



Oxidative Stress in Children and Adolescents with Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta-Analysis



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ABSTRACT

RESULTS

Background: The etiology of attention deficit hyperactivity disorder (ADHD) is multifactorial and mounting evidence suggests that oxidative stress dysregulation may be associated with the underlying mechanisms of ADHD. This meta-analysis was conducted to investigate the levels of oxidative stress and antioxidant markers in children and adolescents with ADHD.

Method: PubMed, Web of Science, and Embase were used to retrieve the studies that evaluated urine and blood levels of oxidative stress biomarkers in children and adolescents with ADHD compared with the healthy control group. The studies were further systematically reviewed and meta-analyzed by following the PRISMA guidelines.

Results: 19 studies met the inclusion criteria that specifically target these biomarkers, including 8-hydroxy-deoxyguanosine (8-OHdG), malondialdehyde (MDA), nitric oxide (NO), superoxide dismutase (SOD), total antioxidant status (TAS), and total oxidation status (TOS). Compared to healthy control, children and adolescents with ADHD were associated with higher 8-OHdG ($P < .00001$) and MDA ($P = .0001$) that are oxidative damage products, higher TAS ($P < .00001$), and lower antioxidant-enhancing enzymes, SOD ($P < .00001$), and TOS ($P < .00001$). However, NO did not differ significantly between groups.

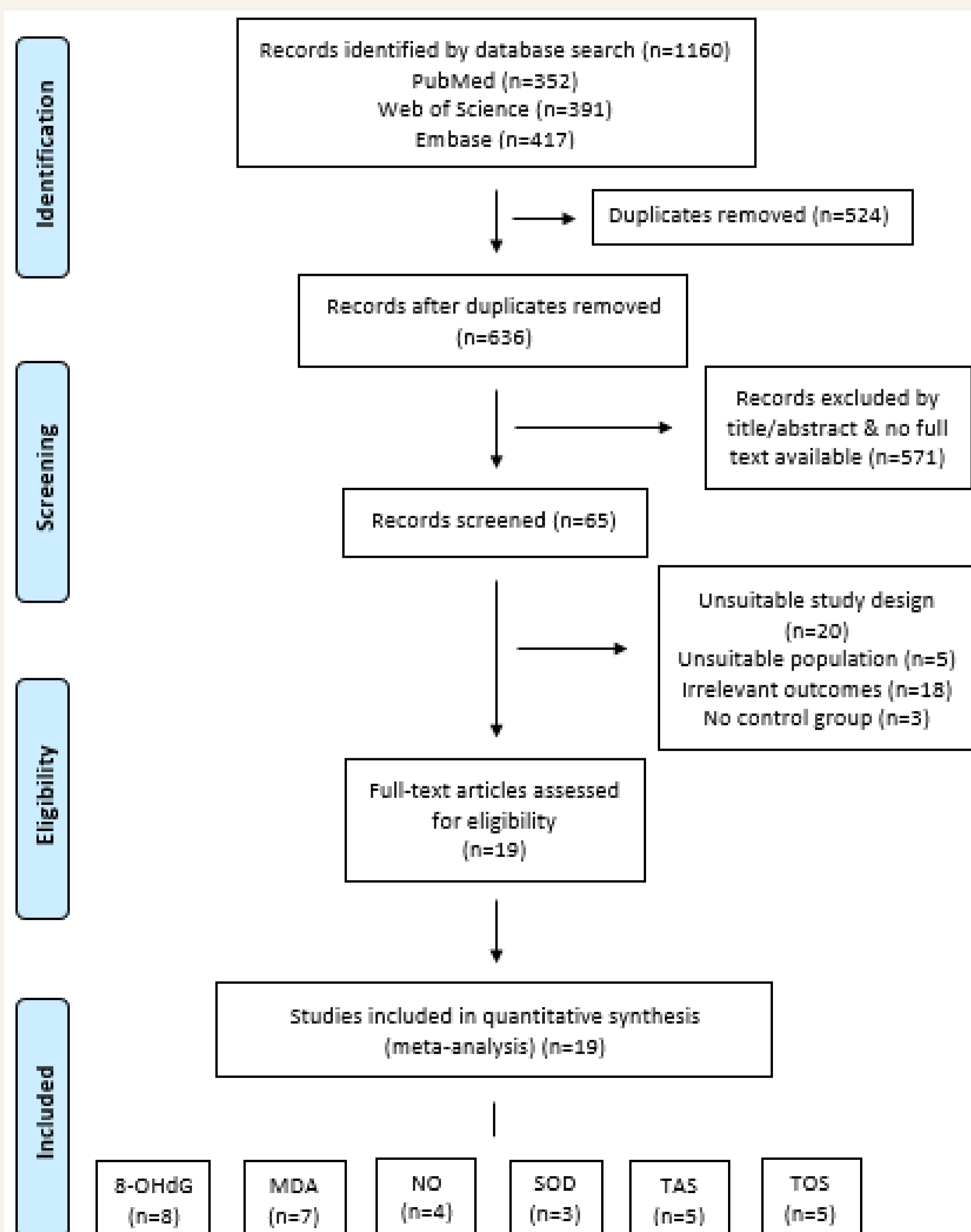
Conclusion: This is the first meta-analysis of oxidative stress particularly in children and adolescents with ADHD that supports the evidence of higher oxidative stress and lower antioxidant activity than healthy controls in ADHD children and adolescents.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in childhood and is characterized by inattention, hyperactivity, and impulsiveness.¹ Increasingly studies discovered oxidative stress plays a role in the pathology of ADHD in children and adolescents, but the results are inconsistent. A previous meta-analysis included limited studies with large age differences, measured only by two subgroups (antioxidant and oxidative stress), and did not assess tissue used difference.²

This study was designed to overcome previous limitations in assessing the role of oxidative stress in ADHD.

METHOD



Relevant studies were retrieved from the electronic databases, including Pubmed, Web of Science, and Embase up to August 30th, 2024. The studies were included if they met the criteria: (1) children and adolescents clinically diagnosed with ADHD without any comorbidities; (2) the comparison of the healthy control group included; (3) only biomarkers that were assessed in at least three studies; (4) clear data on biomarkers were reported in mean and standard deviation (Fig 1).

Figure 1. The studies included selection through a PRISMA guideline flow chart.

References:

- Faraone S.V., Asherson P., Banaschewski T., Biederman J., Buitelaar J.K., Ramos-Quiroga J.A., Rohde L.A., Sonuga-Barke E.J., Tannock R., Franke B. Attention-deficit/hyperactivity disorder. Nat. Rev. Dis. Primers. 2015;1:15020. doi: 10.1038/nrdp.2015.20.
- Joseph N, Zhang-James Y, Perl A, Faraone SV. Oxidative Stress and ADHD: A Meta-Analysis. J Atten Disord. 2015 Nov;19(11):915-24. doi: 10.1177/1087054713510354. Epub 2013 Nov 14. PMID: 24232168; PMCID: PMC5293138.

Abbreviations: 8-OHdG: 8-hydroxy-2'-deoxyguanosine; MDA: malondialdehyde; SOD: superoxide dismutase; NO: nitric oxide; TAS: total antioxidant status; TOS: total oxidation status; fig: figure

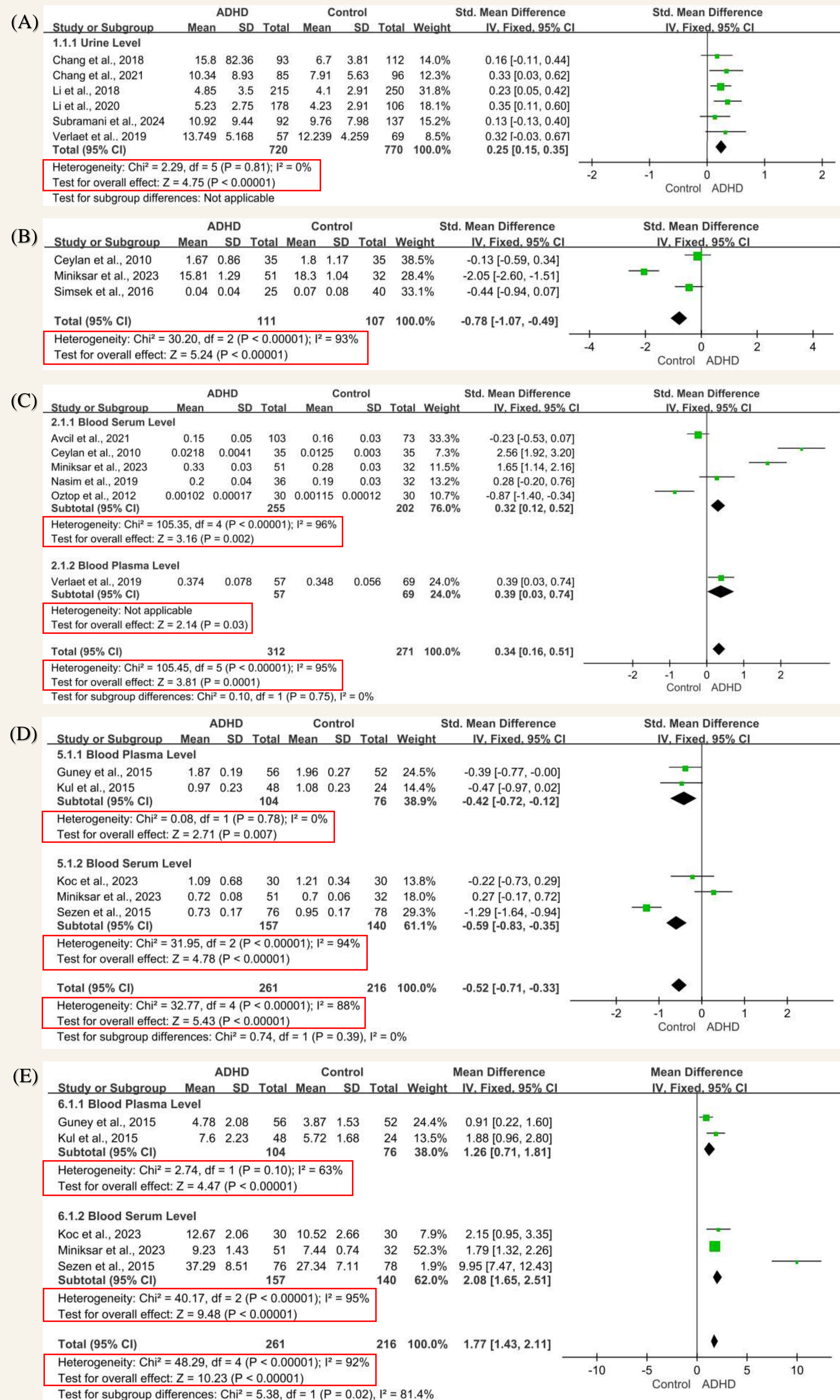


Figure 2. Forest plot of (A) 8-OHdG (B) SOD (C) MDA (D) TAS (E) TOS. The red rectangle highlights the heterogeneity and the overall effect sizes of the included studies.

Six studies examined the levels of 8-OHdG in urine and found a significant increase in the children and adolescents with ADHD compared to the healthy control (SMD: 0.25; 95% CI: 0.15 to 0.35; $P < .00001$) (Fig. 2A). The SOD levels in serum were analyzed in three studies and showing a significant reduction was found in those with ADHD (SMD: -0.78; 95% CI: -1.07 to -0.49; $P < .00001$) (Fig. 2B). In both serum and plasma, six studies found MDA levels to be significantly elevated in participants with ADHD (SMD: 0.34; 95% CI: 0.16 to 0.51) (Fig. 2C). Moreover, five studies confirmed that ADHD children and adolescents have lower levels of TAS (SMD: -0.52, 95% CI: 0.71 to 0.33; $P < .00001$) but higher levels of TOS (SMD: 1.77; 95% CI: 1.43 to 2.11; $P < .00001$) (Fig. 2D, E).

CONCLUSION

Children and adolescents with ADHD have lower levels of antioxidant activity, and they have increasing levels of oxidative stress.