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Saliva as a Diagnostic Tool for Attention-Deficit/Hyperactivity Disorder (ADHD): A Scoping Review

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ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly common neurodevelopmental disorder marked by inattention, hyperactivity, and impulsivity. ADHD is often under/misdiagnosed. Current diagnosis relies on clinical interviews and behavioral assessments, which do not include objective biomarkers. Saliva is a non-invasive fluid that can reflect underlying physiological and molecular processes, and it has shown potential in research on ADHD. Studies have examined various salivary biomarkers, including alpha-amylase, immunoglobulins, cortisol, trace metals, such as copper, zinc, and manganese, and DNA methylation patterns. Eight out of the nine studies included showed a difference in various biomarker levels in ADHD in comparison to controls. Results are mixed, with some markers elevated, some reduced, and others showing no clear differences from controls. This variability highlights that research in this area is still exploratory. Future studies should focus on combining multiple salivary markers into integrated profiles, which may improve diagnostic accuracy and provide a better understanding of the biological processes involved in ADHD.

Keywords: ADHD, Saliva, Salivary biomarkers, Non-invasive diagnosis, Neurodevelopmental disorders.

1. Introduction

Attention is a cognitive function that arises from the brain's ability to process a limited amount of relevant information at any given time. The prefrontal cortex focuses on specific content while inhibiting irrelevant stimuli to facilitate adaptive behavior (1). A wide variety of disorders may affect this function. Attention disorders involve difficulty in maintaining focus, regulating attention, or controlling impulsive behaviors. Many conditions are present with attention-related challenges, such as autism spectrum disorder (ASD), anxiety, depression, Parkinson's disease, and traumatic brain injury (TBI). As of now, Attention-Deficit/ Hyperactivity Disorder (ADHD) is the only officially recognized attention disorder in diagnostic frameworks, like the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (2).

ADHD presents persisting traits of less attention and hyperactivity, that significantly impact development or functioning (DSM-5) (2). ADHD is further categorized into three presentations: predominantly inattentive, impulsive due to hyperactivity, and a combination of the two. Each presentation reflects distinct challenges, from trouble in concentrating on and organizing tasks to excessive restlessness and impulsive actions (3).

Its etiology is multi-factorial, involving genetic, environmental, and neurobiological factors (4). Studies suggest that ADHD could be linked with dysregulation in several regions of the brain, especially those that take part in attention, and control of impulse, such as the

prefrontal cortex and the dopamine system (5). The pathophysiology of ADHD is thought to involve alterations in neurotransmitter systems, including dopamine and norepinephrine, both of which have pivotal roles in controlling attention and behavior. According to a recent study, ADHD present in children and teenagers is anticipated to be 8%, with boys two times as likely to be diagnosed compared to girls (4,6). Although the prevalence is high, there is no singular test that can be carried out to diagnose ADHD (7). Instead, diagnosis is based on several symptoms that can vary from one person to another. Although ADHD is typically diagnosed through clinical interviews and behavioral assessments, the absence of a definitive diagnostic test presents challenges in early detection and management.

Saliva is a promising non-invasive diagnostic tool, reflecting real-time biological processes through various biomarkers, like proteins, lipids, and metabolites. Its collection is safe and straightforward and eliminates the need for invasive procedures, making it particularly advantageous for diagnosing and monitoring various conditions. Saliva has been used to diagnose several conditions, including but not limited to: cardiovascular diseases, renal conditions, cancers, infections, and mental health disorders (8).

In cardiovascular disease, salivary biomarkers, such as C-reactive protein (CRP), myoglobin, and myeloperoxidase, have been used as an adjunct to other diagnostic techniques, like Electrocardiograms (ECGs) (9). Additionally, biomarkers, like cortisol, uric acid, and creatinine in saliva, have been observed in conditions, such as end-stage renal disease and chronic renal failure (10,11). Furthermore, saliva has also been used to test for diabetes. Salivary analysis in type 2 diabetes demonstrates higher levels of glucose, amylase, total protein, potassium, urea, chloride, and calcium in diabetic patients (12).

Last, but not least, saliva has recently gained traction as a diagnostic tool for mental health diseases. In neuropsychiatric research, salivary biomarkers, like cortisol, lysosomes, and other neurochemicals, have shown promise in diagnosing and monitoring anxiety, stress, and depression (13). Salivary diagnostics are particularly beneficial in individuals with mental disorders, as they are easier to perform and are met with less resistance. They also offer a more objective approach than behavioral assessments. While these findings show saliva's role in mental health diagnostics, its role in diagnosing ADHD remains largely unexplored. Exploring the salivary contents of patients with ADHD could provide us with insights regarding its diagnostic potential. Additionally, if consistent biomarker profiles could be established, then saliva can also help us understand the pathophysiology of ADHD and assist in monitoring the disease.

2. Materials and Methods

2.1 Literature Search Strategy

A literature search has been performed across online databases, including: PubMed, MEDLINE, Embase, Cochrane Library, SpringerLink, Elsevier, Wiley Online Library, Google Scholar, and IOS Press. The search covered studies published from January 2010 to August 2025, including the most up-to-date and relevant literature. Keywords and MeSH related to ADHD, saliva, salivary biomarkers, and oral health were used. Boolean operators (AND, OR) were applied to refine the search strategy. Additional sources, such as gray literature and reference lists of included studies, were also screened. Ethical approval was waived, as the study was a scoping review (Table 1).

2.2 Inclusion and Exclusion Criteria

Studies were included if they:

1. Examined the relationship between saliva and ADHD.
2. Focused on saliva as a diagnostic or monitoring tool for ADHD.
3. Were human studies published in peer-reviewed journals.
4. Reported original data and included measurable outcomes related to salivary analysis.

Studies were excluded if they:

1. Lacked salivary biomarker data or focused solely on neuroinflammation.
2. Were reviews, conference abstracts, or duplicates.
3. Were published in languages other than English or lacked full-text availability.

2.3 Study Selection

Two reviewers independently assessed the titles and abstracts of studies for eligibility. Based on the inclusion and exclusion criteria, the full texts of potentially relevant studies were evaluated. Discrepancies or uncertainties during selection were resolved by

consulting each other for clarification or consensus.

Table 1: List of studies included

Author (s)	Year	Study Type	Sample Size	Results (Salivary Biomarkers)
Krahel et al.	2021	Cross-sectional	132 (60 ADHD, 72 controls)	↑ alpha-amylase, sIgA, IgM; no cortisol difference
El Ghamry et al.	2021	Cross-sectional	209 (129 ADHD, 80 controls)	↓ cortisol in ADHD; cortisol correlated with ADHD aggression
Angeli et al.	2018	Cross-sectional	102 (62 ADHD, 40 controls)	↓ morning/evening cortisol; reduced cortisol awakening response
Isaksson et al.	2012	Observational	422 (201 ADHD, 221 controls)	↓ cortisol at waking, 30 min post-waking, bedtime
Robinson et al.	2024	Cross-sectional	283 (110 ADHD, 173 controls)	Altered copper, zinc, manganese levels in ADHD
Wilmot et al.	2016	Observational	112 boys	DNA methylation differences (VIPR2, MYT1L genes)
Barry et al.	2020	Case-control	180 (90 ADHD, 90 controls)	↑ salivary mercury (not statistically significant)
Boyle et al.	2021	Observational	92 ADHD children	No significant changes in oxytocin
Belal et al.	2025	Case-control	90 (60 ADHD, 30 controls)	↑ oxytocin in ADHD ($p = 0.031$); no link with empathy/executive function

2.4 Data Extraction

Data was extracted by the single reviewer using a pre-designed extraction sheet tailored to include the following details:

- **Study Name and Author(s)**: Identifying the study and its primary investigator(s).
- **Study Type**: Specifying the study's design (e.g. observational, cross-sectional, randomized controlled trial).
- **Sample Size**: Recording the total number of participants included in the study.
- **Results**: Summarizing key findings related to salivary biomarkers and their association with ADHD.
- **Remarks**: Highlighting significant observations, limitations, or additional comments relevant to the study's objectives.

The extracted data was organized in a table format for straightforward interpretation and comparison.

Findings were synthesized qualitatively, highlighting recurring themes and key insights related to salivary biomarkers in ADHD and their potential as diagnostic tools, as well as ADHD, saliva, and oral health (Figure 1).

3. Results

3.1 Salivary Changes in ADHD

Out of the nine studies included in this review, eight reported changes in salivary biomarkers among patients with ADHD, while one study found no significant differences compared with healthy controls. The studies looked at a range of biomarkers, which can be grouped into stress and immune markers, hormonal markers, trace metals, and epigenetic markers.

3.2 Stress and Immune Biomarkers

Krahel et al. (2021) found higher levels of salivary alpha-amylase (sAA), secretory immunoglobulin A (sIgA), and immunoglobulin M (IgM) in children with ADHD (14). Cortisol, a key hormone reflecting stress

and HPA axis activity, was examined in several studies. El Ghamry et al. (2021), Angeli et al. (2018), and Isaksson et al. (2012) reported lower cortisol levels in children with ADHD compared with controls, suggesting potential dysregulation of the stress response system (15-17).

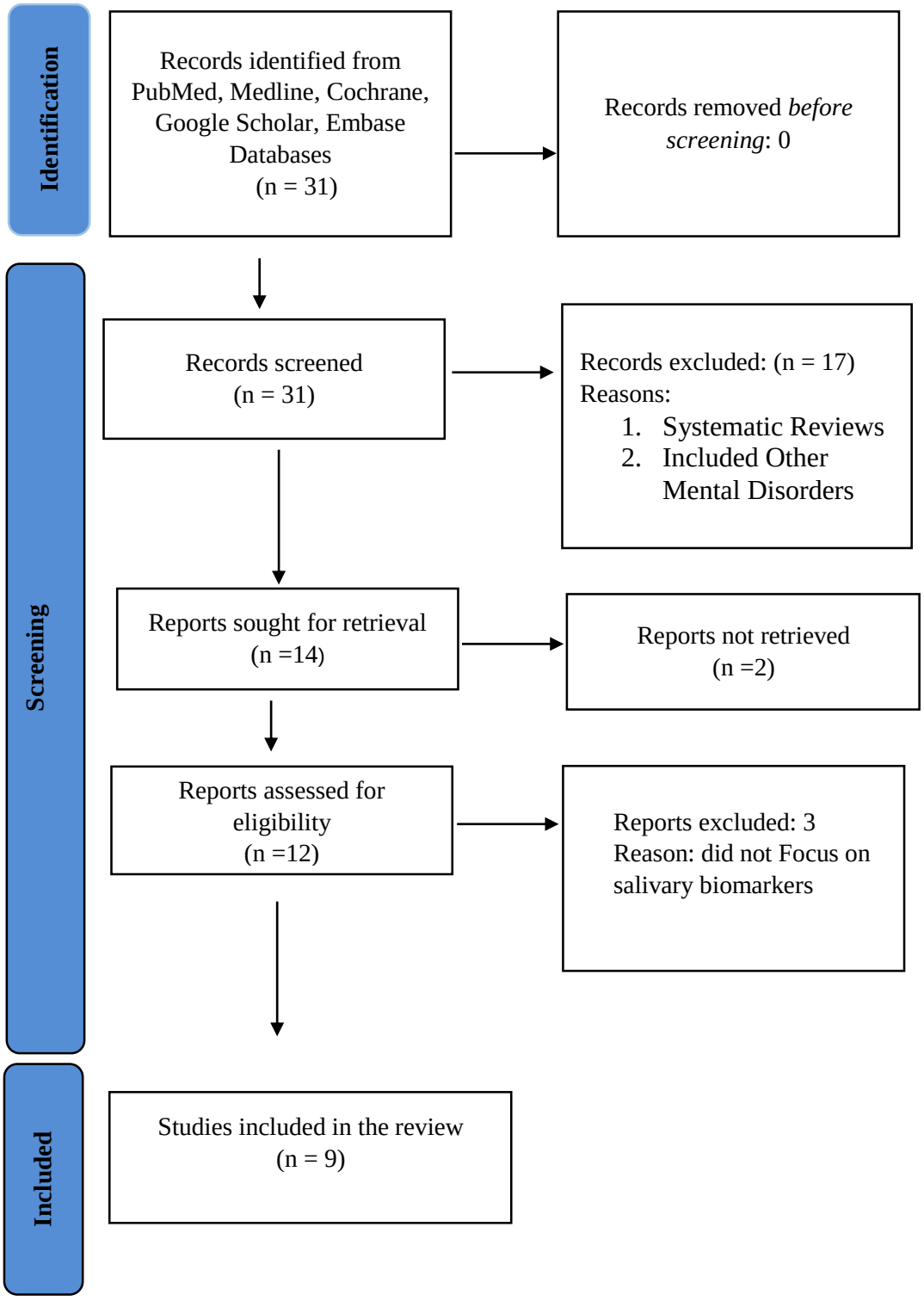

Figure 1: Summary of the systematic review workflow using PRISMA chart

3.3 Hormonal Biomarkers (Oxytocin)

Findings for oxytocin were inconsistent. Boyle et al. (2021) found no significant association between salivary oxytocin and ADHD symptoms, whereas Belal et al. (2025) reported higher oxytocin levels in children with ADHD, although this did not relate to empathy or executive functions (18,19). However, this inconsistency could be attributed to the small sample size of both studies.

3.4 Trace Metals

Robinson et al. (2024) observed higher salivary levels of copper, zinc, and manganese in children with ADHD, while Barry et al. (2020) reported increased mercury levels that were not statistically significant (20,21).

3.5 Genetic/Epigenetic Biomarkers

Wilmot et al. (2016) identified altered DNA methylation in the *VIPR2* and *MYT1L* genes, pointing to possible gene–environment interactions relevant to ADHD (22).

Overall, most studies found some changes in salivary biomarkers in patients with ADHD, but because each study looked at different biomarkers, it is hard to draw firm conclusions about their overall diagnostic value.

4. Discussion

This scoping review highlights emerging data on the association between ADHD and salivary biomarkers. The findings from the included studies underscore the multi-faceted nature of ADHD and its systemic implications.

4.1 Salivary Biomarkers in ADHD

The current review demonstrates that the saliva of affected individuals contains biomarkers, such as elevated salivary alpha-amylase (sAA), immunoglobulins (sIgA, IgM), altered DNA methylation patterns, and specific metal concentrations, all of which are associated with ADHD. Epigenetic mechanisms, particularly DNA methylation, have been increasingly recognized as potential contributors to ADHD risk and phenotype. Cecil and Nigg (2022) emphasized that while the field of epigenetics and ADHD is still in its infancy, methylation-based approaches hold promise for advancing prediction, management, and personalized interventions, provided methodological challenges are addressed (23). These markers may reflect differences in stress response, immune function, and gene–environment interactions in ADHD. For example, salivary cortisol patterns can provide information about hypothalamic-pituitary-adrenal (HPA) axis activity, while higher sAA and metals, such as copper, zinc, and manganese, may indicate systemic physiological changes associated with ADHD.

4.2 The Efficacy of Saliva as a Diagnostic Tool for ADHD

With ADHD being notoriously difficult to diagnose objectively, recent research has emphasized the potential role of biomarkers. A review by Chen et al. (2023) highlighted a range of potential ADHD biomarkers across radiographic, molecular, and physiological domains, suggesting that such markers may improve diagnostic accuracy, particularly in individuals with comorbidities that complicate behavioral assessments (24). Similarly, Hurjui et al. (2025) summarized emerging biomarkers, including neuroimaging measures, electrophysiological parameters, cortisol, vitamin D, microbiome analysis, and experimental techniques, such as eye-tracking and pupillometry, which could provide more objective insights into ADHD symptoms (25).

However, not all reviews tell a consistent story. Parlatini et al. (2024) examined the available research on candidate biomarkers for ADHD and found that, despite extensive studies across genetic, biochemical, neuroimaging, and neuropsychological areas, no biomarker has yet proven reliable or reproducible enough for clinical use (26). They noted key challenges, such as small sample sizes, methodological differences between studies, and a lack of standardization, which have shown the translation of biomarker research into practical diagnostic tools.

Similarly, Cortese et al. (2023) conducted the first large-scale systematic review of candidate biomarkers for neurodevelopmental disorders in children and adolescents. They screened over 10,000 references and included 780 studies covering biochemical, neuroimaging, neurophysiological, neuropsychological, and genetic approaches. Even with this wide-ranging evidence, the review concluded that no biomarker reached the benchmark of ≥80% sensitivity and specificity in independent studies (27). The authors also

highlighted common obstacles, including methodological variability, reliance on single biomarkers rather than combined profiles, and inconsistent reporting of predictive values.

Taken together, these findings suggest that while salivary biomarkers and other emerging measures show potential, the current evidence is still too variable to support their use in routine clinical practice.

4.3 Salivary Diagnostics in Other Mental Disorders

Interestingly, saliva-based diagnostics have also shown promise in conditions, such as autism spectrum disorder (ASD). A mini-review by Sharma et al. (2023) highlighted the potential of salivary biomarkers, such as mRNA, in diagnosing ASD (28). This mirrors the findings in ADHD, where biomarkers, such as cortisol and immune proteins, also exhibit significant deviations from neurotypical controls. Although both disorders share neurodevelopmental origins, the distinct salivary biomarker profiles observed in ASD and ADHD suggest that saliva can serve as a disorder-specific diagnostic medium. For instance, ASD studies commonly report elevated inflammatory markers and altered microRNA expressions, which are linked to neuroinflammation. In contrast, ADHD studies highlight stress markers, like sAA and cortisol, reflecting dysregulated HPA axis activity. These differences underscore the specificity of salivary biomarkers in capturing the unique pathophysiological features of ADHD and ASD. Comparing ADHD *vs*. ASD biomarker profiles may aid in disorder-specific diagnostic tool development.

4.4 Limitations

This review has several limitations that should be considered when interpreting the findings. First, the included studies varied widely in terms of sample size, the specific salivary biomarkers analyzed, and the criteria used to diagnose ADHD. This heterogeneity makes it difficult to generalize the results to the broader ADHD population. Second, differences in saliva collection methods, including the time of day and collection techniques, may have affected biomarker levels and introduced variability across studies. Third, most of the studies were observational, which limits the ability to draw conclusions about causal relationships between salivary biomarkers and ADHD. Additionally, factors, such as the age of participants, medication status, and the presence of comorbid conditions, were not consistently accounted for, even though they can significantly influence salivary composition. These limitations highlight the need for future research to use standardized methodologies, larger and more diverse samples, and careful consideration of potential confounding factors to provide more reliable and clinically meaningful insights.

4.5 Future Directions

There is a strong need for multi-disciplinary collaboration in the study of salivary biomarkers in ADHD. Future research should focus on establishing standardized protocols for saliva collection, ensuring consistency in timing, method, and storage conditions. Multi-center trials with larger, more diverse populations would help validate current findings and improve generalizability. Additionally, the development and validation of portable saliva-testing devices could facilitate real-time monitoring and broader clinical application.

Integrating expertise from dentists, psychologists, and pediatricians will be essential to address the complex factors affecting salivary biomarkers, including medication use, age, and comorbidities. Future studies could also investigate whether salivary biomarkers might reflect oral health status in ADHD populations, potentially expanding the role of saliva beyond diagnosis. By comparing salivary biomarker profiles in ADHD with those in other neurodevelopmental disorders, such as ASD, researchers can identify disorder-specific patterns and advance the development of targeted diagnostic tools and individualized therapeutic strategies. Future studies should ideally be longitudinal in order to better track biomarker changes over time and in response to interventions.

In addition, saliva provides a practical medium for studying epigenetic changes, such as DNA methylation, which may help clarify how genetic and environmental factors interact in ADHD. Exploring this line of research could support the development of more personalized diagnostic and therapeutic strategies in the future.

5. Conclusions

Salivary biomarkers hold significant promise for advancing our understanding of ADHD, yet their translation into clinical practice remains challenging. Saliva provides a non-invasive window into

physiological processes, including stress response, immune activity, metal homeostasis, and epigenetic regulation, such as DNA methylation. While individual markers, such as alpha-amylase, immunoglobulins, cortisol, and specific metals, show associations with ADHD, findings are heterogeneous, and no single biomarker has demonstrated consistent sensitivity or specificity sufficient for diagnostic use.

Given the exploratory nature of this field, future research should prioritize larger, well-characterized cohorts, standardized collection and analytic protocols, as well as longitudinal designs. Importantly, developing integrated biomarker profiles that combine multiple salivary measures may help capture the complex biological landscape of ADHD, reduce variability, and enhance predictive value. Such multi-level approaches could ultimately support earlier detection, more personalized interventions, and refined monitoring of ADHD in clinical settings.

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Conflict of Interests

The authors declare no conflict of interests related to this work.

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