



# Urinary p-Cresol As a Potential Biomarker for Autism Spectrum Disorders in Children: A Systematic Review and Meta-analysis

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## ABSTRACT

**Introduction:** Autism spectrum disorders (ASD) are neurodevelopmental disorders with an elusive pathophysiology. Diagnosis of ASD relies on behavioral evaluations, indicating a need for biomarkers. Production of some uremic toxins such as p-cresol- is elevated in children with ASD. The urinary levels of p-cresol correlate with the severity of symptoms in ASD. This study aimed to investigate whether p-cresol levels in children's urine samples could aid in ASD diagnosis.

**Search Strategy:** This systematic review followed the PRISMA guidelines and Cochrane systematic review protocols. An extensive search was carried out in online databases, including PubMed, Web of Science, and Scopus, from April 2024 to May 2024. The terms searched were (autism\* OR ASD) AND (p-cresol\* OR cresyl\* OR uremic). Google Scholar search engine was used to identify grey literature. All English observational studies that compared levels of urinary forms of p-cresol in ASD children and healthy age-matched controls were selected. Reviews, conference abstracts, and animal studies were excluded. After removing duplicates, two researchers performed title and abstract screenings and full-text assessments independently. Relevant data, such as urinary p-cresol levels in ASD and control groups, were extracted. The Newcastle-Ottawa Quality Assessment Scale was utilized to evaluate case-control studies. Using Stata (v.14.2), a random-effects meta-analysis was conducted based on standardized mean differences (Cohen's d) of p-cresol levels. The heterogeneity of the studies was measured using  $I^2$ .

**Results:** After removing duplicates, 59 studies remained, 12 of which passed the title and abstract screening and proceeded to full-text assessment. Seven studies comprised 398 ASD patients (16.48% female) and 299 controls (32.24% female). The mean age of the patients and controls were 7.16 and 6.93, respectively. studies reported a significant increase in urinary p-cresol levels in ASD, and one reported a non-significant decrease. Meta-analysis of all eligible studies ( $n = 3$ ) found significantly higher urinary p-cresol levels in ASD compared to controls (Cohen's  $d = 3.21$ ; 95% CI= 2.50 and 3.93), with non-significant heterogeneity ( $I^2=1\%$ ;  $p = 0.41$ ).

**Conclusion and Discussion:** Urinary p-cresol levels seem capable of differentiating between children with ASD and controls and may be used as a biomarker for ASD.

### Citation:

Forouzandegan M,  
Forouzandegan R. Urinary p-  
Cresol as a Potential Biomarker  
for Autism Spectrum Disorders  
in Children: A Systematic  
Review and Meta-analysis.  
*Iranian biomedical journal.*  
Supplementary (12-2024): 365.

**Keywords:** Autism Spectrum Disorder, Biomarkers, Systematic review

