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Pubertal hormones and mental health problems in children and adolescents: a systematic review of population-based studies

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Summary

Given the increased prevalence of mental health problems during adolescence, there is considerable interest in understanding potential biological mechanisms including the contribution of pubertal hormones. This systematic review of 55 papers aimed to synthesize the evidence for the effect of pubertal hormones on the risk for mental health problems in children and adolescents. The pattern of findings from included studies suggested associations of testosterone and estradiol with certain types of mental health problems, but with inconsistencies relating to DHEA and DHEA-S. However, the state of evidence for the causal effects of hormones was determined to be weak given assessment of bias from confounding, hormone measurement error, selection bias and missingness. Further investigations with careful consideration of study design and analysis, particularly accounting for short-term variation of hormone levels and appropriate selection of confounders, is necessary to advance our understanding of hormonal effects on mental health. Such efforts will improve knowledge of risk mechanisms, and may support the development of targeted intervention efforts for mental health problems.

Keywords: Puberty; Hormones; Mental health; Children; Adolescents

Introduction

Puberty is the process of biological maturation during late childhood and adolescence that ultimately supports reproductive capacity. This period is also associated with many social, emotional and health changes, including increased risk for the onset of mental health problems.[1,2] Half the cases of any mental disorder reportedly start before 18 years of age, with the peak age of onset at around 14.[2] Individual differences in the timing of pubertal maturation, particularly earlier maturation relative to peers, have been found to increase risk for a wide range of mental health problems in both females and males.[3] As hormonal changes underlie the external physical signs of pubertal development, it raises the question of whether pubertal hormones contribute to the onset and course of mental health problems in adolescence. These hormones have an effect on the developing brain via receptors distributed across critical emotional and cognitive neural systems which further enhances the hypothesis that there is an effect of hormones on mental health.[4] Understanding the strength of these hormonal pathways in the general population is important for advancing our knowledge of risk processes that contribute to mental health problems during a critical developmental period.

Puberty comprises two distinct but overlapping biological processes, adrenarche and gonadarche, which lead to a cascade of secretion of different types of hormones. Adrenarche involves maturation of the adrenal cortex and the subsequent rise of adrenal steroid hormones: dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), androstenedione, and testosterone.[5–7] This rise in adrenal hormones typically occurs at age 6–8 years and these hormones continue to increase into the third decade of life.[6] Body changes associated with adrenal hormones include increased skin oil and acne, skeletal maturation, and pubic hair growth. Gonadarche follows adrenarche approximately 1–2 years later.[5,6] Reactivation of gonadotropin-releasing hormone (GnRH) leads to the secretion of estradiol and testosterone from the gonads, which support sexual maturation and reproductive capability. Estradiol and testosterone (which can be converted into estradiol) show steep increases during early and middle adolescence in females and males respectively, before leveling

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off in young adulthood.[8] Secretion of estradiol leads to the development of breasts, ovaries, and the uterus in females, while testosterone leads to the development of the penis, pubic hair and testes in males.

Multiple reviews and meta-analyses[3,9,10] have concluded increased risk for mental health problems in individuals going through puberty earlier than their peers. However, these studies have focused on the physical signs of puberty, namely breast and pubic hair development in females and testicular and pubic hair development in males.[11,12] While it is often postulated that rising hormone levels may be responsible, hormone levels do not closely map to specific stages of physical maturation, with overlap across physical ('Tanner') stages.[5] Moreover, hormones begin to increase well before physical changes are visible, as hormones must reach concentrations high enough to meet the sensitivity of the target tissue.[5] As such, investigation of the effects of pubertal hormones may further improve our understanding of risk processes contributing to mental health problems.

Several potential mechanisms might underlie the effect of pubertal hormones on mental health. One is that pubertal hormones can impact structural and functional properties of the developing brain via hormone receptors, and thereby affect mental health.[13,14] For example, there are high levels of pubertal hormone receptors in limbic brain regions that are involved in the processing and regulation of emotions.[4] It has also been shown that the size of limbic regions, such as the hippocampus, may mediate the relationship between early exposure to testosterone and depressive symptoms.[15] Another potential mechanism is that the physical changes associated with hormonal shifts during puberty might evoke changes in social responses, which may in turn impact mental health.[16] For example, it has been shown that harsher parenting following the early maturation of adolescent girls leads to higher risks of internalizing and externalizing problems.[17] Early developers are also more likely to experience peer exclusion, which might contribute to their emotional problem.[18] They are also more likely to associate with older peers who look more similar to themselves (especially early developing females), and are thus exposed to more risky behaviours that increase with age.[19,20]

Three systematic reviews have thus far examined the associations between pubertal hormones and mental health problems in children and adolescents. In 2014, Duke and colleagues conducted a systematic review of 27 studies (one longitudinal) on the effects of endogenous testosterone on behaviour and mood in healthy males during adolescence.[21] The majority of studies focused on aggression as the outcome, and the authors concluded that there was insufficient evidence to confirm an effect of testosterone on aggression.[21] A similar systematic review of 14 studies (three longitudinal) on the effect of estradiol on mood and behaviours in female adolescents was published by the same authors in 2015.[22] Findings suggested possible positive associations between estradiol and depression and mood variability for at least some stages of puberty, but again, the authors concluded there was insufficient evidence to confirm a causal effect of estradiol on mental health.[22] In 2017, Byrne and colleagues systematically reviewed 17 studies (two longitudinal) that examined the levels of DHEA and DHEA-S in relation to indices of mental health, ten of which reported a positive association between higher levels of DHEA or DHEA-S and mental health symptoms or a risk of mental disorder.[23]

Overall, it is difficult to draw strong conclusions from these reviews regarding the effect of pubertal hormones on mental health in children and adolescents. These reviews also had some limitations. Firstly, none conducted a risk of bias assessment.[21–23] Studies on pubertal hormones and mental health problems have used varied approaches to participant sampling, measurement of hormones and mental health problems, and covariates included in the analyses.[21–23] These methodological choices can introduce bias in the evidence generated within a given study, which highlights the importance of a comprehensive risk of bias assessment of existing studies to more reliably describe the state of evidence for the effect of pubertal hormones on mental health. Secondly, at the time of these reviews, very few longitudinal studies were available, which are methodologically powerful for investigating the effect of hormones on mental health problems. Thirdly, to our knowledge, there has been no systematic review of the effects of testosterone on mental health in female adolescents, or of estradiol on mental health in male adolescents, notwithstanding the possibility of these hormonal influences on the brain.[4] Finally, prior reviews have incorporated studies of clinical or at-risk samples. Proper adjustment for confounding might be more challenging in these studies, and they may be more prone to selection bias. Further, the findings from these studies may not be readily generalisable to the general population.

Considering these limitations, the aim of this study was to systematically review and synthesize evidence from population studies of the effect of pubertal hormones on the risk of mental health problems in children and adolescents, as well as to assess the quality of the existing evidence.

Methods

The review protocol was registered with PROSPERO (CRD42023406540). The review is reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[24]

Search strategies

A comprehensive search strategy was used to identify published studies which analyzed the associations between pubertal hormones and mental health problems in children and adolescents. Three electronic databases (Medline, Embase, and PubMed) were searched. Searches were run on March 10, 2023 (updated on April 3, 2024), with no restrictions on language or publication period. Animal studies, case reports, comments, editorials, letters, preprints and reviews were excluded. The combination of three categories of terms was used: populations or developmental stages (child, adolescent, puberty, adrenarche, and gonadarche), pubertal hormones, and mental health problems. Searches focused on six endogenous pubertal hormones including DHEA, DHEA-S, androstenedione, estradiol, testosterone, and progesterone, and four types of common mental health problems which have also been identified in prior studies on pubertal timing (i.e., physical development) including internalizing problems, externalizing problems, eating disorders, and substance use problems. The full search terms and strategies are provided in the appendix (Supplement 1).

Study selection and data extraction

After removal of duplicates, identified records were imported into Covidence web-based software.[25] Titles and abstracts were screened by the primary reviewer (DL) according to the eligibility criteria. The full texts of potentially eligible records were obtained and screened by the primary reviewer. Ten percent of records were double screened (NV) and disagreements were resolved in discussion with other co-authors to reach a consensus. The primary reviewer extracted the data. When any doubt arose during the screening or data extraction process, decisions were made after discussion with co-authors.

Studies were included if: 1) participants were children and/or adolescents from community samples; 2) there was measurement of basal levels of pubertal hormones (DHEA/DHEA-S, androstenedione, estradiol, testosterone, and progesterone) when participants were 5–19 years old; 3) there was assessment of mental health problems (internalizing, externalizing, eating disorders, and substance use/abuse) using validated instruments, contemporaneously and/or following the measurement of pubertal hormones; and 4) there was analysis of associations between pubertal hormones and mental health problems. The considered age range (5–19 years) was to ensure that studies capturing the early rise of adrenarchal hormones were included. Exclusion criteria were: animal studies, studies with non-English language full texts, studies of clinical or at-risk populations, or studies involving exogenous hormone use.

Risk of bias assessment

The Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E) tool[26,27] provides a structured approach to assessing the risk of bias in observational epidemiological studies evaluating the effect of an exposure on an outcome. Using this tool as a guide, we examined six key domains of potential bias for each study: confounding, measurement of exposure, selection of participants into the study or the analysis, missing data, measurement of the outcome, and selection of the reported result. We did not examine bias for the domain "due to post-exposure interventions" because none of the included studied had interventions to counter the effects of hormones. Criteria for the assessment of each bias domain and overall risk of bias can be found in Supplement 2.1. In order to assess confounding bias, we developed a causal model to depict the assumed causal relationships between hormones, mental health outcomes and related variables (Fig. 1, details in Supplement 2.2). Based on the model, we defined a minimum set of confounders that the papers must have adjusted for to reduce confounding bias (sex, age, and race/ethnicity) and variables that should not have been included in the adjustment set to avoid over-adjustment bias (i.e., variables that were identified to be on the causal pathway from hormones to mental health outcomes, such as pubertal stage or timing). The primary reviewer led the risk of bias assessment; ten percent of articles were double assessed (SGD) and disagreements resolved in discussion with co-authors to reach a consensus.

Results

Description of included studies

In total, 3717 records were identified from the searches. After removing duplicates, 2654 articles were assessed, from which 55 articles were included (Fig. 2). Most of these articles were from the USA (n = 29) or Europe (n = 20) (Table 1). Participants were recruited from schools (n = 35) or communities (n = 20). Ten studies used a longitudinal design; follow-up ranged from one to three years and the number of waves ranged from two to six.

The sample size of the included articles ranged from 30 to 11,844. Thirty articles included both females and males (with the proportion of female participants ranging from 42 to 59%), 10 included only females, and 15 only males. Pubertal hormones were measured in blood (n = 23), saliva (n = 31), or urine (n = 1) samples. In each article, mental health was measured using one or more of the following approaches: self-reported questionnaires (n = 35), parent-reported questionnaires (n = 14), peer-reported questionnaires (n = 7), or clinical interviews (n = 7). One article measured aggression in 5-year-old children through videotaping their interactions with their peers. Common confounders used in analyses of cross-sectional studies were: age, sex, race/ethnicity, family socioeconomic status, body mass index (BMI)/body fat percentage,

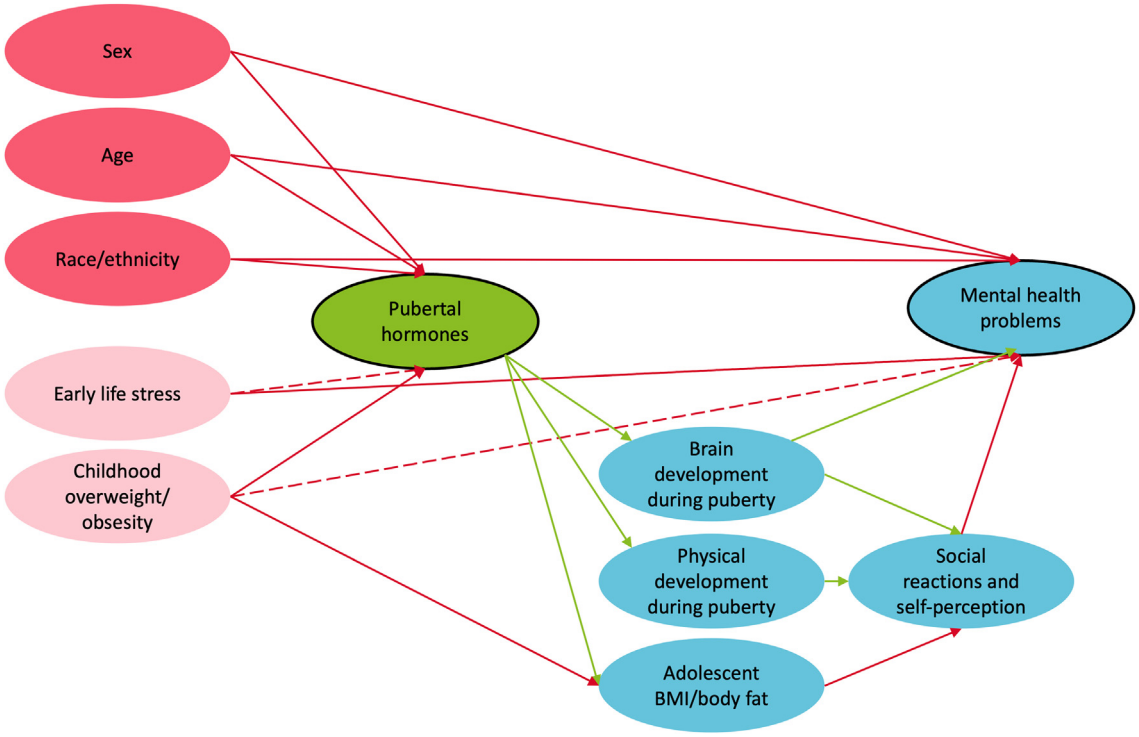

Fig. 1: **The causal model of the effect of pubertal hormones on mental health problems**. BMI, Body mass index. We established this causal model to depict the assumed causal relationships between hormones, mental health outcomes, and related variables. Arrows have been drawn from causes to outcomes. Dashed lines represent that there is no conclusive evidence on the causal relationship between variables according to literature or expert opinion. Sex, age, and race/ethnicity are identified as important confounding factors in the causal relationship between pubertal hormones and mental health problems and are deemed necessary to control. Early life stress and childhood overweight/obesity are potential confounding factors but not in the minimum adjustment set as at least one of the arrows from these variables to hormones or mental health is not robustly established. On the other hand, brain development during puberty, physical development during puberty, adolescent BMI/body fat, and changes in social reactions and self-perception are variables on the causal pathway from hormones to mental health and controlling for these factors is likely to lead to bias. The complexity of drivers of disparities in mental health outcomes by race/ethnicity, which are socially constructed variables, is not depicted in this simplified causal diagram. Similarly, although we have used the variable sex in the causal diagram, it is important to acknowledge that gender, which also is a socially constructed variable, may also impact mental health outcomes. More details on the development of this model can be found in Supplement 2.2.

pubertal status, and pubertal timing. Three of the ten papers from longitudinal studies also adjusted for baseline mental health status.

Risk of bias assessment

The overall risk of bias was judged as high for all 55 articles (Fig. 3). Detailed risk of bias assessment for each study is provided in Supplement 3. Most articles were likely to be impacted by confounding (51 were assessed at high risk). Specifically, 26 studies failed to control for age and 41 studies failed to control for race/ethnicity in their analyses (where the age or race/ethnicity distribution of a sample warranted its consideration as a confounder, or if it was unclear whether adjustment was warranted). Furthermore, 13 studies adjusted for pubertal stage or timing in the analyses. Exposure measurement was another major source of bias, as hormone measurement in some studies did not account for diurnal rhythms and/or monthly variation of hormone levels; 20 articles had high risk and 31 articles had some concerns for this domain. Forty-three articles were at high risk of bias for participant selection, mainly because selection was likely to be related to both puberty and mental health. Missing data (32 articles had high risk) and selection of the reported results (no articles had high risk but 52 had some concerns) were also common sources of risk of bias. There were no concerns of risk of bias arising from outcome measurement in any of the articles (such that it may have been biased by hormone exposure levels).

Synthesis of findings across studies

For each hormone, findings are synthesized for internalizing problems/depression/anxiety, externalizing problems/aggression/rule-breaking, and substance use. Findings are further summarized by sex (male/female) consistent with reporting practices in the included papers. We specifically categorise findings into three

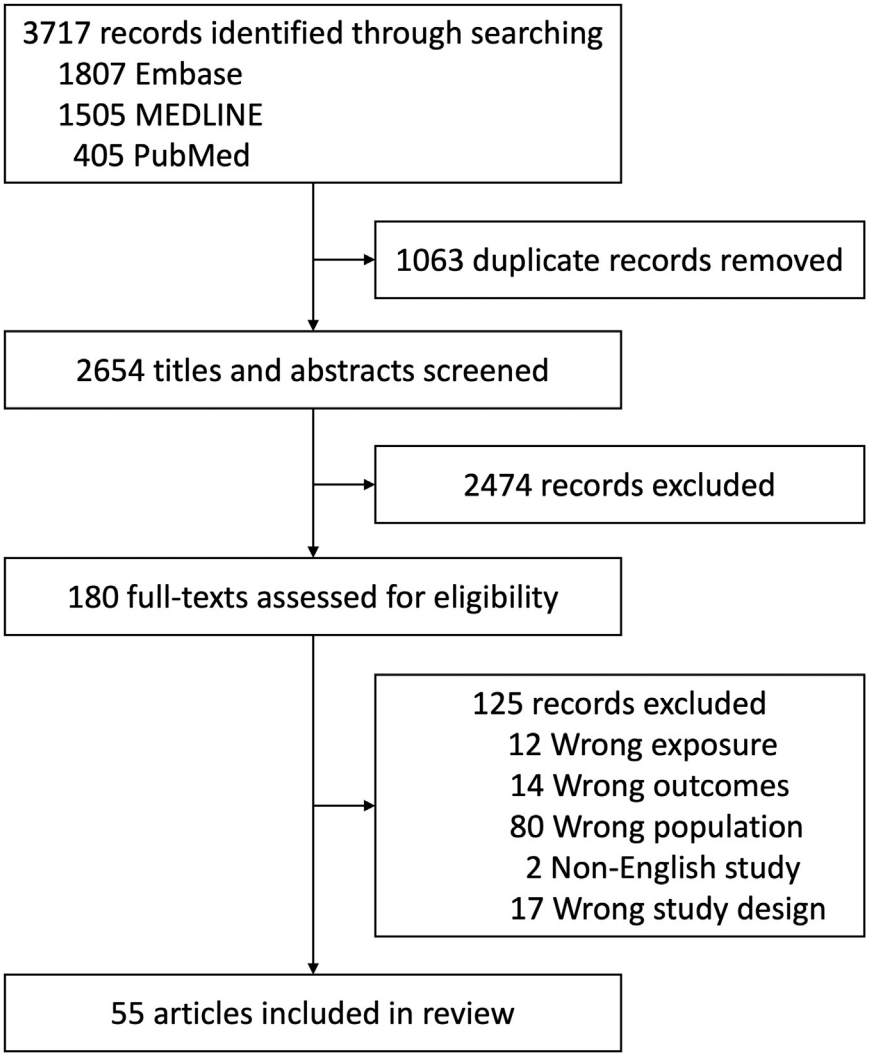

Fig. 2: **PRISMA flow diagram of article identification retrieval and inclusion.**

categories, given that many studies do not report exact *p-values*: positive estimate & *p-value* ≤ 0.05 (*'Positive/p-value ≤ 0.05'*), negative estimate & *p-value* ≤ 0.05 (*'Negative/p-value ≤ 0.05'*), and *p-value* >0.05 (*'p-value > 0.05'*). The synthesis of findings across studies is illustrated in Fig. 4. Results from each study are summarized in Supplement 4–6, by hormone.

DHEA/DHEA-S

Internalizing problems. For females, five studies assessed internalizing problems,[28–32] four depression[32–35] and three anxiety in relation to DHEA/DHEA-S.[32,33,36] The majority of associations (n = 9) between DHEA/DHEA-S levels and internalizing problems,[28–31] depression,[32–35] or anxiety[33] fell in the *'p-value > 0.05'* category. In the *'positive/p-value ≤ 0.05'* category, there was one association between DHEA and anxiety symptoms and diagnoses from a cross-sectional study, although analyses adjusted for pubertal stage rather than age.[36] In the *'negative/p-value ≤ 0.05'* category, there was one longitudinal study reporting two negative associations between baseline DHEA-S (based on blood samples) and baseline internalizing problems and one-year follow-up of anxiety symptoms (note, *p-value > 0.05* for DHEA from the same study).[32]

For males, four studies assessed internalizing problems,[28–30,32] three depression[32–34] and two anxiety in relation to DHEA/DHEA-S.[32,33] The majority of the associations (n = 5) with internalizing problems,[28,32] depression,[33,34] or anxiety[33] were in the *'p-value>0.05'* category. Three associations were in the *'positive/p-value ≤ 0.05'* category. This included findings from one cross-sectional study that had a larger sample size (n = 1239, 45% were males) and included younger participants (aged 8–9 years).[30] The other two were from the longitudinal study using blood samples, and included

		Analytic design (for longitudinal studies, follow-up years, number of waves), study name	Source of participants	Recruited sample size (analytic sample size range)	Female, %	Baseline age range, years M (SD), years	Pubertal hormones (sample type)	Outcome measures (reporting method)	Covariates
1	Copeland et al., 2019, USA	CS, GSMS	Schools	3005 (1916)[a]	100	9–16 NR	T, E2 (B)	Depression diagnoses: CAPA (CI)	T: Age, Tanner stage, pubertal timing, and prior depression status E2: none
2	Angold et al., 1999, USA	CS, GSMS	Schools	1283 (982)[a]	100	9–15 NR	T, E2 (B)	Depression diagnoses: CAPA (CI)	None
3	Rowe et al., 2004, USA	CS, GSMS	Schools	2125 (1669)[a]	0	9–15 NR	T (B)	Aggressive and non-aggressive CD symptoms: CAPA (CI)	Non-aggressive CD: Age, peer deviance Aggressive CD: none
4	Mulligan et al., 2020, USA	CS	Community	317 (286)	100	8–14 12.57 (1.72)	DHEA, T, E2, P4 (S)	Anxiety symptoms: SCARED (Self) Anxiety symptoms and diagnoses: K-SADS-PL (CI)	DHEA, T: PDS E2, P4: none
5	Black et al., 2019, USA	CS, SBTS	Community	490 (389)	47	8.27–11.73 9.27 (0.44)	T (S)	Internalizing and externalizing problems: CBCL (Parent)	Sex, age, race (white/non-white), PDS, parental history of depression
6	Mundy et al., 2015, Australia	CS, CATS	Schools	1239 (1124)	55	8–9 9.0 (0.4)	DHEA, DHEA-S, T (S)	Emotional and behavioural problems: SDQ (Parent)	Age, family SES
7	Culbert et al., 2014, USA	CS, MSUTR	Community, twins	213 (NR)	0	10–15 12.74 (1.62)	T (S)	Disordered eating symptoms: MEBS (Self) and EDE-Q (Self)	Age, depression, anxiety, body fat percentage, BMI
8	Culbert et al., 2022, USA	CS, MSUTR	Community, twins	213 (213)	0	10–15 12.74 (1.62)	T (S)	Depressive symptoms: CDI (self) Anxiety symptoms: MASC (self) Aggressive behaviours: EATQ-R (self)	Age, BMI, and PDS. For anxiety symptoms, aggression, depression and parent-child conflict were additionally adjusted for. For aggressive behaviours, depression, anxiety, and parent-child conflict were additionally adjusted for.
9	Chronister et al., 2021, Ecuador	CS, ESPINA	Community, agricultural settings	533 (512–514)	50	11–17 14.5 (1.76)	DHEA, T, E2 (S)	Depression symptoms: CDI-2 short (Self) Anxiety symptoms: MASC-2 (Self)	Age, BMI-for-age z-score, parental education, household income, hemoglobin concentration, Tanner stage
10	Halpern et al., 1993, USA	L (3, 6), Halpern (1993)	Schools	127 (NR)	0	12–13 NR	T (B)	Aggressive behaviours: OMAI subset (Self), other eight aggression measures (Self)	None
11	Drigotas et al., 1993, USA	L (1, 3), Halpern (1993)	Schools	126 (NR)	0	12–13 NR	T (B)	Problem behaviours: 26 mild to serious deviant behaviours (Self)	Autonomy, religiosity
12	Barendse et al., 2022, USA	L (1.5, 2), TAG	Schools	174 (NR)	100	10.0–13.0 11.63 (0.82)	DHEA, T, E2 (S)	Depressive symptoms: CES-DC (Self) Anxiety symptoms: SCARED-R short (Self) Diagnoses of depression, anxiety, internalizing, distress and fear disorders: K-SADS-PL (CI)	Baseline internalizing psychopathology, threat-related early life stress, baseline BMI
13	Olweus et al., 1980, Sweden	CS, Olweus (1980)	Schools	58 (58)	0	15–17 16 (NR)	T (B)	Aggression: OMAI (Self), OQI (Self), and a peer rating scale (Peer) Anti-social behaviours: a 9-item scale (Self) Trait anxiety: MCA (Self)	None

(Table 1 continues on next page)

		Analytic design (for longitudinal studies, follow-up years, number of waves), study name	Source of participants	Recruited sample size (analytic sample size range)	Female, %	Baseline age range, years M (SD), years	Pubertal hormones (sample type)	Outcome measures (reporting method)	Covariates
(Continued from previous page)									
14	Olweus et al., 1988, Sweden	CS, Olweus (1980)	Schools	58 (58)	0	15–17 16 (NR)	T (B)	Provoked aggressive behaviours: OMAI (Self) Unprovoked aggressive behaviours (Peer)	Aggressive behaviours and low frustration tolerance measured 3 years earlier, temperamental variables, child rearing variables
15	Chafkin et al., 2022, USA	L (1.7, 3), TLSASR	Schools	79 (47–54)	100	Ninth-grader NR	E2 (S)	Depressive symptoms: CDI (Self)	Ethnicity
16	Pascual-Sagastizabal et al., 2019, Spain	CS, Pascual-Sagastizabal (2014)	Schools	165 (139)	42	8 NR	T (S)	Aggressive behaviours: DIAS (Peer)	None
17	Pascual-Sagastizabal et al., 2019, Spain	CS, Pascual-Sagastizabal (2014)	Schools	165 (139)	42	8 NR	T, E2 (S)	Aggressive behaviours: DIAS (Peer)	Empathy, cortisol
18	Azurmendi et al., 2016, Spain	L (2, 2), Pascual-Sagastizabal (2014)	Schools	NR (49)	0	8 NR	T, E2 (S)	Aggressive behaviours: DIAS (Peer)	Change in cortisol level
19	Pascual-Sagastizabal et al., 2014, Spain	CS, Pascual-Sagastizabal (2014)	Schools	165 (159)	44	8 NR	A4, T (S)	Physical and indirect aggression: DIAS (Peer)	Parenting styles
20	Sanchez-Martin et al., 2011, Spain	CS	Schools	124 (90)	51	9 NR	A4, T (S)	Physical, verbal and indirect aggressive behaviours: DIAS (Peer)	Sex, impulsivity, state anger, trait anger, anger control
21	Del Puerto-Golzarri et al., 2023, Spain	CS	Schools	279 (NR)	45	8 8.15 (1.23)	T (S)	Reactive and proactive aggressive behaviours: RPQ (self)	Cortisol, parenting style
22	Lewis et al., 2018, UK	L (3, 2), ROOTS	Schools	1238 (753–842)	56	14.5 NR	DHEA (S)	Depressive symptoms: MFQ long (Self)	Age, baseline BMI, baseline depressive symptoms
23	Chen et al., 2018, USA	CS, HBB	Community	446 (439–442)	49	11–12 11.93 (0.60)	T (S)	Proactive and reactive aggression: RPQ (Self)	Race, Tanner, household income, harsh discipline
24	Chen et al., 2015, USA	CS, HBB	Community	446 (NR)	49	11–12 11.88 (0.59)	DHEA-S (S)	Internalizing and externalizing problems: YSR (Self), CBCL (Parent)	Age, ethnicity, puberty timing, BMI, cortisol
25	Portnoy et al., 2015, USA	CS, HBB	Community	446 (434–436)	49	11–12 11.92 (0.59)	T (S)	Externalizing problems: YSR (Self), CBCL (Parent)	Age, race (black/not black), social adversity, BMI, puberty timing, digit ratio (2D:4D)
26	Serio et al., 2022, USA	CS, ABCD	Schools	11,844 (7138–7157)	48	9–10 9.91 (0.63)	DHEA, T, E2 (S)	Internalizing problems: CBCL (Parent)	Sex, amygdala response to fearful face
27	McNeilly et al., 2022, USA	CS, ABCD	Schools	11,878 (9253)	48	9–10 NR	T (S)	Internalizing problems: CBCL (Parent)	Age, race, ethnicity, BMI, household income, highest parental education
28	Susman et al., 1987, USA	CS, Nottelmann (1987)	Community	108 (NR)	48	9–14 M 12.7 (NR), F 12.0 (NR)	DHEA, DHEA-S, T, E2, A4 (B)	Rule-breaking and aggressive behaviours: CBCL (Parent)	Age, LH, FSH, T/E2, TeBG
29	Susman et al., 1991, USA	L (1, 3), Nottelmann (1987)	Community	108 (NR)	48	9–14 M 12.7 (NR), F 12.0 (NR)	DHEA, DHEA-S, T, E2, A4 (B)	Internalizing problems: CBCL (Parent) Depression and anxiety symptoms: DISC (Self)	Age, Tanner, baseline negative affect, LH, FSH, cortisol

(Table 1 continues on next page)

		Analytic design (for longitudinal studies, follow-up years, number of waves), study name	Source of participants	Recruited sample size (analytic sample size range)	Female, %	Baseline age range, years M (SD), years	Pubertal hormones (sample type)	Outcome measures (reporting method)	Covariates
(Continued from previous page)									
30	Nottelmann et al., 1987, USA	CS, Nottelmann (1987)	Community	108 (NR)	48	9–14 M 12.7 (NR), F 12.0 (NR)	DHEA, DHEA-S, T, E2, A4 (B)	Internalizing and externalizing problems: CBCL (Parent) subscales	Age, LH, FSH, T/E2
31	Martin et al., 1999, USA	CS	Schools	94 (80)	100	15–19 16.6 (1.0)	T, E2 (B)	Current alcohol use: alcohol use within the past month (Self)	None
32	Warren et al., 1989, USA	CS, Warren (1989)	Schools	100 (100)	100	10.6–13.3 12.1 (NR)	E2 (B)	Depressive affect and aggression: YBP (Self) Impulse control: SIQYA (Self)	Age
33	Paikoff et al., 1991, USA	L (1, 2), Warren (1989)	Schools	103 (72)	100	10–14 12.16 (0.88)	DHEA-S, T, E2 (B)	Depressive affect: depressed-withdrawal items of YBP (Self), CES-D (Self), PI-DMI (Parent) Aggression and delinquency: YBP (Self)	None
34	Udry et al., 1990, USA	CS, Udry (1990)	Schools	101 (101)	0	13–16 NR	T (B)	Problem behaviours: 14 mild to serious deviant behaviours (Self)	TeBG, good child, grades
35	Udry et al., 1991, USA	CS, Udry (1990)	Schools	101 (101)	0	13–16 NR	T (B)	Alcohol use ever try (Self)	SHBG, age, father absence
36	Vermeersch et al., 2008, Belgium	CS, ADORISK	Schools	279 (258)	100	13–17 14.25 (0.59)	T, E2 (B)	ART and NART: scales developed for the ADORISK project (Self)	Age, Tanner
37	Vermeersch et al., 2008, Belgium	CS, ADORISK	Schools	301 (286)	0	13–18 14.4 (0.74)	T, E2 (B)	ART and NART: scales developed for the ADORISK project (Self)	T: Age, Tanner E2: none
38	Vermeersch et al., 2010, Belgium	CS, ADORISK	Schools	283 (NR)	0	13–18 14.4 (0.74)	T, E2 (B)	Depressive symptoms: CES-D (Self)	T: Age, Tanner, body fat percentage, alcohol consumption during the prior day, CAG repeat length E2: none
39	de Water et al., 2013, Netherlands	CS	Schools	168 (NR)	49	12–17 M 14.66 (1.64), F 14.66 (1.81)	T, E2 (S)	Lifetime and recent (over the past 30 days) alcohol use (Self)	Age
40	Foshee et al., 2007, USA	CS	Schools	424 (409)	49	11–14 NR	T, E2 (S)	Cigarette and alcohol involvement (Self)	Age, PDS, perceived puberty timing, substance-specific contextual variables
41	Kunz et al., 2005, Austria	CS	Schools	336 (335)	0	Eighth-grader 14.5 (NR)	T (B)	Present smoking (Self)	Age
42	Azurmendi et al., 2006, Spain	CS	Schools	129 (129)	53	5.0–5.9 5.4 (NR)	DHEA, T, A4 (S)	Aggression (victimization, offensiveness, provocation): subjects' social interactions with their peers were videotaped and evaluated	None
43	Reardon et al., 2016, Canada	CS, Tackett (2014)	Community	NR (106)	56	13–18 16.01 (1.29)	T (S)	Externalizing behaviours: CBCL (Parent)	Age, sex, personality, internalizing behaviours
44	Tackett et al., 2014, Canada	CS, Tackett (2014)	Community	NR (106)	56	13–18 16.01 (1.29)	T (S)	Externalizing behaviours: CBCL (Parent), YSR (Self)	Age, sex, cortisol, personality

(Table 1 continues on next page)

		Analytic design (for longitudinal studies, follow-up years, number of waves), study name	Source of participants	Recruited sample size (analytic sample size range)	Female, %	Baseline age range, years M (SD), years	Pubertal hormones (sample type)	Outcome measures (reporting method)	Covariates
(Continued from previous page)									
45	Tackett et al., 2015, Canada	CS, Tackett (2014)	Community	NR (105)	55	13–18 16.00 (1.29)	E2 (S)	Externalizing behaviours: CBCL (Parent)	Age, sex, cortisol, personality
46	Gerra et al., 1998, Italy	CS	Schools	30 (30)	0	12 12.7 (0.3)	T (B)	Aggressiveness: subjects were divided into 3 groups (low-normal, medium-normal, and high-normal aggressiveness) (Self, CI)	None
47	Gerra et al., 1997, Italy	CS	Schools	42 (30)	0	18–19 18.7 (0.6)	T (B)	Aggressiveness: subjects were divided into 2 groups (low-normal and high-normal aggressiveness) (Self, CI)	None
48	Davison et al., 2007, USA	L (2, 2)	Community	178 (168)	100	11 11.33 (0.28)	E2 (B)	Depressive symptoms: CDI (Self)	None
49	Booth et al., 2003, USA	CS	Community, family with two children	800 (449–608)	48	6–18 M 13.39 (1.95), F 13.00 (1.85)	T (S)	Risk behaviour: RBS (Self) Depressive symptoms: an adaption of CES-D or CDI (Self)	Age, age squared, parents' testosterone levels
50	Parker et al., 2021, USA	CS, CGBS	Community	120 (87)	59	8–18 12.98 (2.68)	T, E2, P4 (B)	Loss of control eating severity: an adaption from EDE assessed using EMA (Self)	Hunger, general cravings, momentary cravings
51	Babarro et al., 2022, Spain	CS, INMA	Community	379 (302)	52	11 NR	T (S)	Bullying: OBVQ (Self)	None
52	Calvete et al., 2023, Spain	CS	Schools	577 (NR)	50	12–17 14.64 (0.96)	T (S)	Offline aggression: R-PEQ (Self) Online aggression: CBQ (Self)	None
53	Peper et al., 2018, Netherlands	CS, BRAINTIME	Community	NR (211)	50	11–15 NR	T, E2 (S)	Impulsive personality: BIS–11 (Self) Aggression: BPA-Q (Self)	Age
54	Susman et al., 2017, USA	CS	Community	135 (NR)	51	8–13 M 10.94 (1.61), F 10.06 (1.64)	T (S)	Externalizing problems: CBCL (Parent) ODD and CD symptoms: DISC-IV (Parent)	None
55	Hazell et al., 2023, Australia	L (3, 4), ARCHER	Schools	342 (277)	43	10–12 M 11.8 (1.02), F 11.6 (0.96)	T, E2 (U)	Depressive symptoms: SMFQ (self), YSR anxious/depressed and withdrawn/depressed subscales (self) Aggressive and rule-breaking behaviours: YSR (self)	None

[a]Number of observations. NR, not reported; CS, cross-sectional; L, longitudinal; F, females; M, males; B, blood; S, saliva; U, urine; A4, androstenedione; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; T, testosterone; E2, estradiol; P4, progesterone; LF, luteinizing hormone; FSH, follicle stimulating hormone; TeBG, testosterone-estradiol binding globulin; SHBG, sex hormone binding globulin; Parent, parent/care-giver reported; Peer, peer reported; Self, self-reported; CI, clinical interview; ART, aggressive risk-taking; NART, non-aggressive risk-taking; CD, conduct disorder; ODD, oppositional defiant disoder; BMI, body mass index; SES, socioeconomic status; ABCD, Adolescent Brain Cognitive Development study; CATS, Childhood to Adolescence Transition Study; CGBS, Children's Growth and Behavior Study; EATQ-R, Early Adolescent Temperament Questionnaire-Revised; ESPINA, Secondary Exposure to Pesticides among Children and Adolescents; GSMS, Great Smoky Mountains Study; HBB, Philadelphia Healthy Brains and Behavior project; INMA, INfancia y Medio Ambiente-(Environment and Childhood) Project Gipuzkoan cohort; MSUTR, Michigan State University Twin Registry Twin Study of Hormones and Disordered Eating across Puberty; ROOTS, The ROOTS study; SBTS, Stony Brook Temperament Study; TAG, Transitions in Adolescent Girls; TLSASR: SSS, Texas Longitudinal Study of Adolescent Stress Resilience: Saturated Schools Sample; ACL, Adjective Checklist; BDHI, Buss-Durkee Hostility Inventory; BIS-11, Barratt Impulsiveness Scale; Version 11. BPA-Q, Buss Perry Aggression Questionnaire; CAPA, Child and Adolescent Psychiatric Assessment; CBCL, Child Behavior Checklist; CBQ, Cyberbullying Questionnaire; CDI, Children's Depression Inventory; CDI-2, Children's Depression Inventory 2nd Edition; CES-D, Center for Epidemiological Studies Depression Scale; CES-DC, Center for Epidemiologic Studies Depression Scale for Children; CPQ, Children Personality Questionnaire; DIAS, Direct and Indirect Aggression Scale; DISC, Diagnostic Interview Schedule for Children; DISC-IV, Diagnostic Interview Schedule for Children: Version IV; EDE, Eating Disorder Examination; EDE-Q, Eating Disorder Examination Questionnaire; EMA, ecological momentary assessment; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version for DSM-IV; MASC, Multidimensional Anxiety Scale for Children; MASC-2, Multidimensional Anxiety Scale for Children 2nd Edition; MCA, Multi-Component Anxiety Inventory; MEBS, Minnesota Eating Behavior Survey; MFQ, Mood and Feelings Questionnaire; OBVQ, Olweus Bully Victim Questionnaire; OMAI, Olweus Multifaceted Aggression Inventory; OQI, Olweus Q Inventory; PDS, Pubertal Development Scale; PI-DMI, Psychiatric Institute Depressive Mood Inventory; RBS, Risky Behaviors Scale; R-PEQ, Revised Peer Experiences Questionnaire; RPQ, Reactive-Proactive Aggression Questionnaire; PRF, Personality Research Form; SCARED, Screen for Child Anxiety Related Disorders; SCARED-R, revised Screen for Child Anxiety Related Disorders; SDQ, Strengths and Difficulties Questionnaire; SIQYA, Self Image Questionnaire for Young Adolescents; SMFQ, Short Moods and Feelings Questionnaire; TAI, Test Anxiety Inventory; YBP, Youth Behavior Profile; YSR, Youth Self-Report.

Table 1: **Description of papers included in this review (n = 55).**

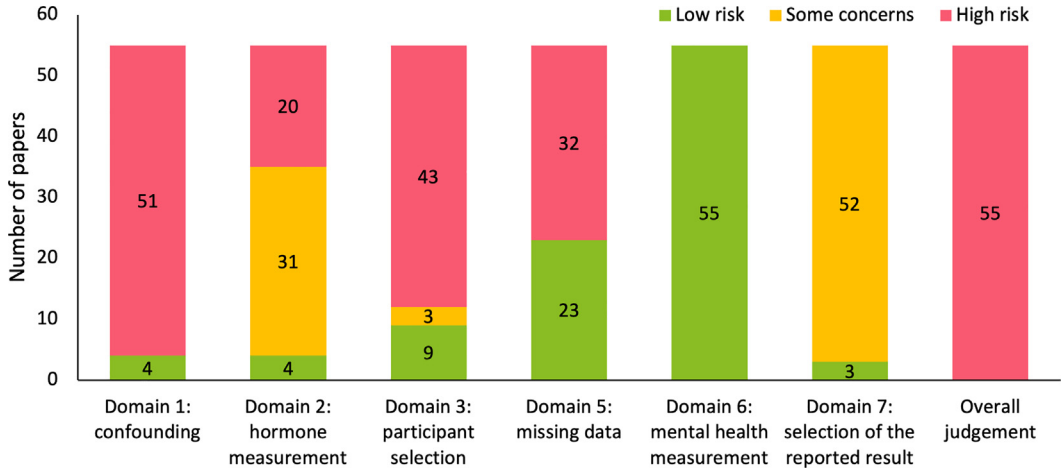

***Fig. 3:* Risk of bias for each domain and overall judgement**. Risk of bias assessment was guided by the Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E) tool. We did not examine bias for domain #4 "due to post-exposure interventions" because none of the included studies had interventions to counter the effects of hormones. There were no concerns of risk of bias arising from mental health measurement in any of the studies as in all studies it was unlikely that the measurement of outcome differed by exposure, or that outcome assessors were aware of the exposure history. Details on the results of risk of bias assessment for each included study can be found in Supplement 3.

positive associations between baseline DHEA and one-year follow-up of both depression and anxiety, when controlling for baseline negative affect (but not for DHEA-S).[32] In the *'negative/p-value ≤ 0.05'* category, there was one association between DHEA-S and self-reported internalizing problems (but not for parent-report) from a cross-sectional study.[29]

Externalizing problems. For females, two cross-sectional studies examined externalizing problems in relation to DHEA/DEHA-S. Both associations fell within the *'p-value > 0.05'* category.[29,30]

For males, there were the same two cross-sectional studies as for females. One association from a study of younger participants (8–9 year olds) for DHEA-S (but not DHEA) and parent-reported conduct problems fell within the *'positive/p-value ≤ 0.05'* category,[30] while one association between DHEA-S and self-reported externalizing problems (but not for parent-report) was in the *'negative/p-value ≤ 0.05'* category.[29]

Four studies (one longitudinal) focused on aggressive behaviours[28,35,37,38] and three (one longitudinal) on rule-breaking behaviours.[28,35,37] All associations from these studies were in the *'p-value > 0.05'* category for females and males.

Testosterone

Internalizing problems. For males, 14 studies assessed internalizing problems,[28,30,32,39] depression,[32,33,40–43] and anxiety[32,33,42,44] in relation to testosterone levels. The majority of associations (n = 13) for internalizing problems,[28,32,39] depression,[32,33,40–43] and anxiety[32,33,42,44] were in the *'p-value > 0.05'* category. Only one association between testosterone levels and emotional problems from a cross-sectional study was in the *'positive/p-value ≤ 0.05'* category.[30]

For females, 15 studies assessed internalizing problems,[28,30–32,39] depression,[32,33,35,41,43,45,46] and anxiety[32,33,36] in relation to testosterone levels. Again, the majority of associations (n = 13) for internalizing problems,[28,30–32,39] depression,[32,33,41] and anxiety[32,33,36] were in the *'p-value > 0.05'* category. Four associations in total were in the *'positive/p-value ≤ 0.05'* category. Two were positive associations with risk of depression diagnosis from two cross-sectional analyses using different observations from the longitudinal Great Smoky Mountains Study (GSMS).[45,46] The other two were positive associations between testosterone levels at baseline and accumulated testosterone levels since baseline (area under curve) and depressive symptoms at one-year follow-up from two longitudinal analyses, although neither of the studies adjusted for age.[35,43]

Externalizing problems. For males, four studies assessed the relationship between testosterone levels and externalizing problems,[30,44,47,48] 20 studies assessed aggression,[8,28,37,38,42–44,47–61] and 10 rule-breaking behaviours.[28,37,41,43,47,48,52,53,62,63] All associations for externalizing problems,[30,44,47,48] 14 for aggression,[8,28,37,38,42,43,47–54,61] and five for rule-breaking[28,37,41,47,48] fell within the *'p-value > 0.05'* category. Six associations for aggression and five for rule-breaking fell within the *'positive/p-value ≤ 0.05'* category. For aggression, three associations were from cross-sectional studies.[44,55–57] Another two were also from cross-sectional studies, but only in individuals with harsh parenting.[58,59] One longitudinal study reported an association between testosterone levels and change in aggression scores over one year.[60] For rule-breaking,

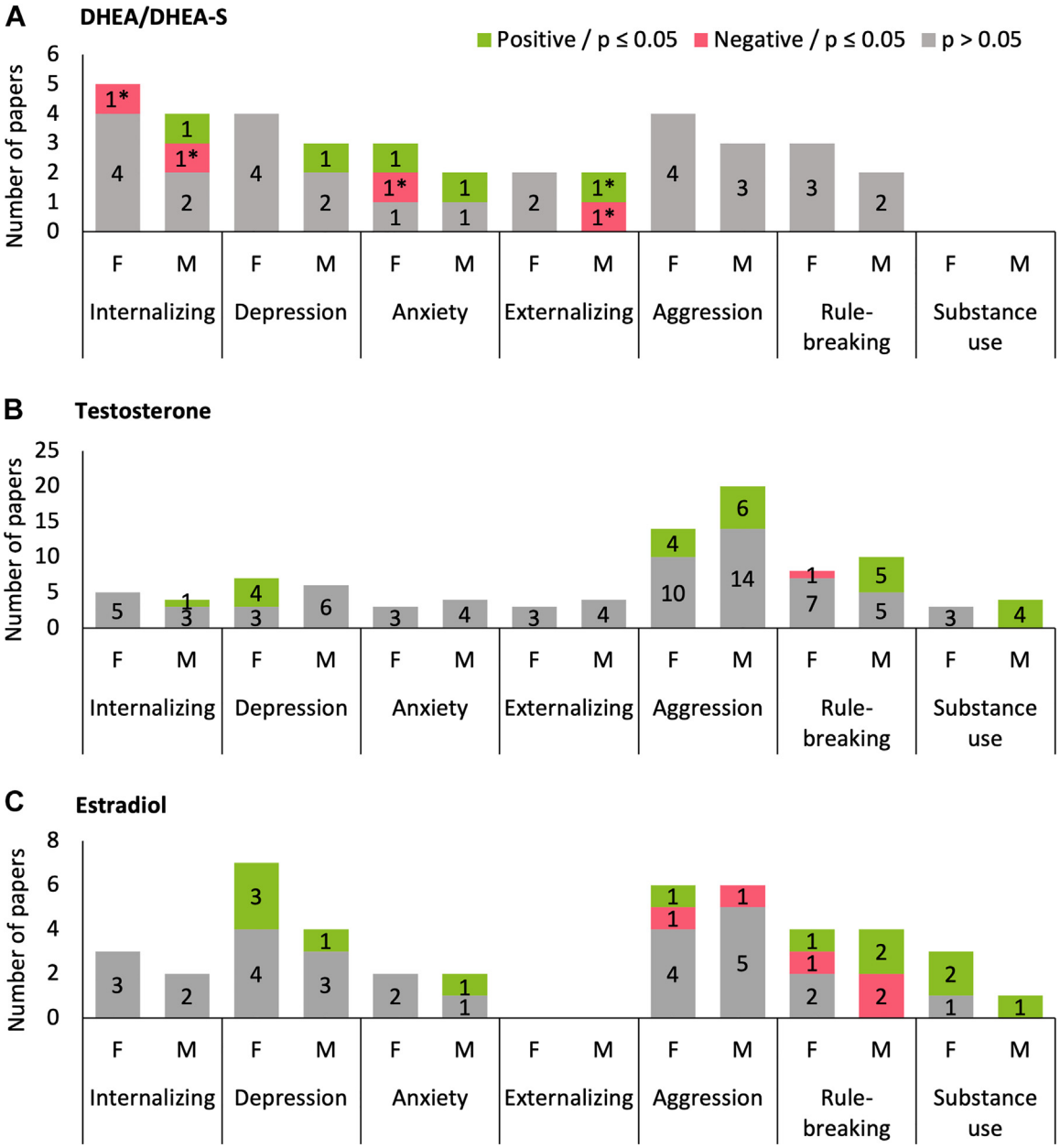

Fig. 4: **Summary of the findings from the included articles**. We specifically categorise findings into three categories: positive estimate & *p-value* ≤0.05 (*'positive/p ≤ 0.05'*, green color), negative estimate & *p-value* ≤0.05 (*'negative/p ≤ 0.05'*, red color), and *p-value* >0.05 (*'p > 0.05'*, grey color). F, females; M, males. * represents that smaller *p-value* was found for DHEA-S rather than DHEA. Two studies which showed non-linear relationship between hormones and mental health outcomes were not included in this figure. We acknowledge that using an arbitrary cutoff of *p-value* (0.05) has limitations; however, the majority of the included studies did not report the exact *p-value* or the confidence intervals around the estimated effect.

three associations were from cross-sectional studies,[52,53,62] and two from longitudinal studies.[43,63]

For females, three studies assessed the relationship between testosterone levels and externalizing problems,[30,47,48] 14 studies assessed aggression,[8,28,35,37,38,43,47–51,58,59,61,64] and eight for rule-breaking behaviours.[28,35,37,41,43,47,48,64] All associations with externalizing problems,[30,47,48] and the majority of associations with aggression,[28,35,37,38,43,47–51,64] and rule-breaking[28,35,37,43,47,48,64] fell within the *'p-value > 0.05'* category. Four associations for aggression fell within the *'positive/p-value ≤ 0.05'* category. This comprised one association between testosterone and aggression from a cross-sectional analysis,[8] and another three from other cross-sectional

analyses, which were limited to only certain types of aggression and depended on parenting styles.[58,59,61] One association between testosterone and risk behaviours (capturing both rule-breaking and substance use) from a cross-sectional analysis fell within the '*negative/p-value ≤ 0.05' category*.[41]

Substance use. For males, four studies assessed the relationship between testosterone levels and substance use (alcohol[65–67] or cigarette[66–68]). All studies were cross-sectional and findings fell within the '*positive/p-value ≤ 0.05'* category. Two studies also suggested that these positive association might be moderated by family or peer contexts.[65,67]

For females, four studies assessed the relationship between testosterone levels and substance use (alcohol[66–68] or cigarette[66–68]). All associations fell within the *'p-value > 0.05'* category.

Estradiol

Internalizing problems. For females, three studies assessed internalizing problems,[28,31,32] eight depression,[32,35,43,45,46,69–71] two anxiety,[32,36] in relation to estradiol levels. All associations between estradiol and internalizing problems[28,31,32] and anxiety,[32,36] as well as four of the associations with depression[32,43,45,71] fell within the *'p-value > 0.05'* category. Three associations fell within the '*positive/p-value ≤ 0.05'* category, although none of the analyses accounted for age.[35,46,69] Specifically, one cross-sectional analysis using GSMS data found that greater estradiol levels were associated with higher risks of depression diagnosis.[46] One longitudinal study showed that baseline estradiol levels were positively associated with depressive symptoms at baseline and at eight-month follow-up (but not 20-month follow-up).[69] Another longitudinal analysis also showed a positive association between baseline estradiol levels and one-year follow-up of self-reported (but not parent-reported) depressive symptoms.[35] A cross-sectional study found a curvilinear relationship between estradiol and depressive symptoms in females, with depressive levels initially increasing and subsequently decreasing with rising estradiol levels.[70]

In males, two studies assessed internalizing problems,[28,32] four depression,[32,33,40,43] two anxiety.[32,33] All associations with internalizing problems fell within the *'p-value > 0.05'* category,[28,32] as well as three associations with depression,[32,40,43] and one with anxiety.[32] Findings from one cross-sectional study fell within the '*positive/p-value ≤ 0.05'* category, for associations with depression and anxiety.[33]

Externalizing problems. Only one study investigated the association between estradiol and externalizing problems but did not stratify by sex.[72]

In females, seven studies assessed aggression[8,28,35,37,43,64,70] and five assessed rule-breaking,[28,35,37,43,64] in relation to estradiol levels. Four associations with aggression,[8,28,37,70] and two with rule-breaking[28,37] fell within the *'p-value > 0.05'* category. Findings from one of the larger cross-sectional studies were *'positive/p-value ≤ 0.05'* for associations with both aggression and rule-breaking in females.[64] However, findings from a longitudinal study, which did not adjust for age, were in the *'negative/p-value ≤ 0.05'* category for associations of estradiol change over one year with both aggression and rule-breaking.[43] Another longitudinal study (also did not adjust for age) found a curvilinear relationship between baseline estradiol and one-year follow-up aggression and rule-breaking behaviours, with these outcomes initially increasing and subsequently decreasing with rising hormone levels.[35]

In males, six studies assessed aggression and four rule-breaking.[28,37,43,53] The majority of associations (n = 5) with aggression fell within the *'p-value > 0.05'* category.[8,28,37,43,53] Two associations, from one cross-sectional and one longitudinal study, fell within the *'positive/p-value ≤ 0.05'* category for the association with rule-breaking behaviours (neither controlled for age).[43,53] Three associations fell within *'negative/p-value ≤ 0.05'*; a longitudinal analysis found that estradiol level changes were negatively associated with aggression changes between ages 8 and 10 years in males,[54] while two cross-sectional analyses found a negative association between estradiol and rule-breaking behaviours.[28,37]

Substance use. For females, three studies assessed substance use in relation to estradiol levels.[66–68] One association with alcohol use (both onset and quantity of lifetime use) was in the *'p-value > 0.05'* category.[66] Findings from two cross-sectional studies were in the *'positive/p-value ≤ 0.05'* category for the associations with alcohol use,[67,68] one of which also showed that estradiol levels were positively associated with cigarette use in females with unfavorable neighborhood contexts.[67]

For males, one study assessed alcohol use in relation to estradiol levels. Findings were in the *'positive/p-value ≤ 0.05'* category, comprising a positive association between estradiol levels and risk of alcohol use onset and higher quantity of lifetime alcohol use in males (but not in females).[66]

Other associations

Only a small set of studies examined andro-stenodione,[28,32,37,38,58,73] or progesterone,[36,74] or measured eating problems.[74,75] These results are reported in Supplement 7.

Discussion

This review systematically synthesized the findings of 55 population-based studies examining the association between pubertal hormones and risk of mental health problems in children and adolescents. Across studies, findings tended towards a positive association between testosterone and aggressive and rule-breaking

behaviours in males, and a positive association between estradiol and depression in females. There were some associations between testosterone and substance use in males, and estradiol and substance use in females, although overall few studies assessed substance use as an outcome. Findings were less supportive of an association between DHEA/DHEA-S and mental health problems. Importantly, this review found that most studies on pubertal hormones and mental health outcomes were at high risk of bias. As such, the state of evidence for a causal effect of pubertal hormones on mental health problems in children and adolescents was determined to be weak.

This systematic review considerably extends prior reviews on pubertal hormones and mental health problems. Apart from including a larger number of studies, most notably longitudinal studies, a strength of this review is the inclusion of a more extensive set of both pubertal hormones and mental health outcomes. In comparison to previous reviews, we aimed to better differentiate the findings by hormone, mental health outcome and sex, with the expectation that this would provide greater accuracy of the association between pubertal hormones and mental health problems. A further strength is that we conducted the first assessment of risk of bias (using a comprehensive tool) of this literature, which is critical for assessing the quality of the current evidence.[26] This approach highlighted important limitations in the field and provided guidance for future studies (Panel 1). We were unable to conduct a meta-analysis due to the extent of differences in both the outcome measurements and statistical analyses across studies, as well as the degree of bias across the included studies. Based on available data, we synthesised findings across studies by grouping reported associations based on *p-values* and the direction of effects.[76] However, there are limitations to interpreting *p-values* without considering the strength of the point estimate and the confidence intervals. A *p-value* > 0.05 does not imply that an effect size is small, while a *p-value* ≤ 0.05 does not necessarily translate to a clinically meaningful change in mental health outcomes in relation to hormone levels.[77]

In contrast to the systematic review by Byrne and colleagues (in 2017) that suggested higher levels of DHEA and DHEA-S were associated with higher levels of mental health problems, we failed to identify such patterns.[23] The prior review[23] identified positive associations[78–83] in many studies of clinical samples[78–80,82–84] and high risk population subgroups (those with higher hormone levels[81,85,86] or higher risk for psychopathology[87,88]), but these are more prone to bias and lack generalizability. In contrast, four of the five population-based studies published since 2017 have not observed such associations across males and females.[31,33,34,89] The systematic review by Duke and colleagues, published a decade ago, reported equivocal and conflicting findings on the association between testosterone and behaviour and mood in adolescent males.[21] While we also found discrepant results, the inclusion of more recent studies led to greater consistency regarding a positive association between testosterone and aggressive and rule-breaking behaviours in male adolescents. Finally, the systematic review published by Balzer et al., in 2015 indicated a potentially positive association between estradiol and depression in female adolescents, consistent with our findings.[22]

As previously noted, due to the high risk of bias in all assessed studies, we cannot conclude any causal relationships between hormones and mental health outcomes. Nonetheless, both biological and psychosocial mechanisms have been postulated. Testosterone may regulate the organization and function of the amygdala (key for emotional control), which has a high density of androgen receptors.[90] A longitudinal study of youth showed that testosterone modulates the structural covariance between the amygdala and the ventromedial prefrontal cortex (key for emotion regulation), thereby

***Panel 1*: Recommendations for future studies**

- Current evidence on the effects of pubertal hormones on mental health suffers from high risk of bias from confounding, hormone measurement, participant selection and missingness. In future studies, obtaining good quality evidence will require careful consideration of these biases.
- As pubertal hormone levels undergo short-term fluctuations due to diurnal rhythm, menstrual cycle phase, and extraneous factors like food and exercise, multiple samples are needed to obtain reliable measures of basal hormone levels.
- Analysis of pubertal hormones requires careful consideration of potential confounders. Study findings could be biased by failing to include key confounders in the adjustment set in addition to including variables that are on the causal pathway from hormones to mental health outcomes. We recommend that studies investigating the effect of pubertal hormones on mental health outcomes consider adjusting for sex, age, and race/ethnicity and avoid adjusting for physical development caused by hormone changes. A causal diagram can be a helpful tool that can guide appropriate confounder selection and explicitly communicate the assumed causal relationships between different variables.
- Future studies should carefully consider recruitment procedures to minimize selection bias.
- Future studies should provide valid report and interpretation of data. Specifically, they should avoid arbitrarily classifying the results into "significant" and "non-significant" based on a *p-value* cut-off, and instead report and carefully examine the size of the estimated effect, the uncertainty around the estimate (i.e., the confidence interval), and the *p-value*.
- Longitudinal studies are needed in this field. Repeated hormone measures would allow estimation of hormonal timing and tempo, which could better characterize how intra-individual hormonal changes (not just absolute levels but also timing and tempo) impact mental health outcomes. Repeated outcome measures would allow investigation of whether any effect of pubertal hormones persist, attenuate, or disappear through adolescence and into adulthood.

contributing to aggression.[90] A study of young adults also showed that testosterone may increase aggression through reducing the functional activity of the orbitofrontal cortex, a brain region implicated in decision making and impulse control.[91] There might be psychosocial explanations as well; it has been shown that advancing pubertal stage is positively associated with aggressive behaviours in adolescents independent of age and sex, mediated by associating with deviant peers.[92] As for estradiol, ovarian steroids may affect brain systems by shifting its sensitivity to stressors during puberty, which may partly account for our findings of a positive association between estradiol and depression in female adolescents.[93,94]

Importantly, our risk of bias assessment points to where greater attention is warranted in the design of future studies. A particular challenge for population studies is short-term variation in hormone levels (e.g., related to diurnal rhythms, food and medication intake, stressful events), which should be accounted for when collecting biological samples to provide a more stable estimate of basal hormone levels. Somewhat disappointingly, only four studies in this review were considered to have appropriately measured the hormone of interest. Multiple samples obtained at waking prior to the consumption of food or tooth brushing are ideal, as is consideration of the measurement of estradiol and progesterone across the menstrual cycle. The "Imaging of Child to Adolescent Transition Study"[95] and the "Transitions in Adolescent Girls" study in the USA[31,96] provide examples of accounting for the short-term variation in hormone levels in adolescent girls by collecting approximately four waking saliva samples with one week intervals between samples.

Confounding was identified as another major source of bias, with as only four studies appropriately accounted for confounding. In our causal model, sex, age, and race/ethnicity were identified as important confounders that need to be considered.[97–99] In addition, controlling for baseline mental health status in longitudinal studies may further reduce bias and better establish temporality; the majority of included longitudinal studies failed to do so. We also recommend not controlling for factors on the causal pathway (e.g., physical changes of puberty) in the analysis when the total effect is of interest. Selection bias was also an issue, as many studies failed to fully describe participant recruitment procedures and the approach to handling missing data. Future studies might also benefit from a more nuanced interpretation of data analytic results.[77] Instead of arbitrarily classifying results into "significant" and "non-significant" based on a *p-value* cut-off (often 0.05), we suggest reporting the estimated size of the effect, the uncertainty around the estimate, and the precise *p-value*.

Finally, cross-sectional studies were included in this review with the assumption that pubertal hormones were more likely to lead to mental health problems than vice versa. Nonetheless, longitudinal designs are ideal to estimate causality and should remain the focus of future investigations. The Childhood to Adolescence Transition Study (CATS)[100] in Australia and the Adolescent Brain Cognitive Development (ABCD) study[101] in the USA both recruited participants with tight age ranges and followed participants annually from late childhood into late adolescence. With a sampling frame that improves population representativeness, these cohorts can also provide more generalizable findings than the more typically used convenience samples.

Puberty is a critical stage in human development that is characterized by major biological and cognitive changes. It is also the period when many mental health problems first manifest.[1,2] Understanding whether the biological processes of puberty, specifically rising pubertal hormones, are causally involved in the emergence of these mental health problem can inform our knowledge of risk mechanisms and potentially identify the timing and nature of intervention targets for these problems. This systematic review did not reveal any robust evidence for causal relationships between pubertal hormones and mental health problems in children and adolescents. Although consistency of some associations was evident in the literature, the credibility of these patterns is likely to be undermined by the high risk of bias within the included studies. While more studies that carefully consider the highlighted methodological challenges will contribute to better quality evidence, clinical and policy-making efforts might benefit from focusing on the psychosocial processes that accompany the development of mental health problems during puberty.

Contributors

DL, SGD, SMS, and NV conceived and designed the study. DL screened all identified abstracts, reviewed all identified articles, extracted the data from articles, and assessed the risk of bias of included articles in consultation with SGD, SMS, and NV. NV double reviewed ten percent of the identified articles. SGD double assessed the risk of bias for ten percent of the included articles. DL, SGD, SMS, and NV contributed to the data interpretation. DL prepared the figures and tables. DL drafted the initial manuscript. SGD, SMS, and NV significantly edited and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102828.

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