity¹⁷; and the rs1360780 SNP in the *FKBP5* HPA-axis gene has been associated with stress-related disorders and aggression.¹⁸⁻²⁰

The purpose of the current study was to investigate the impact of maternal and genetic influences, together with an NHV program, on the development of externalizing behaviors in children aged 2 through 18 years, including the externalizing behaviors of alcohol and drug use disorder (AUD, DUD) and smoking behavior at age 18 years.

METHOD

Full details of the study, including participant retention rates and visit attendance patterns, have been published.^{15,21,22} A total of 1,289 eligible women, living in highly disadvantaged urban neighborhoods, were consecutively recruited from a public system for obstetric and pediatric care between 1990 and 1991. Of these, 151 declined to participate. In all, 1,138 primarily self-described African American women at less than 29 weeks gestation with no previous live births and with at least 2 of 3 risk factors (unmarried, <12 years education, unemployed) were randomly assigned to 4 treatment groups.¹⁵ Two groups were used to examine birth outcomes only and were not followed after childbirth. The focus of the current study is on the other 2 groups (N = 742), as follows: a control group (n = 514), in which women were provided free transportation for scheduled prenatal care plus developmental screening and referral services for the child at ages 2, 6, and 12 years; and a treatment group (n = 228) that, in addition, had intensive NHV during pregnancy (mean [SD] visits = 7.5 [3.8]) and through the child's second birthday (mean [SD] visits = 27.9 [13.8]). There was no difference in the characteristics of mothers between the 2 groups at recruitment.¹⁵

When children were 18 years old, a total of 657 mothers and 669 children were eligible for follow-up. The attrition in numbers was predominantly due to maternal and child deaths. Only 27 mothers/children chose to drop out before the 18-year follow-up. Of the eligible participants, 94% of mothers and children were interviewed. Saliva for DNA extraction was collected from 96% of these children, and 94% of the mothers and genotypes were available for 600 children (NHV group n = 186, controls n = 414) and 561 mothers. There was no difference in baseline characteristics of

mothers in the NHV and control groups (Table S1, available online). Mothers lost to the study did not differ from mothers retained in the study at 18 years in baseline mental health or Pearlin Mastery scores. In the control group only, mothers lost to the study had significantly higher baseline self-efficacy scores than study-retention mothers.

The study was approved by the University of Rochester institutional review board, with secondary approval by the University of Colorado. The mothers provided informed consent before randomization and re-consent at each follow-up assessment. Mothers gave consent for their children under age 18 years, and the children provided assent. Youth age 18 years and older provided informed consent.

Mothers' Assessments at Baseline During Pregnancy

Mental Health. A mental health composite score (MH), based on measures of depression, anxiety, and emotional dysregulation, was derived from the 38-item Rand mental health battery.²³

Self-Efficacy. The self-efficacy scale was created specifically for the NHV program based on Bandura's work.²⁴ Mothers were asked a series of 10 questions focusing on their confidence in their ability to perform parenting-specific tasks such as understanding the baby's needs and feelings, talking, reading to and playing with the baby, and taking the baby for regular clinic/doctor check-ups.²⁵ Scores per question ranged from 1 (low confidence) to 5 (high confidence). Cronbach's α was 0.68.²⁵

Pearlin Mastery. The Pearlin Mastery score (PM), a measure of an individual's personal sense of mastery and control over one's own behavior and life opportunities, was derived from the 7-item Pearlin Mastery Scale that has been widely used since 1978.²⁶

The MH, self-efficacy, and PM scores were standardized to a mean of 100 and an SD of 10. Higher scores denote better functioning.

Maternal Smoking, Alcohol, and Drug Use

Mothers were questioned about cigarette use (Table S1, available online) and alcohol and drug use at baseline during pregnancy and when their children were aged 6 and 12 years. As we were primarily interested in the influence of maternal smoking/non-smoking on the child, the smoking phenotype used in analyses was average cigarettes per day over the past 30 days in the total sample that included smokers (≥ 1 cigarette per day) and nonsmokers. The proportion of mothers with any alcohol/drug use was very low (see Supplement 1, available online), and therefore these data were not included in any analyses.

Behavioral Measures in Children

Achenbach Child Behavior Checklist. Mothers completed the Achenbach Child Behavior Checklist (CBCL) for preschoolers²⁷ at child age 2 years and the CBCL for school-age children²⁸ at child ages 6, 12, and 18 years. The composite externalizing disorders continuous total scores (ED) (rule-breaking behavior, aggressive behavior) were derived. Numerically higher ED scores signify more disturbed behavior.

Assessment of Alcohol/Drug Use Disorders and Smoking at Age 18 Years

DSM-IV diagnoses of AUD and DUD were derived from the Substance Abuse Module (SAM) of the Composite International Diagnostic Interview (CIDI), which was completed by youth at age 18 years. The smoking history assessment included average cigarettes per day over the past 30 days.

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