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# Relation between basal cortisol and reactivity cortisol with externalizing problems: A systematic review☆

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ABSTRACT

Delinquent behavior describes one of the most severe forms of antisocial and aggressive behavior, causing the highest mental health and public expenditures of problematic behavior in adolescence. Literature suggests that different concentrations of cortisol may serve as a biological marker for a severe antisocial subgroup of adolescents, although from the environmental risk factors that play a role in the development of severe delinquent and aggressive behavior, other neurobiological factors may be important. This review aims to analyze the association of cortisol levels with the development of delinquent behavior. Studies related to the topic were obtained from multiple databases, through rigorous exclusion and inclusion criteria. Only papers with empirical and quantitative methodologies from scientific and academic publications were included. Aims, methodological aspects (sample and instruments), and main conclusions were extracted from each study. Overall, the data suggest that regardless of the literature relating low cortisol levels to conduct problems and antisocial behavior, the lack of consensus in the examined studies demonstrates that more studies are needed to reveal the role of biosocial mechanisms in this hormonal-behavior link, and how these mechanisms are involved in establishing and maintaining delinquent behavior.

Antisocial behavior during childhood and adolescence can lead to harmful behaviors against others, as well as crime, and psychopathology, in adulthood [11,31]. Within antisocial behavior, callous-unemotional (CU) traits, predominantly present in individuals with high psychopathy, and other manifestations of psychopathic traits are associated with current and future criminal behavior in adults (e.g., [14]). The construct of externalizing problems refers to a group of behavior problems that are manifested in children and adolescents, which reflect negative actions on the external environment [3,9]. Although these externalizing problems consist of disruptive, hyperactive, and aggressive behaviors [22], in this paper, we will focus on antisocial behavior (e.g., aggressive and delinquent behavior), conduct disorder (CD; e.g., aggression that causes physical harm), and oppositional defiant disorder or disruptive behavior disorder (ODD or DBD; e.g., disobedient, hostile behavior toward parents and defiance of authority figures) [1].

Fig. 1.

Researchers have shown a growing interest in developmental factors, including biopsychological factors, associated with the development of behavioral problems in children. The study of child development has become an area of particular interest, not only for researchers who study its environmental, behavioral, and psychological aspects, but

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The authors do not have any interests that might be interpreted as influencing the research. The study was conducted according to APA ethical standards.

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also for researchers who are interested in genetic and other biological factors. One of the biological systems of interest for research is the hypothalamic-pituitary-adrenal axis (HPA axis), which has cortisol as a hormonal product, due to its importance in the individual response to stressful events or situations. Basal levels of cortisol have been examined, as well as cortisol changes in reaction to stressors (e.g., [66,67]). Reactivity to stressors in early adolescence and its relation to antisocial behavior is a particularly important problem, since stress and aggression are related [23].

Cortisol is continuously produced, and these basal levels of cortisol follow a diurnal rhythm: before wakening, cortisol begins to rise from very low levels and shows a distinct peak around wakening time. Levels then decrease throughout the rest of the day [6,8], unless individuals are subjected to certain biological conditions or stressful situations. Psychosocial stress is an important factor in the development and course of many disorders of diverse nosological frameworks. However, there is substantial intra-individual variability with respect to the impact of psychosocial stress on mental health. This may be related to differences in the activity of the HPA axis, indexing the HPA functioning as the main physiological stress response system [66,67].

The relationship between cortisol reactivity and antisocial behavior has been considered negative [10,17,36], positive (e.g., [36]), or statistically absent [26]. Studies that have hypothesized that lower levels of baseline cortisol and lower cortisol reactivity are associated with higher rates of externalizing behavior [24,42,43,65] propose a series of hypothetical mechanisms underlying the association between the reduction of HPA axis activity and antisocial behavior. One mechanism may be that individuals who are characterized by low autonomic activation are prone to seeking stimulation to increase their arousal levels [71]. In turn, those who frequently seek stimuli and, therefore, can often be involved in dangerous and stressful situations may become familiarized with these stimuli and eventually show a dull stress response [67]. The inverse relationship between cortisol and externalizing behavior is also in agreement with Raine's theory of fearlessness (1996). This theory states that children who have high levels of externalizing behavior are less sensitive to stress and less physiologically stimulated than non-externalizing children. As a result, they have low levels of anxiety and may engage in more frequent externalizing behaviors.

Theoretical assumptions point to the regulation of the HPA axis, due to the experience of stress and to problems of internalization in association with hypersensitivity to stress [15,26,35,54]. Conversely, externalization problems are considered secondary to hyposensitivity to stress and low fear [2,52,67]. In fact, increased HPA axis activity, as reflected in higher baseline levels of morning cortisol, has been related to anxious and depressive (internalizing) symptoms not only in adults [29,59,68,69], but also in children and adolescents [16,35,36,50,59], although these relationships in children are not as well established as in adults.

Aggression was associated with baseline cortisol, but not with cortisol reactivity to a stressor [2]. Studies in the last 10 years are equally inconsistent as to whether cortisol reactivity is positively or negatively related to aggression. These inconsistencies are explained by serotonergic system dysfunctions, differences in brain development, sample composition, outcome measures [67], and variations in exposure to violence [44]. An additional explanation is that adverse conditions that produce high cortisol in early life are postulated as contributing to the development of hypocortisolism in adult life [19,60]. Alternatively, Gunnar and Vazquez [19] suggest that hypo- and hyperactivity may reflect normal variations in cortisol reactivity in children. Thus, the reduced or increased cortisol may represent a biopsychological correlate of internalization or externalization problems, respectively (e.g., [20]).

However, the associations between cortisol and problems of internalization or externalization seem to be weaker and more inconsistent than previously assumed [12,16,21]. Therefore, the goal of this systematic review is to synthesize the findings regarding the role of cortisol in the development of behavioral problems. We intend to acquire a better notion of the level of evidence concerning the link cortisol-externalizing problems which is essential knowledge to better prevent and intervene in such problems. This review intends to answer the following research question: are basal cortisol and cortisol reactivity associated with behavioral problems, such as CD and ODD?

## 1. Method

The literature search was conducted in accordance with PRISMA guidelines [41], which aim to ensure clarity and transparency in systematic reviews, reducing the risk of failures and bias [41]. Given the evidence that conclusions are often misinformed in systematic reviews, the use of a method that helps to overcome this problem brings a number of advantages [33]: PRISMA guidelines foster the quality of the reviews, ensure that the reviews are presented with a defined structure and format, common to other reviews (uniformity), allow readers to assess the strengths and weaknesses, and make replications easier.

### 1.1. Search and study selection strategy

Studies were identified through a search in multiple databases from EBSCOhost, namely CINAHL Plus with Full Text, PsycInfo, Medline, Medline with Full Text, as well as in Web of Science and Pubmed. In order to avoid publication and source selection biases, searches were supplemented by a manual search. The following search expression was used in titles only: (cortisol* or “salivary gland secretions” or “hypothalamic—pituitary—adrenal”) AND (Callous* OR unemotional OR psychopath* OR sociopath* OR antiso* OR delinq* OR “extern* behavior” OR “behavio* disord*” OR “conduct disord*” OR “conduct problem*” OR oppositional* OR “behavio* problem*” OR defiant) NOT psychopatho*. The search was not restricted by any geographic, temporal, or linguistic factors.

### 1.2. Inclusion and exclusion criteria

As recommended by the PRISMA guidelines, the selection of studies for eligibility and data extraction was performed by two independent reviewers, as to reduce the probability of missing a study or errors in classification [41]. To select the studies, the following inclusion criteria were used: (a) empirical study – the study had to report empirical findings; (b) variables related to salivary cortisol and externalizing problems – the study had to include analyses of salivary cortisol and externalizing problems, or the interaction between both; (c) ODD/CD diagnosis or referred sample; and (d) the study had to include individuals below 21 years of age, assessed for ODD/CD.

The selected studies were analyzed for the following exclusion criteria: (a) methodological issues – studies that do not provide sufficient data as to allow replication, or in which the objectives or the methodology implemented are not perceived; (b) missing data – studies that do not describe the direction of the results; and (c) cortisol assessment – studies with plasma, blood, and urine collected to assess cortisol. This study focuses on salivary cortisol because saliva sampling is a non-invasive method for measuring cortisol, which is especially important in infants and children, while remaining reliable and less likely to confound results than other methods, including venipuncture [27]. In addition, samples can be repeatedly obtained and are easily collected in naturalistic environments without increasing ethical concerns, making this method well-suited to the study of mal-adaptive responses (see [27]).

The agreement index in the study selection process was assessed with Cohen's Kappa and revealed substantial agreement, $K = 0.74$, $p < .001$ [32]. The disagreements among reviewers were discussed and resolved by consensus.

### 1.3. Quality and risk bias of quantitative studies

The Quantitative Research Assessment Tool (QRAT; [4]) was used to assess the methodological quality of the studies included in this review. The QRAT comprises 12 items regarding the methodological features of the studies. Items can be rated −1, 0, 1, or NA (not applicable), except for the 12th question, where NA is not an option. According to the QRAT specifications, studies with lower scores should be regarded with more caution compared with studies that have higher scores, which are methodologically more robust. Substantive part of the studies included in this review (40%) had a score of seven or above (see Table 1).

### 1.4. Identification and screening

A total of 336 studies, published between 1971 and 2020, were identified from all databases and search methods, and a total of 263 studies were selected for eligibility analysis (73 studies were duplicates). From their abstracts, 74 were retained for full text eligibility, having been eliminated 189 studies, because: they were not related to the theme ($n$ = 171); participants were over 21 years of age ($n$ = 13); and/or cortisol assessment was performed through plasma collection or other collection ($n$ = 5). Six studies were included from manual search, making a total of 80 articles for full text analysis. Fifty-four articles were excluded after this analysis because: there was no specific diagnosis for ODD/CD or no (sub)clinical sample ($n$ = 27); no relation between cortisol and ODD/CD was presented ($n$ = 16); the studies included only participants over the age of 21 ($n$ = 4); cortisol was analyzed through plasma collection ($n$ = 4); they were theoretical articles ($n$ = 3). In total, this systematic review comprised 26 articles: 14 from Academic Search Complete; eight from Medline; two from Eric; one from Web of Science; and one from PsychoInfo. The objectives, methodological aspects (sample/instruments), and main conclusions were extracted from each study.

## 2. Results

### 2.1. Characteristics of included studies and salivary cortisol collection

Details regarding salivary cortisol collection protocols in individual studies are presented in Table 2. The studies included in this systematic review were published from 1991 to 2020, and about 40% of the

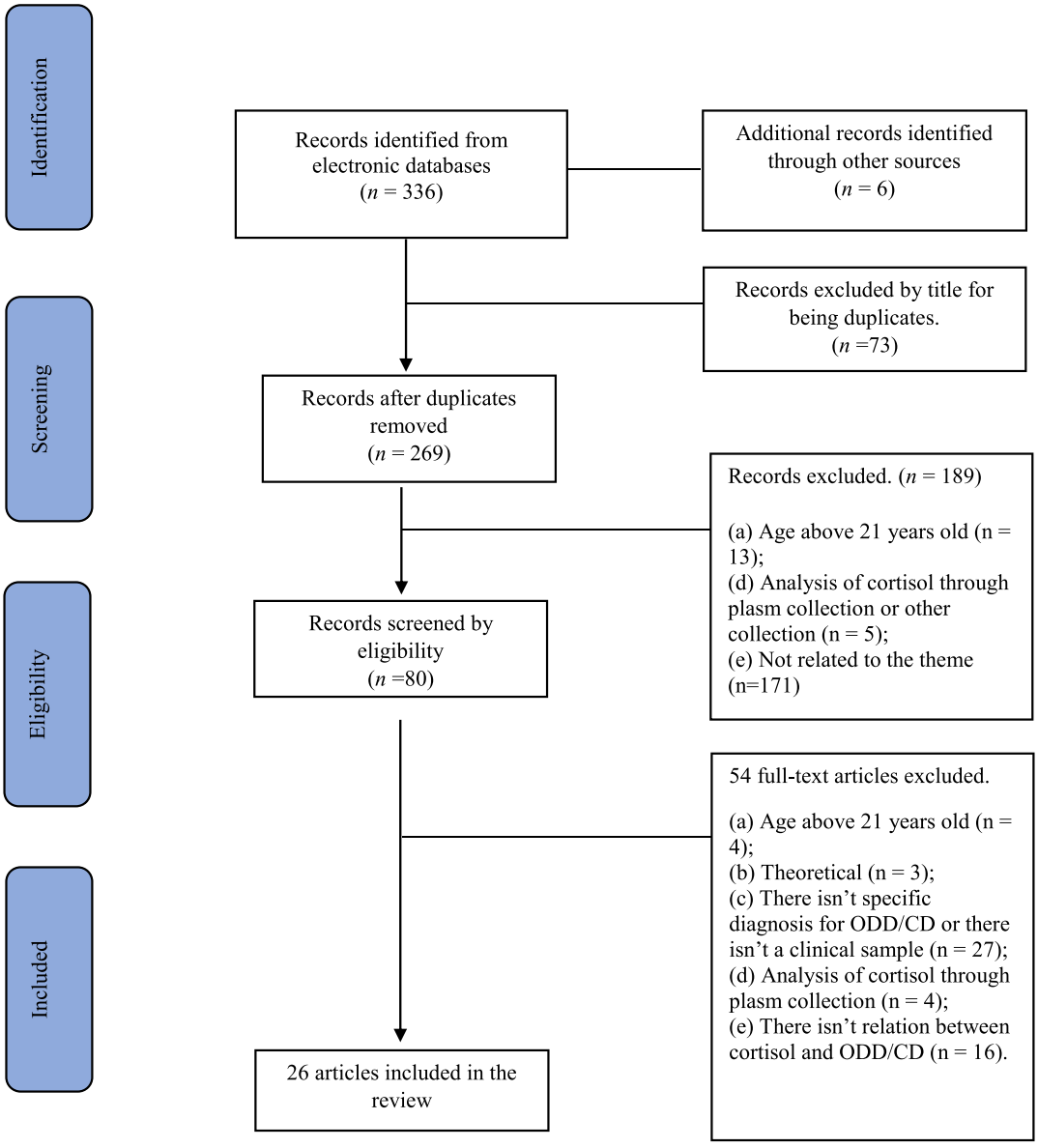


**Fig. 1.** Flowchart of Literature Review Process. In total 26 papers are cited in the current review.

**Table 1**
Quality and risk bias of quantitative studies.

| Study ID | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 | Item 10 | Item 11 | Item 12 | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabbs & Jurkovic [5] | 1 | 0 | 0 | −1 | 1 | N/A | −1 | 1 | 1 | 0 | 1 | −1 | 2 |
| Dietrich et al. [7] | 1 | −1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 |
| Feilhauer, Cima, Korebrits, & Nicolson [13] | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 |
| Kempes, Vries, Engeland, & Hooff [25] | 1 | 0 | 0 | −1 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | −1 | 4 |
| Kimonis, Goulter, Hawes, Wilbur, & Groer [28] | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | −1 | 8 |
| Kohrt et al. [30] | 1 | 0 | −1 | −1 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | 1 | 5 |
| Loney, Butler, Lima, Counts, & Eckel [34] | 1 | 0 | 0 | 0 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | −1 | 4 |
| Lopez-Duran, Olson, Hajal, Felt, & Vazquez [36] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| McBurnett et al. [38] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | −1 | 1 | −1 | 1 | −1 | 1 |
| McBurnett, et al. [40] | 1 | 0 | −1 | −1 | 1 | 1 | −1 | −1 | 1 | 1 | 1 | 1 | 3 |
| McBurnett et al. [39] | 1 | 0 | 0 | 1 | 1 | 1 | −1 | 0 | 1 | −1 | 1 | −1 | 3 |
| Platje et al. [45] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 6 |
| Popma et al. [46] | 1 | 0 | 0 | −1 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | −1 | 4 |
| Popma et al. [47] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Portnoy et al. [48] | 1 | 0 | 1 | −1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | −1 | 3 |
| Salis, Bernard, Black, Dougherty, & Klein [51] | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | −1 | 8 |
| Schoorl, Rijn, Wied, Goozen, & Swaab [53] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | 0 | 1 | −1 | 1 | −1 | 2 |
| Shoal, Giancola, & Kirillova [56] | 1 | 0 | 1 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | 1 | 6 |
| Snoek et al. [57] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | 1 | 1 | −1 | 1 | 1 | 5 |
| Snoek, Van Goozen, Matthys, Buitelaar, & Engeland [58] | 1 | 0 | −1 | −1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Susman et al. [61] | 1 | 0 | 0 | 0 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | 7 |
| Susman et al. [62] | 1 | 0 | 0 | −1 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | 6 |
| Susman, Peckins, Bowes, & Dorn [63] | 1 | 0 | 0 | −1 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | 6 |
| van Bokhoven et al. [64] | 1 | 0 | 0 | 0 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | −1 | 5 |
| van Goozen et al. [72] | 1 | 0 | −1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Wright, Hill, Pickles, & Sharp [70] | 1 | 0 | 0 | 1 | 1 | 1 | 1 | −1 | 1 | 1 | 1 | 1 | 8 |

Item 1 – Population; Item 2 - Randomized Selection of Participants; Item 3 - Item 4 - Response and Attrition Rate; Item 5 - Main Variables or Concepts; Item 6 - Operationalization of Concepts; Item 7 -Numeric Tables; Item 8 – Missing Data; Item 9 – Appropriatness of Statistical Tecnhiques; Item 10 – Omitted Variable Bias; Item 11 – Analysis of main Effect Variables; Item 12 – Ethical Approval.

studies were published in the last decade. Most studies used clinical samples ($n$ = 15, 60%), between four and 18 years of age. A variety of psychometric instruments were used for behavior assessment, as described in Table 2. The most used instrument was the Child Behavior Checklist (CBCL; [1]; $n$ = 12), followed by the Diagnostic Interview Schedule for Children (DISK; Shaffer et al., 2000; $n$ = 9).

There is also some heterogeneity regarding the cortisol evaluation method. The most common method is the radioimmunoassay (RIA; $n$ = 15, 57%), which is a very sensitive technique to measure concentrations of substances, followed by the enzyme linked immunoassay method (ELISA; $n$ = 5, 19%), which uses a solid-phase enzyme immunoassay (EIA) to detect the presence of a ligand (commonly a protein) in a liquid sample, through antibodies directed against the protein to be measured. Less common methods, but also reported in the articles, were the chemilumenescence-immuno-assay (CLIA; $n$ = 3, 12%) and the dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA; $n$ = 3, 12%). Regarding the cortisol gathering protocol, all studies perform saliva collection for a period of time of 1 day ($n$ = 26). The number of samples collected per day ranges between a minimum of one sample ($n$ = 7, 24%) up to a maximum of 17 samples ($n$ = 1, 4%), but most studies collected one sample per day. Eleven studies (42%) collected five or more samples per day. The moment when saliva is collected is quite variable among the studies. Of the 26 studies, only four (15%) collected saliva after wakening, suggesting that many studies did not use wakening as the reference time for subsequent diurnal sampling points.

### 2.2. Basal cortisol levels

Thirteen studies examined the relationship between basal and diurnal cortisol and externalizing problems. Several of the reviewed studies provide evidence of different concentrations in diurnal levels of cortisol, in adolescents diagnosed with externalizing problems [7,28,30,34,38,40,45,47,51,53,61], but others did not find significant results for this association [5,13,36].

Low levels of basal cortisol are associated with measures of aggression, evaluated through the Peer Conflict Scale (PCS; [37]) [28], specifically with the early onset of aggression and its persistence [40], both in participants diagnosed with DBD and forensic samples (offenders or delinquent adolescents). Similar results were found for adolescents diagnosed with ODD [30,56]. Boys meeting criteria for ODD consistently displayed lower diurnal salivary cortisol compared to boys without ODD diagnoses [30,53]. In contrast, van Bokhoven et al. [64] found higher cortisol levels in boys with CD than in boys without CD. In addition, boys with an aggressive form of CD had higher cortisol levels than boys who showed a covert form of CD [64]. These findings are inconsistent with previous results showing that antisocial children have lower levels of cortisol [40,43,56]. Moreover, Shoal et al. [56] analyzed cortisol in a preschool group and found that low resting salivary cortisol concentration was associated with later (5 years later) aggressive behavior in adolescence, assessed through the Youth Self Report (YSR; [1]).

Concerning the circadian rhythm of cortisol, the results of Popma et al. [47] show that a group of children with DBD, compared with normal controls, was characterized by a slower decrease in the diurnal cortisol cycle. A longitudinal study [51] found that a flattened diurnal rhythm of cortisol is associated with behavioral problems, assessed through the CBCL, and predicts increased behavior problems in later years.

It was also reported that male students attending the 6–12 grade-levels of a large school in the Southeastern United States and exhibiting elevated CU traits, were uniquely characterized by low cortisol concentrations (saliva samples were obtained at 9 a.m.), relative to male comparison groups [34]. Conversely, differences in cortisol levels were not significant between an antisocial group (forensic sample) and a comparison group, regardless of slightly lower levels in the participants of the former group [13].

The association between morning cortisol or cortisol awakening response (CAR) and behavioral problems was also examined in the reviewed studies. With the aim of investigating relationships between

**Table 2**
Summary of the studies' characteristics.

| Study ID | Sample Type | Total N (% male) | Controls | Age/ Mean age | Measures ODD/CD Assessment | Psychopathy dimensions Assessment | Salivary cortisol collection Assayed Methods of Cortisol | Saliva collection protocol | Basal/ React | Stressor | Main Cortisol findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dadds and Jurkovic [5] | Clinical | *N* = 113 (100%) | N/A | 17–18 | Personality and background items from NYS, QPOS, and CPS databases | N/A | RIA | T1 = 9am; | B | N/A | There isn't a significant main effect between violence and cortisol levels. |
| Dietrich et al. [7] | Clinical | *N* = 357 (n/a) | N/A | 10–12 | DISK; ASBQ, YSR. | N/A | RIA | T1 = immediately after awakening; T2= 30 min later | B | N/A | This study indicates that aggression is associated with higher morning cortisol levels in girls, and suggests a trend for lower morning cortisol levels mainly in boys |
| Feilhauer, Cima, Korebrits, and Nicolson [13] | Clinical | *N* = 125 (100%) | *N* = 62 healthy volunteers | 15 – 17 | DISK; RPQ; | ICU; NPIC; | CLIA | three predefined time points (10 h, 16 h, and 21 h) on two different days. | B | N/A | Low basal cortisol levels appear to be more closely related to a general deficit in behavioral regulation. |
| Kempes, Vries, Engeland, and Hooff [25] | Community | *N* = 120 (100%) | *N* = 40 normal control + 40 normal peer. | 8–12 | DISK; CBCL; PRPA | N/A | RIA | T1 = - 15 min before play session; T2= at the time when the children met in our research room; T3-T5= before the start of the zoo game, the free play and the domino game; T6= after the domino game had ended. | *B + R* | Play session | The cortisol levels of the normal control children decreased over time consistently. In contrast, DBD children appeared to increase in their cortisol level in sample cort3, approximately 20 min after first meeting the unknown play partner, where it normally would have continued to decrease. |
| Kimonis, Goulter, Hawes, Wilbur, and Groer [28] | Clinical | *N* = 232 (100%) | N/A | 14–18 | PCS | ICU | ELISA | Four saliva samples colleted between 14:00 and 16:30 hr | B | N/A | aggressive secondary CU variants had lower afternoon DHEA concentrations and higher cortisol-to-DHEA ratios and comorbid psychopathology compared with all other groups. |
| Kohrt et al. [30] | Clinical | *N* = 46 (100%) | N/A | 4.4–10.3 | ECRS; | N/A | RIA | morning (within 90 min of waking), early afternoon (between 2 and 6 h post-waking), late afternoon (between 6 and 10 h post-waking), and evening (greater than 10 hours post-waking) | B | N/A | Boys meeting criteria for ODD displayed consistently lower diurnal salivary cortisol levels compared to boys without ODD diagnoses. |
| Loney, Butler, Lima, Counts, and Eckel [34] | Community | *N* = 108 (49%) | *N* = 32 | 12–18 | APSD; | N/A | RIA | T1 = 9h | B | N/A | Male participants exhibiting elevated CU traits were uniquely characterized by low cortisol levels relative to |

(*continued on next page*)

**Table 2** (*continued*)

| Study ID | Sample Type | Total N (% male) | Controls | Age/ Mean age | Measures ODD/CD Assessment | Psychopathy dimensions Assessment | Salivary cortisol collection Assayed Methods of Cortisol | Saliva collection protocol | Basal/ React | Stressor | Main Cortisol findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | male comparison groups ($p < .05$). |
| Lopez-Duran, Olson, Hajal, Felt, and Vazquez [36] | Community | *N* = 73 (54%) | N/A | 6–7 | ABTC; | N/A | RIA | T1 = −30 min before stress task; T2 = −20 min; T3 = −10 min; T4 = −5 min; T5 = 0 min after stress task; T6 = 5 min; T7 = 10 min; T8 = 15 min; T9 = 20 min; T10 = 25 min; T11 = 30 min; T12 = 35 min; T13 = 40 min; T14 = 45 min; T15 = 50 min; T16 = 55 min; T17 = 60 min. | *B + R* | Calkins; Novel frustration condition | Examination of pure reactive, proactive, combined, or non-aggressive children indicated that reactive aggressive children had higher cortisol reactivity than proactive and non-aggressive children. |
| McBurnett et al. [38] | Clinical | *N* = 81 (100%) | N/A | 8 – 13 | In Walker et al. (1991) | N/A | RIA | Before the psychologica assessment began | B | N/A | Boys with CD showed significantly higher levels of cortisol when comorbid anxiety disorder was present than absent. Anxious boys were not higher in cortisol when the anxiety was not complicated by CD. |
| McBurnett, et al. [39] | Community | *N* = 335 (100%) | N/A | 7–17 | CBCL; TRF; | N/A | RIA | T1 = 8h27; T2 = 9:11; T3 = 9h32 (post stressor task); T4 = 9h40 (post stressor task); T5 = 9h52 (post stressor task); T6 = 10h08 (post stressor task); T7 = 10h26 (post stressor task). | *B + R* | TSST | Cortisol concentrations collected soon after the first challenge were positively related to CP in a post hoc subset of youths with extreme CP. |
| McBurnet, Lahey, Rathouz, and Loeber [40] | Clinical | *N* = 38 (100%) | N/A | 7 – 12 | CD sumptons from the 4 annual child psychodiagnostic evaluations. Structured interviews (NIMH Diagnostic Schedule for children) | N/A | RIA | The time of day of saliva collection could not be controlled and was allowed to vary across the day (e.g., 8:30 a.m.; 1:00 p.m.; 6:00 p.m.) | B | N/A | The salivary cortisol concentrations are strongly and inversely related to aggressive CD, peer aggression nominations, and ODD and also related (less clearly to covert CD. Cortisol concentration was directly linked to aggression and indirectly to covert CD |
| Platje et al. [45] | Clinical | *N* = 390 (57%) | N/A | 15 – 17 | YSR; | N/A | CLIA | T1 = 0 min after awakening; T2 = +30 min; T3 = + 60 min | B | N/A | Decreased levels of cortisol at awakening predicted adolescents' rule-breaking |
| Popma et al. [46] | Clinical | *N* = 71 | *N* = 30 | 12–14 | DISK | N/A | RIA | T1 = −20 min before PST; T2= before preparing the PST-talk; T3 = before the talk, T4 = immediately after the talk; T5 = 20 (after finishing the talk), T6 = +40 (after finishing the talk); | *B + R* | PST | The DP+ group, but not the DP- group, showed a significantly decreased cortisol response during the PST as compared with the NC group. |

(*continued on next page*)

**Table 2** (*continued*)

| Study ID | Sample Type | Total N (% male) | Controls | Age/ Mean age | Measures ODD/CD Assessment | Psychopathy dimensions Assessment | Salivary cortisol collection Assayed Methods of Cortisol | Saliva collection protocol | Basal/ React | Stressor | Main Cortisol findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | T7 = + 60 min (after finishing the talk). | | | |
| Popma et al. [47] | Clinical | *N* = 121 (100%) | *N* = 32 | 12–14 | DISK | N/A | RIA | T1 = + 30 min after awakening<br>T2 = +60 min after awakening<br>T3 = before lunch; T4 = 15h40; t5 = 8pm T6 = before going bed, | B | N/A | The DP + group, but not the DP_ group, showed a significantly slower decrease of cortisol during the diurnal cycle than the NC group. Furthermore, the DP + group had significantly lower cortisol levels in the first hour after awakening as compared with the NC group. |
| Portnoy et al. [48] | Community | *N* = 446 (100%) | N/A | 11–12<br>*M* = 11.92 | YSR<br>CBCL | N/A | ELISA | T1 = morning<br>T2 = Immediately prior to the laboratory tasks<br>T3 = 5 min after the end of the stress task<br>T4 = 20 min after the end of the stress task<br>T5 = 40 min after the end of the stress task | *B + R* | TSST | prenatal testosterone interacted with cortisol reactivity to predict externalizing behavior in males, but not females. In males, low cortisol reactivity was associated with higher levels of aggression and rule-breaking behavior, but only among subjects with low 2D:4D (i.e., high prenatal testosterone). |
| Salis, Bernard, Black, Doughert, and Klein [51] | Community | *N* = 283 (100%) | N/A | 6–9 | CBCL | N/A | DELFIA | T1 = 30 min after awakening<br>T2 = 30 min before bedtime | B | N/A | There is a negative association between cortisol slope and behavior problems |
| Schoorl, Rijn, Wied, van Goozen, and Swaab [53] | Clinical | *N* = 88 (100%) | *N* = 34 | 7.8 – 12.9 | DISK-IV; APSD; | N/A | DELFIA | T1 = Baseline<br>T2 = + 120 min<br>T3 = +20 min<br>T4 = +20 min<br>T5 = +20 min<br>T6 = +20 min<br>T7 = +20 min<br>T8 = +20 min | *B + R* | Psychosocial stress induction procedure | Within those with ODD/CD, callous-unemotional traits were predictive of high baseline cortisol levels. A high number of CD symptoms predicted reduced cortisol stress reactivity. |
| Shoal, Giancola, and Kirillova [56] | Clinical | *N* = 314 (100%) | N/A | 10–12 | YSR; MPQ | N/A | DELFIA | T1 = before stressor task<br>T2 = after stressor task | R | event-related potential task | Low cortisol in preadolescence was associated with low harm avoidance, low selfcontrol, and more aggressive behavior 5 years later, during middle adolescence. |
| Snoek et al. [57] | Clinical | *N* = 35 (63%) | *N* = 15 | 7–12 | CBCL; TRF | N/A | RIA | T1 = 8h30 am; T2 = 9h30 am;<br>T3 = 10h30 am; T4 = 11 am;<br>T5 = 11h30 am; T6 = 12 am. | R | Stress Responsiveness - CORT response | Children with ODD had lower CORT levels throughout the procedure and they did not differ from the NC children on subjectively reported stress. |

(*continued on next page*)

**Table 2** (*continued*)

| Study ID | Sample Type | Total N (% male) | Controls | Age/ Mean age | Measures ODD/CD Assessment | Psychopathy dimensions Assessment | Salivary cortisol collection Assayed Methods of Cortisol | Saliva collection protocol | Basal/ React | Stressor | Main Cortisol findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Snoek, Van Goozen, Matthys, Buitelaar, and van Engeland [58] | Clinical | *N* = 72 (68%) | *N* = 26 | 7–12 | DISK; CBCL; | N/A | RIA | experiment between 1 and 4 PM | *B + R* | Competitive setting inducing frustration, provocation, and aggression. | No baseline differences were found in cortisol between the four groups. However, the ODD and ODD + ADHD groups showed a significantly weaker cortisol response to stress compared to the ADHD and NC groups. |
| Susman et al. [61] | Community | *N* = 111 (50.4%) | N/A | 8–13 | DISK; CBCL; RAS; | N/A | ELISA | T1 = obtained immediately on wakening; T2 = 20 min postwake time; T3 = 40 min postwake; T4 = 4pm; T5 = at bedtime; | B | N/A | Early pubertal timing was associated with boys' rule-breaking and attention behavior problems and CD symptoms and girls' relational aggression. |
| Susman et al. [62] | Community | *N* = 135 (49%) | N/A | 8 – 13 | CBCL | N/A | ELISA | T1 = −20 min before TSST-C; T2 = −5 min; T3 = 0 min; T4 = +10 min; T5 = +20 min | R | TSST-C | As cortisol reactivity increased so did antisocial behaviours and rule breaking in later timing of puberty adolescents. |
| Susman, Peckins, Bowes, and Dorn [63] | Community | *N* = 135 (49%) | N/A | 8 – 13 | CBCL; DISK-IV; | N/A | ELISA | T1 = −20 min before TSST-C T2 = −5 min T3 = 0 min T4 = +10 min T5 = +20 min | R | TSST-C | boys with low cortisol reactivity were reported have more behavior problems; |
| van Bokhoven et al. [64] | Community | *N* = 194 (100%) | *N* = 159 | 14–16 | DISK-2.25; | N/A | RIA | Immediately upon arrival at the laboratory at between 8h45 am and 9h55 am. | B | N/A | Higher cortisol levels were found in boys with conduct disorder (CD) than in boys without CD. In addition, boys with an aggressive form of CD had higher cortisol levels than boys who showed a covert form of CD.. |
| van Goozen et al. (1998) | Clinical | *N* = 52 (100%) | *N* = 31 | 8- 11 | CBCL; TRF | N/A | RIA | T1 = −45 min before stressor task; T3 = during stressor task; T4 = 30 min after stressor task; | *B + R* | general setting of competition that involved frustration, provocation, and aggression | Cortisol levels in the ODD group were overall lower than those of the NC group, and the effect of stress seemed to be minimal and similar for both groups; however, individual differences were large. |

(*continued on next page*)

**Table 2** (*continued*)

| Study ID | Sample Type | Total N (% male) | Controls | Age/ Mean age | Measures ODD/CD Assessment | Psychopathy dimensions Assessment | Salivary cortisol collection Assayed Methods of Cortisol | Saliva collection protocol | Basal/ React | Stressor | Main Cortisol findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wright, Hill, Pickles, and Sharp [70] | Community | *N* = 283 (62%) | N/A | 5–7 | CBCL | APSD; | CLIA | T1 = 11h58 a.m | R | audiotaped recording of an argument between two adults | the highest levels of aggression at age 7 years were predicted by the combination of high CU traits and low cortisol reactivity |

Legend: N/*A* = not applicable; NYS= National Youth Survey; QPOS = Quay Personal Opinion Survey; CPS= Carlson Psychological Survey; RIA = radioimmunoassay; ELISA = method enzime linked immunoassay; YSR = Youth Self Report; ASBQ = Antisocial Behavior Questionnaire; DISK = Diagnostic Interview Schedule for Children; RPQ = Reactive-Proactive Aggression Questionnaire; ICU = Inventory of Callous-unemotional traits; NPIC = Narcissistic Personality Inventory for Children; CLIA = chemilumenescence-immuno-assay; DBD = Disruptive Behavior Disorder; CBCL = Child Behavior Checklist; PRPA = Parent-rating scale Reactive and Proactive Aggression; PCS = Peer Conflict Scale; DHEA = Dehydroepiandrosterone; ECRS = Emory Combined Rating Scale; ODD = oppositional defiant disorder; APSD = Antisocial Process Screening Device; CU = callous-unemotional; ABTC = Aggression Behavior Teacher Checklist; CD = conduct disorder; TRF = Teacher's Report Form; TSST = Trier Social Stress Test; PST = Public speaking task; DP = Delinquency diversion project; NC = Normal control; DELFIA = dissociation enheced lanthanid fluroimmunoassay; MPQ = Multidimensional Personality Questionnaire; CORT = Cortisol; RAS = Relational Aggression Scale; ADHD = Attention deficit hyperactivity disorder; *B* = cortisol basal; *R* = Cortisol Reactivity; *T* = time.

HPA axis activity (basal morning cortisol levels and CAR) and psychopathological problems, in 10- to 12-year-old children from a general population cohort, Platje et al. [45] found that decreased levels of cortisol at awakening predict adolescents' rule-breaking. Furthermore, 12 to 14-year-old boys who attended a delinquency diversion program showed significantly lower cortisol levels in the first hour after awakening than did the control group. Contrary to these results, measures of morning cortisol were significantly and positively associated with several measures of aggressive behavior in girls, but not in boys [7]. This overall pattern of results was found both in the general population and in a clinic-referred cohort.

### 2.3. Reactivity cortisol levels

Thirteen studies reporting a relationship between cortisol reactivity to a stressor and externalizing problems were reviewed. Several of the studies associate low cortisol reactivity with externalizing problems [46,48,53,58,63,70], but others find higher cortisol reactivity in children that reveal DBD or CD [25,36,39], as well as in boys with CD, in comparison to girls with CD, suggesting that sex can be an important moderator [62].

Shoal et al. [56] determined the resting cortisol concentration in a clinical sample of preadolescents with ODD and CD (without control group), at the beginning and after an event-related potential task. The authors found that low cortisol was associated with low harm avoidance, low self-control, and more aggressive behavior. The stress responsiveness procedure (salivary cortisol response), used by Snoek et al. [57], identified lower cortisol levels in children with ODD, throughout the procedure, but they did not differ from the control group on self-reported stress.

Comparing children with ODD/CD to controls, it is verified that the former has a lower cortisol response than the latter [46,53,58]. Specifically, according to Snoek et al. [58], the control group responded to the psychological stressor with a clear increase in cortisol, compared with ODD and CD groups, but when they were compared with an ADHD group without ODD/CD, no difference was found. Additionally, this study shows a tendency for a continuous decline of the cortisol response in ODD and CD groups, whereas the cortisol response increases in controls [58]. The continuous decline of cortisol for ODD and CD groups might reflect very frequent exposures to stress, which may have resulted in a habituation among ODD children to some types of stress [58]. In the same line, when Popma et al. [46] compared a DBD group, a delinquent group without DBD diagnosis, and a control group (NC), these authors found lower cortisol reactivity concentrations in the DBD group than in the NC group. Specifically, analysis of cortisol response showed a significantly smaller area under the curve for the delinquent group with DBD diagnosis compared with the control group. Boys with low cortisol reactivity were also reported, by Susman et al. [63], to have more externalizing problems. However, some studies show different results [25,36], with DBD groups having higher cortisol reactivity levels than controls. In contrast, comparing high CD with low CD participants during a stress task [39], the results showed that the most antisocial youth exhibited higher cortisol after the worst-event challenge.

Lower cortisol levels for ODD or CD participants, compared to controls, were found in stress exposure studies in a competition setting with elements of frustration, provocation, and aggression [58]. Similar results were found when using a psychosocial stress induction procedure [53], a stressor test with Public Speaking Task [46] or audiotaped recording [70]. However, concerning the Trier Social Stress Test (TSST; [39,62,63]) or in a play session with measures of aggressive behavior [25], there is an increase in cortisol reactivity after a previous stress task, for CD and DBD groups, as well as for participants with high CU traits. Although, Portnoy et al. [48], using TSST as a stressor task, found that low cortisol reactivity was associated with higher levels of externalizing behavior in males with high prenatal testosterone.

Additionally, when comparing basal cortisol with reactive cortisol, most studies suggest that, in the pre-stress phase, there are no significant differences between the ODD group and controls, but there are differences in cortisol levels during the stress phase of the experimental procedure [36,46,53,58]. The findings of these studies are similar to those found in children with CD [39]. Nonetheless, Kempes et al. [25] reported differences between the DBD and control groups, both for basal and reactive cortisol, despite the results for basal cortisol being marginally significant. The DBD group had low basal cortisol levels before the stress task, but approximately 20 min after first meeting the unknown play partner, the DBD group showed high cortisol concentration, and less decrease over time, compared with the normal group.

## 3. Discussion

Researchers have shown a growing interest in factors associated with the development of behavioral problems in children, including biopsychological factors. This review aimed to investigate whether there is an association between cortisol levels and externalizing problems, in order to answer the following research question: are basal cortisol and cortisol reactivity associated with behavioral problems, such as CD and ODD? A total of 25 studies examining possible relationships between cortisol levels and behavior problems in children and adolescents, mostly using cross-sectional comparison designs, were reviewed.

Firstly, it was verified that researchers apply a considerable variety of psychometric instruments to assess externalizing problems. These differences in the evaluation protocols hinder the comparison of results in order to obtain a consensual profile of the children and adolescents with externalizing problems. Although the most used instruments are the CBCL and the DISK, different questionnaires may lead to different results regarding the association between cortisol levels and externalizing problems, across different studies.

In the same way, cortisol was evaluated in different situations and contexts. In some studies, baseline cortisol was collected in a family environment, such as home or school (e.g., [7,45,47,51]), while in other studies it was collected upon arrival at the laboratory (e.g., [36,53,70]), sometimes as a pre-stressor assessment. This unfamiliar environment could result in anticipatory stress, affecting baseline levels of cortisol and biasing the results. Additionally, the reviewed studies reveal a variety of stress-induction tasks, making it difficult to compare results, as some tasks can evoke more stress than others. Using the example of Alink et al. [2], it is plausible that social stressors, such as a playground session with unknown colleagues, versus a public speaking task do not produce the same level of stress. In addition, the moment at which the cortisol is collected may have implications for the results obtained. The cortisol level is dependent on the time of day: due to the daytime cortisol rhythm, it is higher approximately 30 min after wakening, followed by a decline during the day [8]. Since cortisol samples are collected at different moments of the day, by different researchers, it is hard to make conclusions on atypical variations of cortisol levels in children with externalizing problems ([7,28,30,34,38,40,45,47]a; [47] b; [51,53,61]).

Another explanation for the mixed results found in the literature may reside in the fact that the existing studies defined ODD or CD in different ways, used either community samples [25, 39, 62, 63, 70] or clinical cases [46, 58], and used different protocols for the collection of cortisol, some involving single measurements under varying conditions.

Regarding the age of the participants, sampling criteria seems to be in accordance with two major developmental stages. Specifically, there is research developed up to the beginning of adolescence, with participants' ages mostly ranging from 4 to 12 years old, and in adolescence, with participants up to the age of 18 years. According to Gunnar and Quevedo [18], taking the striking changes in early life and early adolescence into account, the evidence suggests that hyporesponsiveness to stress, in these developmental stages, may have an effect on the development of behavioral problems in later adolescence and/or in adulthood.

Most studies analyzed associations between low cortisol levels and high behavioral problems, either in childhood or adolescence. Although the studies do not directly compare these developmental stages, it seems that the pattern of results is similar for both. Concerning the findings of van Bokhoven et al. [64], which do not show the same direction, they could be due to differences in the type of participants involved. The sample of van Bokhoven et al. [64] was drawn from a large population-based sample, followed prospectively from kindergarten to adolescence, whereas other studies assessed clinical cases.

As a general observation, a significant relationship between cortisol levels and externalizing problems has been found in several studies. Specifically, aggression and other characteristics of DBD co-occur with changes (higher or lower) in diurnal levels of cortisol. Almost all studies report that participants with DBD show lower cortisol levels ([7,13, 30, 34, 38, 40, 46, 47, 51, 56, 61]) and/or decreased cortisol concentrations throughout the day [45]. However, there are also reports of high levels of basal cortisol co-occurring with high levels of aggression, in female participants [7], as well as in male juvenile offenders with high levels of aggression and callous-unemotional traits [28].

Regarding cortisol reactivity, findings are not as consistent, with some researchers associating lower cortisol reactivity with externalizing problems [46, 48, 53, 58, 63, 70], while others associate higher cortisol reactivity with DBD or CD [25, 36, 39].

Most studies associated low reactivity and basal cortisol with externalizing problems. The hypoactivation of the HPA axis, reflected in low cortisol, may generate an unpleasant physiological state and a concomitant need to seek stimulation, which can be achieved through, for example, antisocial behavior [71]. Thus, sensation seeking and fearlessness manifestations may be secondary to the low levels of cortisol. As an alternative or supplementary explanation, according to Raine [49], individuals with low cortisol tend to have lower levels of fear. In turn, the lack of fear can lead individuals to not anticipate the negative consequences of antisocial behavior.

Although most studies indicate a negative association between basal and reactive cortisol and behavioral problems, it is necessary to consider other factors (such as environmental and social factors) that may offer explanations for externalizing problems. Indeed, it is possible that the influence of social factors, such as peer groups, increases during adolescence and overrules the relationship with cortisol [2], or masks the association of behavioral problems with low levels of cortisol [5]. Furthermore, the combination of environmental and biological factors can explain behavioral problems more consistently than can each type of factors alone. It is important to understand when environmental factors can positively or negatively influence the hypo(re)activity of the HPA axis. Considering the example of Alink et al. [2], the hypo(re) activity of the HPA axis, when associated with environmental risk factors (such as parent or peer factors), can be more effective in inducing antisocial behavior. Conversely, when combined with adaptive environmental factors, a stress-resistant physiology can positively influence the course of life [2].

This systematic review presents limitations, namely the risk of bias of report, since only studies published in identified sources were included, and the difficulty to understand the specific influence of cortisol concentrations, considering the sample type, the task used, and the psychometric instruments. Despite said limitations, this review helps shed light on the association between cortisol concentrations as part of a stress-response mechanism and externalizing problems. Knowledge concerning the link cortisol-externalizing problems could be particularly important and useful to better prevent and intervene in such behavior problems, to the extent that an intervention that improves early social experiences in children at risk of antisocial behaviors should result in a more normalized stress-response, which may play a positive role on the prevention of conduct disorders. Additionally, interventions

can be redirected to better meet the needs of young people with externalizing problems and specific stress response profiles. On one hand, therapists may help young people characterized by high cortisol levels to build skills for reducing arousal or exposure to daily hassles (see [55]). On the other, youth whose stress response systems are not activating in response to stress may benefit from interventions designed to help them become more attuned to the effect of their externalizing behaviors and to punishment cues. In this sense, intervention on externalizing problems could be individualized, depending on high or low cortisol levels, because these levels may lead to different individual responses.

In summary, there is evidence to support the influence of cortisol concentrations on externalizing problems, although it is also necessary take into account the influence of other biopsychosocial factors. Other factors can even act protectively, helping to understand how low basal or reactive cortisol do not lead to the development of behavioral problems. Therefore, future studies may benefit from the combined research of biological and environmental factors to better understand the development of behavioral problems.

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