



## Uric acid excretion predicts increased aggression in urban adolescents



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### HIGHLIGHTS

- Elevated levels of uric acid have been linked with impulsive behavior
- Greater excretion of uric acid predicts more aggressive behavior in urban youth
- The role of uric acid in adolescent aggression does not vary by gender

### ARTICLE INFO

#### Article history:

Received 18 February 2016

Received in revised form 26 April 2016

Accepted 10 May 2016

Available online 11 May 2016

#### Keywords:

Uric acid

Aggression

Adolescence

### ABSTRACT

Elevated levels of uric acid have been linked with impulsive and disinhibited behavior in clinical and community populations of adults, but no studies have examined uric acid in relation to adolescent aggression. This study examined the prospective role of uric acid in aggressive behavior among urban, low income adolescents, and whether this relationship varies by gender. A total of 84 adolescents (M age 13.36 years; 50% male; 95% African American) self-reported on their physical aggression at baseline and 1.5 years later. At baseline, the youth also completed a 12-h (overnight) urine collection at home which was used to measure uric acid excretion. After adjusting for baseline aggression and age, greater uric acid excretion predicted more frequent aggressive behavior at follow up, with no significant gender differences. The results suggest that lowering uric acid levels may help reduce youth aggression.

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### 1. Introduction

Uric acid is the end product of purine metabolism in humans [7]. Elevated levels of uric acid have been implicated in the development of multiple health problems, including the metabolic syndrome, hypertension, gout, and kidney disease [5,11]. In recent years, elevated levels of uric studies have also been linked with impulsive and disinhibited behavior, with convergent results across clinical populations, community samples, and animal models [37,43]. Although most of these studies used cross-sectional design, the causal role of uric acid in disinhibition has been supported by randomized clinical trials of uric acid lowering medications in bipolar manic patients [17,27]. However, no prospective, observational studies have linked uric acid levels with changes in behavior over time. Additionally, most studies on uric acid and behavior have focused on manic symptoms in psychiatric patients with bipolar disorder, so less is known about uric acid's relationships with other forms of disinhibited behavior in community populations. Thus, this longitudinal study examines a prospective relationship between uric

acid and aggressive behavior among low income, mostly African American adolescents, who are at a higher risk for both elevated uric acid levels [14] and aggression [28].

The most extensive evidence about the role of uric acid in behavior comes from clinical studies. Specifically, elevated uric acid levels have been reported in patients with psychiatric disorders characterized by impulsivity and disinhibition, including bipolar disorder [2,20] and attention deficit-hyperactivity disorder [33], compared to healthy controls and those with psychiatric disorders not involving disinhibition (e.g., major depressive disorder). In addition, genetic disorders of purinergic metabolism that lead to overproduction of uric acid (e.g., Lesch-Nyhan syndrome) also involve behavioral abnormalities, including impulsive, aggressive, and self-injurious behavior [13]. In patients with bipolar disorder, uric acid levels are higher during manic episodes (characterized by disinhibition) and are not due to psychotropic medications [2,30,37]. Strong support for the causal role of uric acid in disinhibition has been provided by randomized treatment studies showing that adding allopurinol (medication decreasing uric acid) to lithium, haloperidol, and/or sodium valproate significantly and substantially reduced mania symptoms and increased remission probability in patients with bipolar disorder [1,17,27]. In these studies, decreases in uric acid levels following treatment also correlated with improvement in symptoms. A recent review provides a comprehensive description of the

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purinergic system's role in the pathophysiology of mood disorders, together with therapeutic implications [32].

Only two studies, both using cross-sectional design, examined relationships between uric acid and behavior in non-clinical populations. One study found small associations between higher levels of uric acid and impulsiveness and excitement seeking in two large community samples of adults [43]. The other reported moderate correlations between higher levels of uric acid and greater disinhibition and drive in a smaller sample of community adults [25]. This was the only study that examined gender differences in the links between uric acid and behavior, finding stronger relationship with disinhibition in females than males. Finally, one study with an animal model demonstrated higher levels of exploratory and novelty-seeking behavior (indicative of impulsivity) in mice that were genetically modified mice to accumulate uric acid, compared to wild type mice who had low uric acid levels [43].

Although no studies have examined the role of uric acid in aggressive behavior, lack of inhibition (which has been linked with uric acid) is a key risk factor for children's aggression [34]. Additionally, two case studies have shown that uric acid lowering medication (allopurinol) dramatically reduced aggressive behavior in patients with neurological conditions [21,22]. Thus, it is possible that elevated levels of uric acid increase the risk for aggressive behavior, a hypothesis examined in this study.

The goal of this study is to examine 12-h urinary excretion of uric acid as a prospective predictor of aggressive behavior among low income, mostly African American adolescents, who are at higher risk for both elevated uric acid levels [14] and aggression [28]. Because one previous study suggested stronger association between uric acid and disinhibition in females [25], we also tested possible gender differences in the role of uric acid in aggression. Although all previous studies of uric acid and behavior utilized serum or plasma levels of uric acid, urinary uric acid excretion can serve as an alternative, non-invasive measure of uric acid production. Serum levels and 24-h urinary excretion of uric acid are positively correlated [47] and show similar relationships to other variables [16,24,46]. In this study, we conducted a 12-h overnight urine collection instead of the standard 24-h collection due to its substantially greater feasibility in community-dwelling youth and high correspondence with 24-h collection values (e.g., ICC = 0.96 for creatinine clearance) [35]. Given previous literature on uric acid and disinhibited behavior, as well as the role of inhibition in aggression, we hypothesized that higher levels of uric acid excretion will predict more aggressive behavior over time in a community population of adolescents, and that this relationship may be stronger in females.

## 2. Material and methods

### 2.1. Participants and procedures

Participants were 84 adolescents who took part in the Coping with Violence Study. The adolescents were recruited from four public middle schools (grades 6–8 or 9) serving low income, urban communities in Birmingham, AL. Across the four schools, 83% to 87% of students were eligible for free or reduced price lunch. Students in regular education classrooms received an envelope that contained a description of the study, contact information form, and informed consent and assent forms. Families interested in participating were instructed to return a completed contact information form to the school. These families were later contacted by study staff and scheduled for an interview at a university laboratory. To capture a representative community sample, there were no exclusion criteria. From approximately 240 invited students, 129 (54%) provided their contact information and 84 of those (65%; 35% of all invited) completed Wave 1 interview (recruitment was curtailed by limited resources; see Fig. 1 for recruitment flow chart). After providing parental informed consent and child assent, parents and adolescents were interviewed separately in private spaces by trained interviewers using computer assisted technology. The child

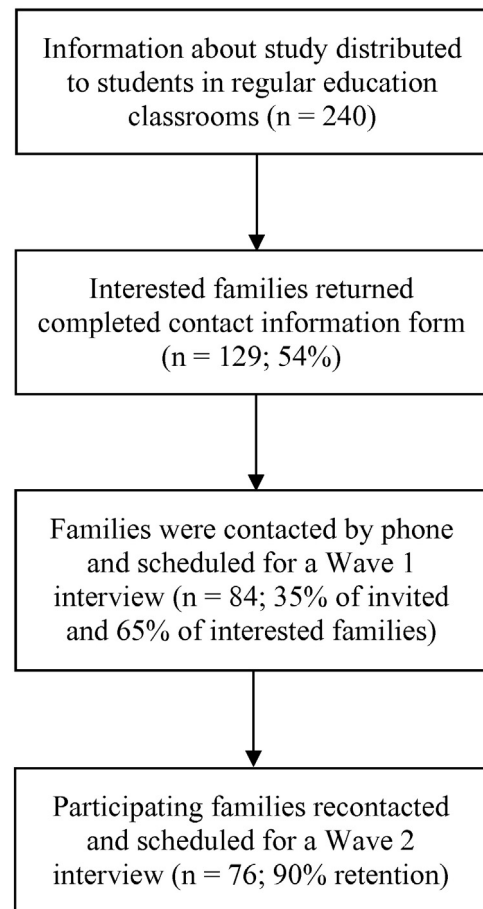


Fig. 1. Recruitment flow chart.

interview included a collection of anthropometric measurements (height and weight). At the end of the interview, the collection of 12-h overnight urine from the child was explained and scheduled during the following week. Approximately 1.5 years after the Wave 1 assessments, families were re-contacted and scheduled for a Wave 2 interview. The 1.5 year lag between assessments was selected to allow sufficient change in aggressive behavior and other behavioral outcomes of interest in the larger study. For example, last month physical aggression is highly stable over a 6-month period ( $r \geq 0.60$ ), but becomes more variable when assessed 1–2 years later ( $r$ 's = 0.40 to 0.50) [8, 10]. A total of 76 (90%) of the families participated in Wave 2. Youth lost to follow up were slightly older than those retained (14.19 vs. 13.28,  $p = 0.009$ ), but the two groups did not differ on any other baseline characteristics. Each interview session took approximately 2 h to complete, and adolescents and their caregivers were compensated for their time with \$50 gift cards. All procedures were approved by the University Institutional Review Board.

### 2.2. Measures

#### 2.2.1. Physical aggression

At both waves, adolescents reported on their aggressive behavior using the 7-item Physical Aggression scale from the Problem Behavior Frequency Scale [9]. Specifically, youth were asked how often they were in a fight, hit, shoved, threatened to hit, or threw something at someone to hurt them in the last 30 days. The 4-point response scale ranged from 'Never' (1) to '6 or more times' (4). Items were summed ( $\alpha = 0.80$  and  $0.76$  at Waves 1 and 2).

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