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Leptin as a biomarker of sleep dysregulation in children with ASD: A drug-free cohort study

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ABSTRACT

Objective: Autism spectrum disorder (ASD), typically diagnosed before the age of three, is characterized by deficits in social interaction, communication, and repetitive behaviors. Sleep disturbances are highly prevalent in ASD and have been associated with altered neuroendocrine regulation. Leptin, a hormone involved in metabolic balance and circadian rhythms, has been proposed as a potential biomarker of sleep and neurodevelopmental dysfunction. This study aimed to explore the association between serum leptin levels, sleep habits, and autism symptomatology in a cohort of children with ASD.

Materials and methods: A total of 76 medication-naïve children with ASD (mean age: 6.86 ± 1.88; range 4–11 years), defined as no current or previous exposure to psychotropic or sleep-modifying medications (including melatonin, stimulants, antihistamines, antidepressants, and antipsychotics), were compared to 105 age-matched typically developing controls. ASD diagnosis was based on DSM-5 criteria and confirmed using ADOS-2, ADI-R, and SRS-2. Sleep disturbances were assessed using the caregiver-reported Sleep Disturbance Scale for Children (SDSC) and fasting morning blood samples were collected to measure serum leptin levels.

Results: Children with ASD showed significantly higher SDSC total scores ($p < 0.001$) and leptin levels ($p < 0.001$) compared to controls. Significant positive correlations were observed between leptin levels and sleep disturbance scores as well as autism severity measures (all $p < 0.001$).

Conclusions: These findings highlight a significant association between elevated serum leptin levels and both sleep disturbances and autism symptom severity in medication-naïve children with ASD. While causality cannot be inferred, the data support the potential role of leptin as a peripheral correlate of sleep and behavioral dysregulation in ASD. Further longitudinal studies are warranted to examine leptin's utility as a monitoring biomarker within neurodevelopmental trajectories.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social interaction and non-verbal communication. The diagnosis is typically established around the age of three, although atypical behaviors and comorbidities, including sleep

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disturbances, may manifest earlier in development [1].

Sleep problems are among the most frequently reported comorbidities in children with ASD, with prevalence estimates ranging from 44% to 83% [2,3]. These disturbances commonly include delayed sleep onset, frequent nighttime awakenings, reduced total sleep time, and poor sleep continuity [4]. Such abnormalities have been associated with specific clinical phenotypes within the autism spectrum [5] and can be documented through objective sleep assessments such as actigraphy and polysomnography [6,7]. In comparison to neurotypical peers, children with ASD demonstrate longer sleep latency, more frequent and prolonged awakenings, reduced sleep efficiency, and abnormal nocturnal motor activity [8].

The etiology of sleep disturbances in ASD is multifactorial and may involve neurobiological, metabolic, and behavioral contributors. Neurochemical dysregulation—including alterations in serotonin, dopamine, gamma-aminobutyric acid (GABA), glutamate, and histamine systems—has been implicated both in the pathogenesis of ASD and in the modulation of sleep [9,10]. Elevated plasma levels of orexin-A and altered oxidative stress markers have also been reported in individuals with ASD [11]. Similarly, increased leptin concentrations—independent of body mass index—have been observed, possibly reflecting autonomic imbalance and thermoregulatory dysfunction [11–13].

Melatonin synthesis and circadian rhythm regulation are also frequently disrupted in ASD, often due to mutations in clock genes and abnormalities in melatonin secretion patterns [14]. Several studies have documented atypically high daytime melatonin levels and low nocturnal levels in children with ASD [15,16], supporting a role for circadian dysregulation in the genesis of sleep disturbances.

Moreover, feeding difficulties—affecting up to 70% of children with ASD—can result in micronutrient deficiencies (e.g., iron), further contributing to conditions such as restless legs syndrome and periodic limb movement disorder [17,18]. Leptin, a hormone implicated in both sleep regulation and metabolism, may also play a central role in this complex interplay, regardless of obesity status [19–21].

Recent systematic reviews confirm the high prevalence of sleep problems in children with ASD and highlight the potential utility of non-pharmacological interventions [22]. Emerging evidence further supports a role for metabolic and neuroendocrine markers—particularly leptin—in the pathophysiology of sleep disruption in this population [23,24].

2. Objective

The present study aims to investigate the relationship between serum leptin levels and caregiver-reported sleep disturbances in a cohort of children with ASD who are naïve to psychotropic and sleep-modifying medications, focusing on both the prevalence of sleep disturbances and their correlation with ASD symptom severity.

3. Material and methods

3.1. Procedure

This study was approved by the Ethical Committee at University of Campania "Luigi Vanvitelli" (Protocol number n°17156/20) and followed the guidelines set forth the Declaration of Helsinki. All subjects signed informed consent forms and understood the purpose and process of the research before participating in this study. All parents signed an informed consent covering the availability of any previous psychological evaluation, and the fact that any results obtained from this study were to be used for scientific purposes.

ASD medication-naïve children diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 5th ed. (DSM-5) (American Psychiatric Association, 2013) within an age-range of 4 to 11 years were recruited. ASD diagnosis was established through clinical evaluation and was supported by the Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al., 2012), ADI-R [25] and by the Social Responsiveness Scale (SRS) (Constantino et al., 2005). Exclusion criteria included current or previous treatment with psychotropic or sleep-modifying medications, including antipsychotics, antidepressants, stimulants, antihistamines, melatonin, or other agents potentially influencing sleep or neuroendocrine parameters; overweight (BMI >85th percentile) and obesity (BMI >95th percentile); cognitive disability (IQ < 70); neurological disorders (e.g., headaches, epilepsy); chromosomal syndromes; and other psychiatric disorders.

The term "medication-naïve" was used to indicate the absence of lifetime exposure to psychotropic or sleep-modifying medications.

Control subjects were recruited from a historical cohort of typically developing children enrolled from schools in the Campania region between 2021 and 2024. Inclusion criteria included typical neurodevelopment and the absence of diagnosed neurological, psychiatric, or sleep disorders based on parental report and clinical screening. Children with chronic medical conditions, neurodevelopmental disorders, or current use of medications potentially affecting sleep or neuroendocrine parameters were excluded.

Blood samples in the control group were collected in the morning following an overnight fast, using procedures comparable to those applied in the ASD group. Samples were processed and stored under standardized conditions and analyzed using the same ELISA methodology.

Participants in both groups were recruited from the same urban area and were matched for age, sex, and BMI z-score. Formal socioeconomic indicators were not systematically collected; however, participants were drawn from comparable educational and social contexts.

Pubertal status was not systematically assessed in this cohort. Given the known influence of puberty on leptin physiology, this represents a potential source of variability.

3.2. Sleep Disturbance Scale for Children (SDSC)

Mothers of children filled out the Sleep Disturbances Scale for Children (SDSC), a standardized questionnaire for the assessment of sleep problems during development, consisting of 26 items grouped into six subscales: Disorders in Initiating and Maintaining Sleep (DIMS), Sleep Breathing Disorders (SBD), Disorders of Arousal (DA), Sleep–Wake Transition Disorders (SWTD), Disorders Of Excessive Somnolence (DOES), and Nocturnal Hyperhidrosis (SHY). The SDSC provides caregiver-reported information on sleep disturbances and does not represent an objective measure of sleep architecture. This scale is widely used in school-aged children. The scale is validated for Italian samples [26]. According to the SDSC validation criteria, scores ≥71 for the SDSC total score, ≥17 for DIMS, ≥7 for SBD, ≥6 for DA, ≥14 for SWTD, ≥13 for DOES, and ≥7 for SHY were used [26]. For the present study, both the percentages of pathological scores for each SDSC subscale and the continuous total and subscale scores were analyzed. Percentages were used for descriptive and group comparison analyses, while continuous SDSC scores were used for correlational analyses with leptin levels.

Since the SHY subscale cannot be considered a sleep disorder category per the ICSD, it was omitted from the analysis.

3.3. Autism Diagnostic Observation Schedule—Second Edition (ADOS-2)

The Autism Diagnostic Observation Schedule—Second Edition (ADOS-2) is a semi-structured, play-based assessment that evaluates communication, social interaction, and restricted behaviors through direct observation of the child by a trained clinician (Lord et al., 2012).

Autism Diagnostic Interview—Revised (ADI-R)

The Autism Diagnostic Interview—Revised (ADI-R) is a structured, caregiver-based interview that explores developmental history and current behavior across key domains, including reciprocal social interaction, communication, and restricted/repetitive behaviors [25].

3.4. Social Responsiveness Scale—Second Edition (SRS-2)

The Social Responsiveness Scale—Second Edition (SRS-2) is a norm-referenced, questionnaire-based tool completed by parents or teachers to assess the severity of autism-related traits in naturalistic settings (Constantino et al., 2012).

3.5. Serum leptin measurement

Patients underwent a blood sample after an overnight fast at 8.00 a.m. Serum was stored at −20 °C until assessment. Serum leptin levels were measured using the commercial ELISA kit (DIAsource ImmunoAssays SA, Nivelles, Belgium). Sensitivity was 0.04 ng/mL and the intra- and inter-assay variabilities were 10 and 10.2% respectively.

ASD and control samples were processed using the same assay procedures and laboratory protocols to minimize methodological variability.

3.6. Statistical analysis

Group differences in age, sex, and sleep disturbances (as measured by SDSC total scores) between children with ASD and typically developing controls were evaluated using chi-square and Student's t-tests.

Correlation analyses were primarily conducted within the ASD group to minimize the influence of between-group clustering effects. Pearson's or Spearman's correlation coefficients were selected based on distributional assumptions and data normality. Associations were explored between serum leptin concentrations and sleep disturbance measures (SDSC subscales and total score), as well as autism diagnostic measures (ADI-R, ADOS-2, and SRS-2). To address potential confounding, additional analyses were performed using multivariable models and/or partial correlations adjusted for age, sex, and BMI z-score. When pooled analyses were considered, diagnostic group was included as an additional covariate.

Sex, age, and BMI z-score were considered as relevant biological covariates in the interpretation of the associations between leptin levels and sleep disturbances.

Logistic regression analyses were conducted to estimate odds ratios (OR) and 95% confidence intervals (CI) for sleep disturbances in the ASD group compared to controls. Leptin distribution was visually inspected and tested for normality. As values approximated a normal distribution, leptin concentrations are presented as mean ± standard deviation; median and interquartile range were considered where appropriate.

All statistical analyses were performed using IBM SPSS Statistics (version 28), and significance was set at a two-tailed p-value <0.05.

4. Results

4.1. Sample characteristics

A total of 76 medication-naïve children with ASD (mean age = 7.09 ± 2.01 years) and 105 typically developing children (mean age = 6.72 ± 1.70 years) were included. No significant differences were observed between the two groups in terms of age (p = 0.09), sex distribution, or BMI z-scores (p = 0.12) (Table 1).

Table 1
Sociodemographic and clinical characteristics of the sample.

Variable	ASD (n = 76)	Controls (n = 105)	*p-value*
Age - M (SD)	7.09 (2.01)	6.72 (1.7)	0.09
z-BMI - M (SD)	0.56 (0.18)	0.57 (0.22)	0.12
SDSC_TOT - M (SD)	79.49 (8.66)	47.6 (8.49)	**<0.001**
ADOS-2 - M (SD)	16.82 (4.43)	NA	NA
ADI-R - M (SD)	31.47 (3.96)	NA	NA
SRS-2 - M (SD)	90.11 (13.26)	NA	NA
Leptin ng/mL - M (SD)	1.54 (0.33)	1.02 (0.27)	**<0.001**

Legend: p-value <0.05 was considered statistically significant.

4.2. Sleep disturbances in ASD

Children with ASD exhibited significantly higher scores on the Sleep Disturbance Scale for Children (SDSC) compared to controls (mean SDSC_TOT = 79.49 ± 8.66 vs. 47.6 ± 8.49, p < 0.001). The odds ratios (OR) for sleep disorders were significantly higher in the ASD group, particularly for Disorders of Initiating and Maintaining Sleep (DIMS, OR = 5.04), Disorders of Arousal (DA, OR = 4.91), Sleep–Wake Transition Disorders (SWTD, OR = 4.69), Disorders of Excessive Somnolence (DOES, OR = 5.25), and the total SDSC score (OR = 15.75), all with p < 0.0001 (Table 2).

4.3. Leptin levels

Serum leptin concentrations were significantly higher in children with ASD than in controls (1.54 ± 0.33 ng/mL vs. 1.02 ± 0.27 ng/mL, p < 0.001) (Table 1), which also depicts the age-related distribution of leptin levels (Fig. 1). These values fall within the expected physiological range for school-aged children but indicate a relative elevation in the ASD group.

4.4. Correlational analyses

Pearson's correlation analyses performed within the ASD group revealed significant positive associations between leptin levels and all SDSC subscales, including the total SDSC score (Table 3; Fig. 2).

In addition, leptin concentrations were significantly correlated with autism severity measures (ADI-R, ADOS-2, and SRS-2) (Table 4; Figs. 3–5).

Table 2
Relationship between children affected by autism spectrum disorders (ASD) and typically developing ones among Sleep Disturbance Scale for Children (SDSC) scales.

	ASD (n = 76)	TDC (n = 105)	OR	95% CI	Z-score	p-value
DIMS	81.7%	19.3%	5.0387	3.2189 - 7.8873	7.073	<0.0001*
SBD	46.1%	21.0%	2.1980	1.4097 - 3.4269	3.476	0.0005*
DA	84.2%	17.1%	4.9123	3.1902 - 7.5638	7.228	<0.0001*
SWTD	89.5%	19.0%	4.6974	3.1431 - 7.0202	7.546	<0.0001*
DOES	75.0%	14.3%	5.2500	3.2286 - 8.5370	6.685	<0.0001*
Total SDSC Score	75.0%	4.8%	15.7500	6.6302 - 37.4141	6.245	<0.0001*

Legend: Disorders in Initiating and Maintaining Sleep (DIMS); Sleep Breathing Disorders (SBD); Disorders of Arousal (DA); Sleep–Wake Transition Disorders (SWTD); Disorders of Excessive Somnolence (DOES); Nocturnal Hyperhidrosis (SHY).
Logistic regression analysis was performed to estimate odds ratios (OR) and 95% confidence intervals (CI).

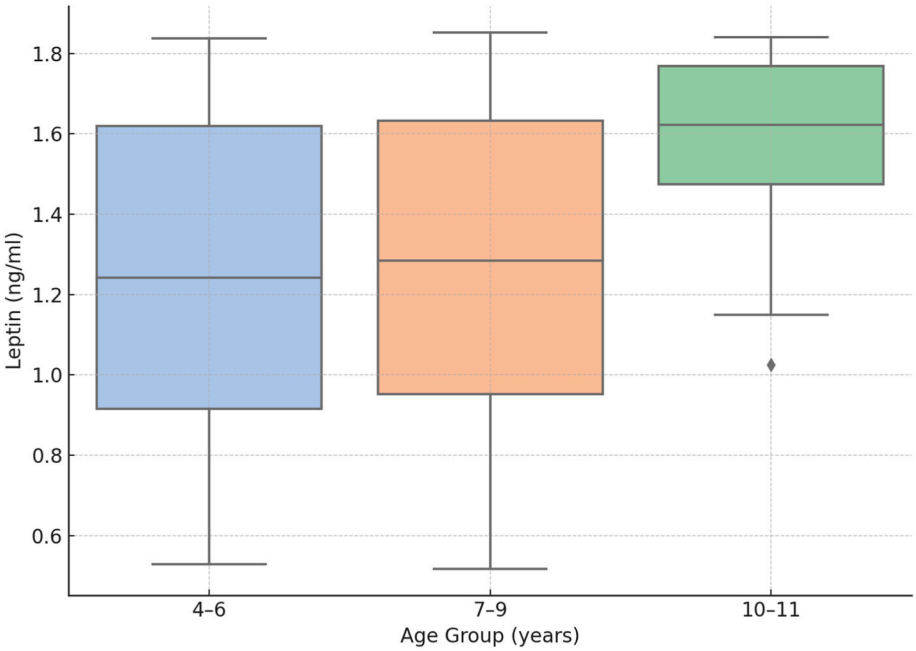

Fig. 1. Serum Leptin Levels by age group in children with ASD.

Table 3
Pearson correlation coefficients between serum leptin levels and SDSC subscales within the ASD group (n = 76).

	DIMS	SBD	DA	SWTD	DOES	Total SDSC Score
Leptin (ng/mL)	0.6421 p < 0.0001	0.3230 p < 0.0001	0.6123 p < 0.0001	0.7297 p < 0.0001	0.5605 p < 0.0001	0.8317 p < 0.0001

Legend: Pearson's correlation analysis revealed significant positive associations between leptin levels and each subscale of the Sleep Disturbance Scale for Children (SDSC), including DIMS, SBD, DA, SWTD, DOES, and the total SDSC score (all $p < 0.0001$).

4.5. Summary of findings

These results indicate that sleep problems are markedly more prevalent in children with ASD compared to typically developing peers. Furthermore, leptin levels are elevated in the ASD group and show statistically significant correlations with both sleep disturbances and autism severity measures, suggesting a potential role of leptin in the sleep–behavior relationship in ASD.

5. Discussion

This study confirms that children with Autism Spectrum Disorder (ASD) show a high prevalence of sleep disturbances and exhibit elevated serum leptin levels compared to typically developing peers [3,24]. Although absolute leptin concentrations remained within physiologically plausible ranges, the consistent group difference suggests a relative neuroendocrine alteration rather than a purely metabolic abnormality. Importantly, leptin concentrations were positively associated with both the severity of sleep problems and core autism symptoms [11,27]. For interpretative purposes, particular emphasis was placed on associations observed within the ASD group, as pooled analyses may partially reflect between-group differences rather than true within-group biological relationships. Similar neuroendocrine pathways involving leptin and orexin have also been implicated in non-ASD populations with sleep disorders, supporting a broader physiological framework [28]. While these findings point toward a biological connection between sleep and behavioral regulation, the study design does not allow for causal inference. The observed associations should be interpreted as correlational, though biologically plausible.

The sleep alterations identified in the ASD group are consistent with prior literature, particularly regarding difficulties with sleep initiation, arousal transitions and nighttime awakenings [6,7,29]. Although frequently reported by caregivers, these issues may remain clinically underprioritized, despite their impact on emotional and behavioral functioning [30,31]. Notably, average sleep scores in the ASD group exceeded established clinical thresholds, reinforcing the notion that sleep dysregulation is not merely a comorbidity but a central component of the ASD phenotype. Given the high prevalence of sleep disturbances observed in the ASD group, odds ratios may overestimate the corresponding relative risks; therefore, effect sizes should be interpreted cautiously. Beyond behavioral regulation, sleep difficulties in ASD have also been associated with impairments in cognitive functioning, learning capacity, and attention, potentially contributing to poorer academic and adaptive outcomes [11,32,33].

Our results also reveal that leptin elevations in ASD occur independently of body weight, suggesting a broader neuroendocrine imbalance rather than a purely metabolic anomaly [12,34]. Leptin is involved in regulating hypothalamic pathways, including those that modulate the suprachiasmatic nucleus (SCN), a key regulator of circadian rhythms [14]. Through these circuits, leptin may influence sleep–wake cycles, thermoregulation, and autonomic arousal—functions frequently altered in ASD [13].

In addition to its hypothalamic actions, leptin is known to interact with several neurotransmitter systems, including serotonin and orexin, both of which are implicated in arousal and sleep–wake regulation [10,15,16]. These interactions may converge with existing abnormalities in GABAergic and serotonergic signaling reported in ASD, including impaired interneuron migration and maturation [35,36]. The observed elevations in leptin may therefore reflect an adaptive—or potentially maladaptive—response to chronic circadian misalignment, neurodevelopmental stress, or low-grade inflammation [9].

The consistent correlations between leptin levels and both sleep disturbances and autism severity suggest an integrative role for leptin within a dysregulated sleep–behavior–metabolism axis. However, these

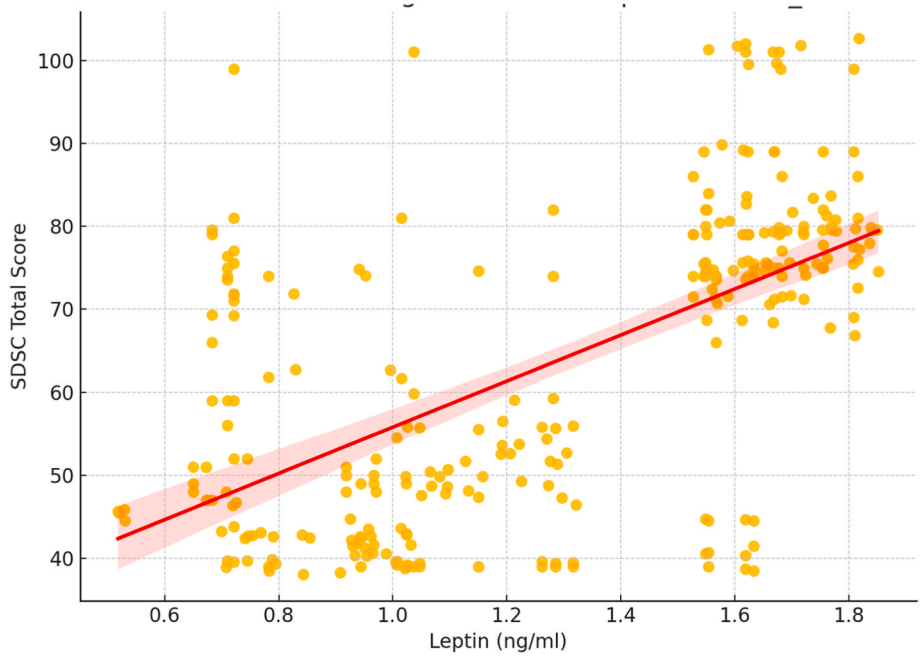

Fig. 2. Scatterplot showing the association between serum leptin levels and caregiver-reported sleep disturbance scores (SDSC-TOT) within the ASD group (n = 76). Pearson correlation analysis.

Table 4
Pearson correlation coefficients between serum leptin levels and autism diagnostic scores within the ASD group (n = 76).

	ADI-R	ADOS-2	SRS
Leptin (ng/mL)	0.8269 $p < 0.0001$	0.8041 $p < 0.0001$	0.8105 $p < 0.0001$

Legend: Pearson correlation analysis showed significant positive associations between leptin levels and ADI-R, ADOS-2, and SRS-2 scores (all $p < 0.0001$).

associations should be interpreted primarily in relation to within-ASD variability, as correlations derived from pooled ASD and control samples may be partially influenced by group-level clustering effects. Although leptin is not currently classifiable as a diagnostic biomarker, our findings suggest that leptin may represent a peripheral biological correlate associated with sleep and behavioral dysregulation in ASD, rather than a clinically established monitoring biomarker.

From a clinical perspective, this association may provide preliminary insights into neurobiological mechanisms potentially relevant to treatment monitoring, particularly in subgroups undergoing behavioral sleep interventions, chronotherapy, or melatonin supplementation [37,38]. These observations are especially relevant given that our sample was free from antipsychotic exposure, minimizing pharmacological interference with leptin metabolism and sleep [39]. Previous studies had reported increased leptin levels in ASD children, although often in

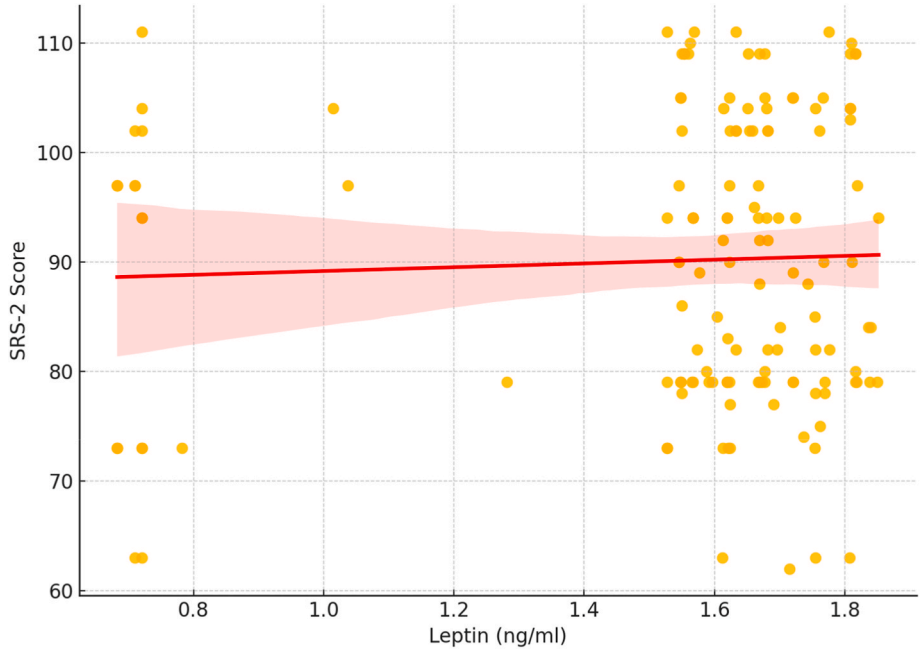

Fig. 3. Scatterplot showing the association between serum leptin levels and SRS-2 scores within the ASD group (n = 76). Pearson correlation analysis.

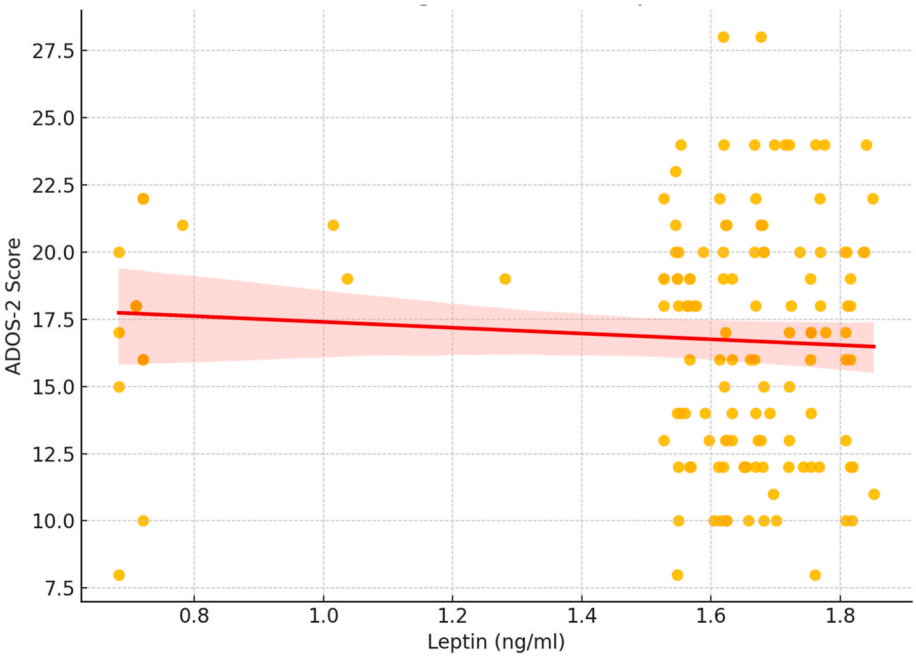

Fig. 4. Scatterplot showing the association between serum leptin levels and ADOS-2 scores within the ASD group (n = 76). Pearson correlation analysis.

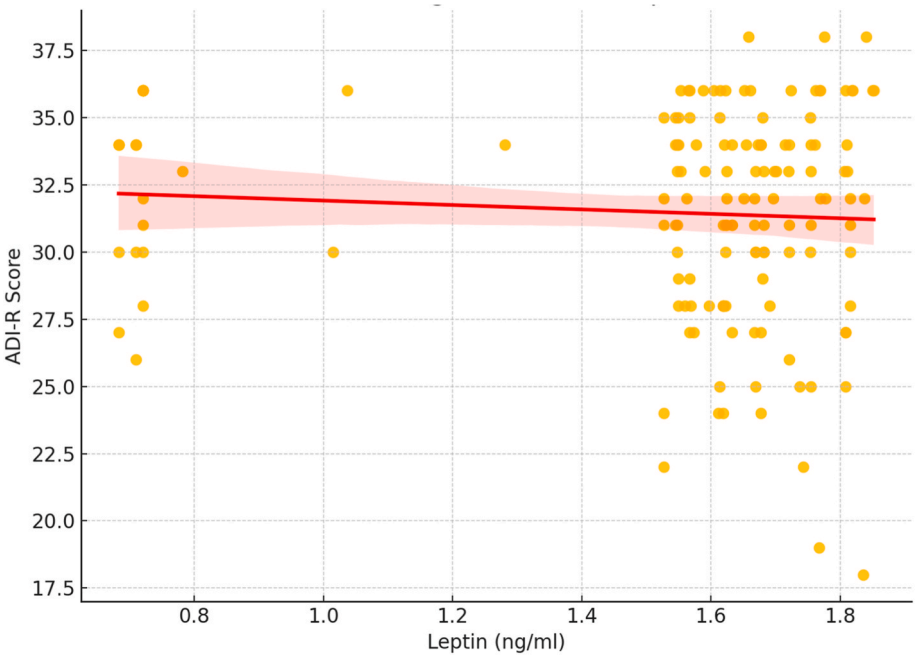

Fig. 5. Scatterplot showing the association between serum leptin levels and ADI-R scores within the ASD group (n = 76). Pearson correlation analysis.

cohorts exposed to medications; our results extend this evidence to a drug-free context [12,40].

These findings align with a growing body of evidence linking ASD to disrupted circadian biology, melatonin signaling abnormalities, and neurotransmitter imbalances [15,41]. Leptin may act as a downstream modulator or amplifier of this dysregulation, contributing to a maladaptive feedback loop involving neurodevelopmental, metabolic and behavioral systems. However, it remains unclear whether leptin contributes causally to these alterations or whether its elevation reflects a downstream consequence of chronic neuroendocrine stress. Rather than a static marker, leptin may participate in a dynamic physiological system, sensitive to internal homeostatic disruption and environmental inputs across developmental stages.

Next, mechanistic insights may come from animal models designed to explore the causal links between leptin signaling, sleep architecture and social behavior. Rodent studies have shown that leptin-deficient mice (e.g., db/db genotype) exhibit altered circadian rhythms, increased sleep fragmentation [42], and that leptin modulates synaptic plasticity in brain regions implicated in social cognition [43]. Such translational work may help clarify whether elevated leptin levels contribute directly to ASD-related phenotypes or instead reflect compensatory responses to behavioral and physiological dysregulation.

The recruitment of medication-naïve children allowed for a more accurate assessment of endogenous neuroendocrine profiles, free from

confounding pharmacological effects. However, this may have selected for a clinically less severe population in terms of externalizing behaviors, potentially limiting generalizability. Although participants were age-matched, additional developmental and environmental factors—such as

Status, diet, and physical activity—were not controlled and may influence leptin and sleep parameters. In addition, coexisting factors such as epilepsy, gastrointestinal disturbances, or environmental changes (e.g., seasonal variation, sleep hygiene) may also contribute to sleep and behavioral fluctuations. However, it remains difficult to determine whether such factors act as primary causes, maintaining conditions, or amplifiers of existing neurodevelopmental dysfunction [44,45].

Another limitation is that sleep disturbances were assessed through parent-reported questionnaires. Although widely used and validated, these tools are susceptible to recall and interpretation bias, particularly in parents of children with complex neurodevelopmental conditions [46]. Therefore, the findings should be interpreted as reflecting perceived sleep disturbances rather than objectively measured sleep dysregulation. Future studies using actigraphy, polysomnography, or sleep diaries are needed to validate leptin's association with sleep continuity, latency, and fragmentation. This may lead to an overestimation of sleep problems in ASD, which should ideally be verified using objective tools such as actigraphy or polysomnography. However, such methods often pose feasibility challenges in this population due to sensory sensitivities and compliance issues.

Although no age–leptin or age–sleep interactions were observed within this cohort, larger and longitudinal datasets will be better suited to address developmental variability and clarify temporal relationships. Future studies could also explore whether leptin trajectories mirror behavioral change across time or treatment, helping to identify more specific ASD phenotypes based on metabolic and sleep profiles [23,47].

5.1. Limitations

Socioeconomic status was not formally assessed and therefore could not be included as a covariate; this should be considered when interpreting sleep-related outcomes, although participants were recruited from comparable social contexts.

The use of a historical control group may introduce unmeasured variability related to recruitment timing and sample handling, although standardized laboratory procedures were applied.

Leptin levels are influenced by several biological and environmental factors, including sex, adiposity, pubertal status, diet, and circadian regulation. In the present study, sex and BMI z-score were considered in the interpretation of results, but pubertal status was not formally assessed. This may represent an additional source of variability in leptin concentrations.

6. Conclusions

In conclusion, this study provides evidence that sleep disturbances in drug-free children with ASD are not only frequent and clinically relevant, but also biologically correlated with elevated leptin levels. These findings suggest that leptin may represent a peripheral correlate of caregiver-reported sleep disturbances in ASD. While causality cannot be established, the strength and consistency of the associations highlight the need for further research exploring leptin's role within an integrative neurodevelopmental framework. Longitudinal and interventional studies are needed to clarify the temporal dynamics of this relationship and to assess leptin's potential utility as a biomarker for monitoring clinical evolution or treatment response in ASD.

CRediT authorship contribution statement

Marco Carotenuto: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Martina Gnazzo:** Writing – original draft, Methodology. **Giuditta Bargiacchi:** Writing – original draft, Methodology. **Valentina Baldini:** Formal analysis. **Giuseppina Rosaria Umano:** Data curation. **Giovanni Messina:** Investigation. **Marcellino Monda:** Investigation. **Daniela Smirni:** Data curation. **Giuseppe Plazzi:** Writing – review & editing, Supervision. **Karen Spruyt:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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