The Effects of Oestradiol on Mood and Behaviour in Human Female Adolescents: A Systematic Review

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Citation: Balzer B.W.R., Duke SA., Hawke C.I., Steinbeck K.S.. The effects of estradiol on mood and behavior in human female adolescents: a systematic review. European Journal of Pediatrics. 2015;174(3):289-98.

Abstract

Mood disorders and health risk behaviors increase in adolescence. Puberty is considered to contribute to these events. However, the precise impact of pubertal hormone changes to the emergence of mood disorders and risk behaviors is relatively unclear. It is important that inappropriate attribution is not made. Our aim was to determine what is known about the effect of endogenous estradiol on human adolescent girls' mood and behavior. The databases searched were MEDLINE, Embase, PsycINFO, ERIC, Pre-MEDLINE, Web of Science and Scopus for all dates to October 2014. For inclusion, contemporaneous hormone and mood or behavioral assessment was required. Data were extracted following a template created by the authors. Fourteen studies met our inclusion criteria. There was some consistency in findings for mood and estradiol levels, with associations between estradiol and depression, and emotional tone and risk taking. Results were less consistent for studies assessing other mood and behavioral outcomes. Most studies were cross-sectional in design; assay methodologies used in older studies may lack the precision to detect early-pubertal hormone levels. *Conclusion:* Three longitudinal and several cross-sectional studies indicate potential associations between estradiol and certain mood or affective states, especially depression and mood variability though there are insufficient data to confirm that the rise in estradiol during puberty is causative. We believe that it is important for health professionals to take care when attributing adolescent psychopathology to puberty hormones, as the current data supporting these assertions are limited.

Keywords: Adolescence; puberty; estradiol; mood; behavior; affect; self-image; aggression; risk-taking

What is known? Mood disorders and health risk behaviors increase in prevalence during adolescence. Popular assertions ascribe these changes to the increase in hormones during puberty. For females, estradiol is the primary sex steroid and is thus implicated in female mood and behavior.

What is new: This study shows that assertions of "puberty blues" due to hormone changes do not have a firm evidence base. Though data suggests some associations between estradiol and depression, consistent longitudinal data showing a causative role is lacking.

List of Abbreviations:

AQ Aggression Questionnaire; BESAA Body Esteem Scale for Adolescents and Adults; CAPA = Child and Adolescent Psychiatric Assessment; CBC Child Behavior Checklist; CDI Children's Depression Inventory; CPA Children's Physical Activity Scale; CPI California Psychological Inventory; CSI Children's Somatization Inventory; DISC Diagnostic interview Schedule; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ERIC Education Resources Information Centre (ERIC); MAACL Multiple Affect Adjective Checklist; MASC Multi-dimensional Anxiety Scale for Children; MEBS Minnesota Eating Behaviors Survey; MTFS Monitoring the Future Survey; OSIQ Offer Self-Image Questionnaire; PACES Physical Activity Enjoyment Scale; PDS Pubertal Development Scale; PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SIQYA Self-Image Questionnaire for Young Adolescents; SPP Self Perception Profile for Children; SSAS Sensation Seeking and Anxiety States Test; YBP Youth Behavior Profile; YSR Youth Self Report

Introduction

Adolescence is a formative time for an individual's identity, development and functioning (1). During this time, long term behavioral and affective patterns emerge, as well as psychopathologies (2). Puberty is the universal biological event of adolescence, the primary purpose of which is to achieve adult reproductive capacity (3, 4). Puberty involves dramatic and well remembered physical changes (5) and it is perhaps unsurprising that intuitively these changes are allocated importance in both physical and psychosocial contexts.

The popular assertions of adolescence as a time of "puberty blues", "storm and stress" or other behavioral changes (6, 7) are palpably not correct (8) for all adolescents. Certain problem behaviors and mental health issues do emerge during adolescence (1, 9), and deterioration in health may be linked to such behavioral changes (10). These include the appearance of sex differences in the prevalence of depression (the prevalence of depression in females is twice that of males) (11), increased sensation seeking (2, 12), substance use (13) and disordered eating (14). For girls, depressive illnesses, self-image and eating disorders are of particular concern. Gender differences and the coincidental increase in pubertal hormones at this time of increased risk implicate some role for sex hormones. However there exists no systematic analysis of the literature.

Given the importance of non-biological factors such as social, family and peer relations in the development of adolescent behaviors and affect (15), it could be postulated that hormones influence adolescent behavior indirectly, either by modulating internal status reactivity to modify affect, and/or by the effect on others of phenotypic development (6). While the hormone levels remain high after puberty, behavioral and mood disorders often ameliorate, giving rise to popular notions of "puberty blues" being confined to this period alone. Why some of these mood and behavioral changes fail to abate in certain individuals is unclear. It is important to understand the true effect and duration of that effect of sex

hormones on adolescent mood and behavior, so that clinicians can target established, evidence-based interventions to those most at risk (5). Additionally, while diagnosable psychiatric conditions increase in prevalence, many parents will describe mood and behavior changes despite absence of an identifiable mental illness. While these changes fall within a normal spectrum of mood or behavior, these can still be confronting and challenging to the parent and adolescent alike.

The age of onset of puberty in many Western countries has declined over the recent decades, (3, 16), with earlier exposure to rising levels of estradiol, the primary puberty hormone in females. This is an additional reason to better understand how estradiol affects the mood and behavior in the pubertal transition, and which girls might be especially at risk for any negative impacts of their puberty hormones.

One specific mechanism for any effect of estradiol might be through central neural monoamine systems, which have been implicated in a wide range of mood and behavioral disorders (17, 18). Estradiol may also induce the formation of new synapses (19). Such a neuroarchitectural effect is part of the organizational and activational effects hypothesis, wherein steroids act during brain development to alter neuroarchitecture, which limits the repertoire of the brain's responses when acted upon by that hormone later in life (activation) (17, 20). An example of such activation is the commencement of reproductive behavior in adulthood, which is programmed earlier during the organization phase of neural development (20).

Animal studies, especially those in rodents (21, 22), have informed the role of estradiol in adolescent behavior. For example, the importance of estradiol in sexually differentiated behavior patterns in rodents (23) and other animals (24) may provide hypotheses as to sex-based behavioral differences in humans. While these studies proffer putative roles for estradiol in human mood and behavior, we know that variation between

different animal species is significant (25) and it is difficult to adequately model the complexities of human behavior and mood in animal settings.

The aim of this systematic review was to determine what evidence exists for the true effect of the endogenous puberty hormone, estradiol, on adolescent girls' mood and behavior.

Methods

Search Strategy

A systematic search was conducted to identify publications on the effect of endogenous estradiol on mood and behavior in healthy adolescent girls (10-19 years) using the terms as laid out in Supplement A. The following databases were searched: MEDLINE, Embase, PsycINFO, Education Resources Information Centre (ERIC), Pre-MEDLINE, Web of Science and Scopus from the date of database inception to October 2014. No language limits were set. The search strategy for MEDLINE is included in Supplement A., with search terms for the other databases modified to their requirements. Where relevant, reference lists were hand searched for further records. No initial restrictions were placed upon publication type.

Inclusion Criteria

To be considered for this review, study participants were female adolescents (10-19 years) from community samples, with no specified diseases. Institutionalized or incarcerated populations were excluded, unless a control group was reported separately, due to potential confounders for behavioral outcomes. Study participants must have undergone, or be undergoing spontaneous puberty. Thus studies involving exogenous estradiol or other estrogens were excluded. Oral contraceptive pill use was also a criterion for exclusion, as these preparations contain synthetic and biologically potent estrogens that suppress endogenous estradiol production. In the event that a study did not explicitly define oral contraceptive use, authors were contacted for further information.

Estradiol measurement in blood, saliva or urine was required, with the laboratory methodology provided. Though assay methodology and quality has improved markedly over the past decades, we did not limit studies by assay type. It should be noted that even now

assays might not be able to detect very low (i.e. pre-and early pubertal) estradiol levels with adequate sensitivity (26). We considered whether to include only studies that used a standardized time of biological data collection, in order to control for known diurnal physiological variation in estradiol in early puberty (3). If we had adhered to this criterion the only study to be excluded would have been a large, longitudinal study in which the collection time for the majority of samples was relatively constant (27). Only one study in females controlled for cycle time (28). In the others there was no stratification for pre- or post-menarchal status, and hence no explicit control for menstrual cycle. We decided to retain these (all cross-sectional) studies, but also to address the inherent limitations of this approach in the discussion. Studies were included if outcomes were mood and/or behavior measured by a recognized, validated tool and with the mood/behavioral measurement concurrent with hormone measurements.

Studies on the effects of estradiol generally do not account for the potential confounding effects of testosterone, and thus testosterone was not addressed in the review. The mood or behavioral effects of progesterone were considered beyond the scope of the review, as we were interested in the pubertal transition, rather than the mature adult ovulatory cycle where progesterone induced mood variation is possible. (29).

Specific moods and behaviors sought included depression, anxiety, eating disorders and self-image disturbance, social interactions, aggressive, disruptive or conduct-disordered behavior; risk taking including substance abuse. Studies were excluded if these addressed primarily sexual behaviors, as such behaviors are essential for reproduction which is the key biological function of puberty (3).

Data Collection and Analysis

Selection of Studies

Once irrelevant studies and duplicates were removed, one reviewer (BB) scanned the title, abstract and keywords of the remaining articles. Where a reference seemed suitable for the review, the full text was retrieved for further analysis by two reviewers (BB, KS) and was either included or excluded on the above criteria.

Data Extraction

Information was extracted from each study into a template developed by the authors. The following information was recorded: participants (sample size, sex and age range), affect or behavior measured (type, measurement tool and its validity), estradiol measurement (assay type, time of day and time of cycle where available), assessment of pubertal status (method used; examination, self-report or parental report), study outcomes and discussion of limitations. These data are described in Tables 1 and 2.

Quality Assessment

A general methodology for quality assessment was followed, based upon checklists for the evaluation of studies (30, 31) and is reported in Tabl3 in the Results section.

Statistical Analyses

Given the heterogeneity of the outcomes and outcome measures in this systematic review, no further analyses (such as meta-analysis) could be performed and the results are presented as descriptive data.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (32) was followed in the writing of this review.

Results

Search Results

The result of the searches is displayed in Figure 1. Of the initial 9904 results obtained from database searches, 9574 were removed. Three additional studies were identified from manual reference list searching. After exclusion based upon abstracts, the remaining 76 citations were inspected in full text. Fourteen of these met the inclusion criteria. The reviewers had full consensus in their findings. All included publications were written in English.

The 62 full text articles which were excluded, as well as the reasons for their exclusion, are detailed in Supplement B. Participant age, lack of estradiol measurement and oral contraceptive use were the main reasons for exclusion.

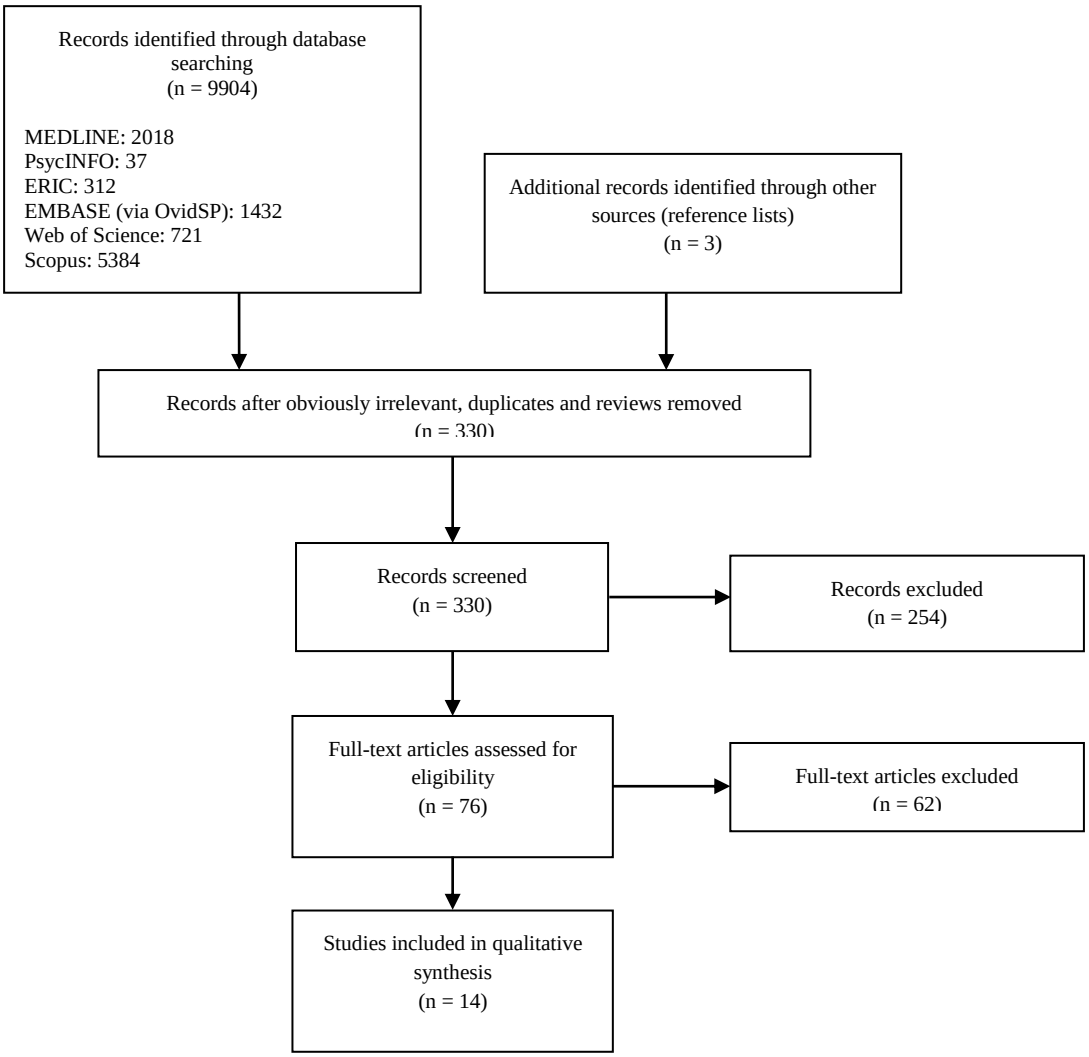

Figure 1 PRISMA Diagram for Study Selection

Included Studies

Fourteen studies met the inclusion criteria. These studies are summarized in Tables 1 and 2. Thirteen studies used standard radioimmunoassay measurement of estradiol for blood samples. One used an enzyme-linked immunoassay in saliva (33). Three studies (27, 34, 35) were longitudinal and the remainder was cross-sectional, whether by study design or analysis. Four of the studies were based upon the same participant sample (35-38). Nine of 14 studies examined mood and affect alone, and 11 of 14 of the studies examined aggression, delinquency and behavioral or conduct disorders. Six of the nine studies on aggression also included an assessment of mood and affect.

For clarity of interpretation, the variables of interest were grouped under four categories: A: mood and affect; B: self-image and social competency and related behaviors; C: risk taking, sensation seeking and substance use; and D: aggression, behavior/conduct disorder and delinquency as shown in Table 1. The groupings describe similar outcomes so that a degree of inter study comparison can be made in the absence of formal meta-analysis. Most of the included studies considered more than one categorical outcome, and in order to reduce repetition we have not looked at the four outcome categories separately. In addition most studies were unable to demonstrate an association, so repetition of negative findings is also reduced. As previously stated, it was not possible, due to heterogeneous outcomes, to perform meta-analysis.

Table 1 Study Characteristics (males are excluded from further analysis)

Author	Year	N	Sex[#]	Setting	Age (mean (SD) or range)	Behavior or affect
Susman *et al.* †*	1991	108	56 Male, 52 Female	USA, community based	10-14 (M); 9-14 (F)	A, D
Slap *et al.*†	1994	54	Female	USA, community based, high schools	10-14	A, B
Angold *et al.* †	1999	339	Female	USA, community based	9-15	A
Susman *et al.**	1985	108	56 Male[#], 52 Female	USA, community based	10-14 (M); 9-14 (F)	A, D
Nottelmann *et al.**	1987	108	56 Male, 52 Female	USA, community based	10-14 (M); 9-14 (F)	B, D
Susman *et al.**	1987	108	56 Male, 52 Female	USA, community based	10-14 (M); 9-14 (F)	A, D
Brooks-Gunn *et al.*	1989	103	Female	USA, community based, private schools	11 (0.8)	A, D
Warren *et al.*	1989	100	Female	USA, community based	10.6-13.3	A, B, D
Martin *et al.*	1999	94	Female	USA, community based, high schools	16.6 (1.0)	C
Graber *et al.*	2006	100	Female	USA, community based, urban high schools	11 (0.8)	A, D
Rapkin *et al.*	2006	106	Female	USA, community based	13.0 (3.0)	A
Davison *et al.*	2007	178	Female	USA, community based	11.3 (0.28)	B, D
Vermeersch *et al.*	2008	298	Female	Belgium, community based, high schools	14.3 (0.59)	C, D
Klump *et al.*	2010	258	Female	USA, twin study, community based	12.0 (1.40)	B

† Longitudinal analysis
* These studies are based upon the same data set
# In studies which included males, only the female data are reported
A = mood and affect; B = self-image and related behaviors; C = risk taking, sensation seeking and substance use; D = aggression, behavior/conduct disorder and delinquency

Table 2 Extracted Study Data

Author	Year	n (Female)	Relevant Scale(s)	Assessment of Pubertal Status	Assessor of Pubertal Status	Control for Cycle	Behavior or affect	Outcomes
Susman *et al.* †	1991	52	DISC, SIQYA, CBC	Tanner	Physician/ Nurse	No	A, D	No significant cross-sectional relation between E_2 and emotional tone, internalizing behavior problems or symptoms of depression/anxiety in girls. **Longitudinal changes in E_2 positively associated with higher emotional tone in girls** ($r=0.26$; $p<0.05$)
Slap *et al.* †	1994	54	SIQYA	Tanner	Physician/ Nurse	No	A, B	No association between change in E_2 and body image/mood variability
Angold *et al.* †	1999	339	CAPA	Tanner	Self-rated	No	A	**E_2 has a linear relationship to depression**
Susman *et al.*	1985	52	OSIQ	Tanner	Physician/ Nurse	No	A, D	No significant relationships observed for girls.
Nottelmann *et al.*	1987	52	OSIQ, CBC (maternal)	Tanner	Physician/ Nurse	No	B, D	No significant relationships between E_2 and behavioral or self-image issues for girls.
Susman *et al.*	1987	52	OSIQ, CBC, Self-ratings, MAACL (maternal)	Tanner	Physician/ Nurse	No	A, D	No significant relation between E_2 and affect in girls
Brooks-Gunn *et al.*	1989	103	YBP	Tanner	Physician/ Nurse	No	A, D	**Non-linear effect of E_2 on depressive affect: most depression during rapid increase in E_2.** No significant relation between E_2 and aggression. Negative life events interacted significantly with hormonal changes for depression
Warren *et al.*	1989	100	YBP, SIQYA, Maternal Depression Questionnaire	Tanner	Physician/ Nurse	No	A, B, D	**Significant curvilinear relationship between estradiol level and depression, impulse control and psychopathology** with depression highest for E_2 184-275 pmol/L. Impulse control was lowest and psychopathology highest at E_2 92-184 pmol/L. (F value for depression relationship 6.78 ($p=0.01$); impulse control 4.45 ($p=0.04$); psychopathology 4.73 ($p=0.03$))

Martin *et al.*	1999	94	MTFS	Nil	Nil	Not stated	C	**Mean E_2 significantly higher in those who used alcohol recently** (F-statistic 69.81, $p<0.001$). No significant difference in E_2 for other drug use. ANOVA showed alcohol use was highest mid-cycle (when E_2 highest)
Graber *et al.*	2006	100	YSR	Tanner	Physician/ Nurse	Not stated	A, D	**Higher E_2 correlated with depressive affect** ($r=0.27$; $p<0.01$). Negative life events mediated effect of E_2 on aggression
Rapkin *et al.*	2006	106	MASC, CDI, CSI	Tanner	Self-rated	No	A	**Anxiety was inversely correlated with trichotomized E_2** ($r=-0.202$; $p=0.038$). No relationship observed for depression or somatization.
Davison *et al.*	2007	178	PACES, CPA, CDI, SPP, BESAA	Tanner, PDS	Nurse (Tanner), Mother (PDS)	Not stated	B, D	**Negative correlation between E_2 and body esteem at 11 years** ($r=-0.19$; $p<0.05$)
Vermeersch *et al.*	2008	298	Self-derived questionnaire	Tanner	Physician	Yes	C, D	**Total and free E_2 positively related with both aggressive and non-aggressive risk taking** ($r=0.21$; $p < 0.001$ for both), controlling for and independent of age and stage. Effects were most evident mid-cycle for aggressive risk taking (but not non-aggressive). Differential association was an important mediator.
Klump *et al.*	2010	258	MEBS	PDS	Self-rated	Not stated	B	**Higher E_2 plays a role in the onset of disordered eating attitudes and behaviors** in a twin study

†Longitudinal analysis; ‡ Differential association refers to the theory that risk-taking behavior is learnt through interactions with risk taking peers (Vermeersch *et al.*)
A = mood and affect; B = self-image and related behaviors; C = risk taking, sensation seeking and substance use; D = aggression, behavior/conduct disorder and delinquency

Study Data

The studies characterized in Table 1 are further detailed in Table 2. To briefly summarize the most important findings:

Mood and affect (Category A)

Most of the studies considered mood and affect. The studies can be summarized as follows: female sample size varied from 52 to 339, with a mean of 122 and median 100. The age ranges of these subjects are listed in Table 1. In the nine publications considering this domain, 13 different measures were used for participant assessment. All of these studies were based on community samples from the United States of America. Mood was investigated in different ways, such as DSM-IV depression (27), emotional tone (variability in mood) (35, 38-40), depressive affect (10, 41), and anxiety (42). While these studies do not all examine the same aspects of mood or affect, all do consider what can be identified as pathological or maladaptive states.

Susman's longitudinal study in 52 girls over one year considered the roles played by several hormones (luteinizing hormone, follicle stimulating hormone, testosterone, estradiol dehydroepiandrosterone and its sulfate, androstenedione and cortisol) in a variety of negative affective states: emotional tone, internalizing behavior problems, symptoms of depression and anxiety. Longitudinal data were given for emotional tone and internalizing behavior problems, though only cross-sectional data were provided for depression and anxiety symptoms. For girls, no significant cross-sectional relationships were observed between estradiol and any of the study outcomes, though longitudinal analyses showed a significant positive relationship between estradiol and increased emotional tone (35). Slap *et al.* found no longitudinal association between estradiol and mood (34). This study followed girls

for one year, focusing on changes in self-image throughout puberty. Emotional tone was one scale of interest for their questionnaire. Regression analyses did not find a relationship between changes in estradiol and changes in emotional tone over one year. It should be noted that there was a significant decline in emotional tone scoring (indicating a more variable mood) though changes in estradiol were not significant between baseline and follow-up. In contrast, Angold's larger (n=339) three-year longitudinal study found an approximately linear relationship between estradiol and depression, which was diagnosed by interview using DSM-IV criteria (27). This study found that the odds ratio of estradiol changes being related to depression was significant (odds ratio 2.5, 95% confidence interval 1.5 to 4.3). Additionally, Angold's study found that estradiol was more strongly related to depression than Tanner stage, supporting, not unexpectedly, the primacy of hormone change over morphological change in providing an etiological basis for depression in their cohort. When estradiol levels were divided into quintiles, the percentage of girls with DSM-IV depression was approximately linear as hormone levels increased.

Two cross-sectional studies observed that estradiol had a non-linear relationship with depressive affect. When estradiol concentration was reported as quartiles, depression was lowest in the pre- and post-pubertal quarters (bottom 25% and uppermost 25% respectively), and highest in the transition between these two (10, 41). For Brooks-Gunn's data, there were significant interactions between negative life events and hormonal levels in depression rating (41). In Rapkin's study, anxiety was inversely correlated with estradiol when hormone levels were tertiled. Without categorization, estradiol was not significantly correlated with anxiety,

however the authors note a trend to this correlation (p=0.051) between the two variables.

Of the seven cross-sectional analyses, emotional tone was considered in three (35, 38, 40). Susman's results from 1991 are reported above, as both longitudinal and cross-sectional analyses were provided. An earlier paper in the same data set did not find any significant cross-sectional relationship with emotional tone and estradiol (38). Both of these studies used different mood assessment tools. In contrast to Susman's studies, more recent work in a larger study population (n=100) observed a correlation between estradiol and emotional tone (40).

Self-image and related behaviors (Category B)

Slap *et al.* (34) found no longitudinal association between changes in estradiol and self-image. In contrast, cross-sectional studies observed correlations between estradiol and body esteem (43) and with the appearance of genetically influenced disordered eating attitudes and behaviors (44). In Davison *et al* a negative correlation between estradiol and body esteem was observed at 11 years in girls, though not at any other time point (43). Nottelmann *et al.* found no association between estradiol and body image (36).

Risk taking, sensation seeking and substance use (Category C)

A significant correlation was found between the level of estradiol and alcohol use in Martin *et al.* (28). No relationship between estradiol and other substance use was identified. In a large Belgian population-based study, Vermeersch *et al.* found positive relationships between total and free estradiol in girls and risk taking (45). Aggressive risk taking was most evident at mid-cycle (defined by the investigators as

an estradiol of greater than 60 pg/mL (220 pmol/L) (28)), with non-aggressive risk taking showing no such cycle effect.

Aggression, behavior/conduct disorder and delinquency (Category D)

There were limited data in this Category. Brooks-Gunn *et al.* and Nottelmann *et al.* both observed no correlation between estradiol and aggression in their studies (36, 41). Graber *et al.* found that aggression only correlated with estradiol in females when negative life events were included as a mediating effect (40).

Quality Assessment

Table 3 provides a detailed description of quality assessment. No study included a power analysis, nor were there adequate descriptions of sampling methods. Four studies specified exclusion criteria. Of the fourteen studies, only Martin *et al.* controlled for menstrual cycle (28). Though Angold's study did not use exact timing of sample collection, approximately three-quarters of samples were collected at consistent times which the authors report as minimizing diurnal variation effect (27). With respect to confounding factors, four studies accounted for or controlled for factors such as age and socio-economic status.

Table 3 Quality Assessment of Included Studies

Author, Year	Was the study setting and population adequately described? (Age, gender, menarcheal status)	Did papers consider a power analysis?	Exclusion criteria described?	Adequate control or adjustment for menstrual cycle?	Appropriate methodology described for variable measures? (Including estradiol assay limits)	Relevant confounders (including age, SES) accounted for or controlled?	All primary outcomes reported in results
Susman *et al.*, 1991	Yes	No	No	No	No (assay limits not stated)	No	Yes
Slap *et al.*, 1994	Yes	No	Yes	No	Yes	No	Yes
Angold *et al.*, 1999	Yes	No	Yes	No	Yes	No	Yes
Susman *et al.*, 1985	Yes	No	No	No	No (assay limits not stated)	No	Yes
Nottelmann *et al.*, 1987	Yes	No	No	No	No (assay limits not stated)	No	Yes
Susman *et al.*, 1987	Yes	No	No	No	No (assay limits not stated)	No	Yes
Brooks-Gunn *et al.*, 1989	Yes	No	No	No	Yes	Yes	Yes
Warren *et al.*, 1989	Yes	No	Yes	No	Yes	No	Yes
Martin *et al.*, 1999	Yes	No	Yes	Yes	Yes	No	Yes
Graber *et al.*, 2006	Yes	No	No	No	Yes	No	Yes
Rapkin *et al.*, 2006	No	No	Yes	No	Yes	Yes	Yes
Davison *et al.*, 2007	Yes	No	No	No	Yes	Yes	Yes
Vermeersch et al, 2008	Yes	No	No	No	Yes	No	Yes
Klump *et al.*, 2010	Yes	No	No	No	Yes	Yes	Yes

Discussion

This systematic review is the first to examine the effect of estradiol levels on mood and behavior in adolescent girls. It is timely because long-standing assumptions and the evidence regarding sex hormone effects on adolescent mood and behavior have never been comprehensively explored. With the growing awareness of mood and behavioral changes in adolescents, confirming or challenging these assumptions is important to develop or refine new paradigms in the diagnosis and management. Given the earlier onset of female puberty (3, 16) it is important to be aware of when any estradiol effects might be expected to occur, especially as there are established links between early onset and later female mood and behavioral problems (14, 36, 46, 47).

The review demonstrated reasonably consistent findings on mood and affect, with depression and increased mood variability being positively correlated with estradiol for at least some stages of puberty. Associations were most consistently observed between estradiol concentrations and depressive states during the transition from pre-pubertal to adult estradiol levels (10, 27, 40, 41), suggesting that tempo or rapidity of hormone change might play a part. A positive correlation was generally observed between estradiol and affective variability (35, 38, 40). While mood variability more likely reflects "puberty blues" than does DSM-IV diagnosed depression (27), both benign and pathological changes in mood and affect are important causes of parental and adolescent concern during puberty. We have shown both of these have some association with estradiol levels. There was no clear

consistency of estradiol effect for behaviors such as aggression, behavior/conduct disorder and delinquency (see 3.3.4). These behaviors are more often (falsely) associated with testosterone, as another review by our group has shown (48).

The cross-sectional nature of all but three studies limits the conclusions of this review. Thus, reported outcomes can only show associations between estradiol concentrations and the affect or behavior of interest. Causality cannot be inferred, as an association could be a persistent relationship, short-term change or mere coincidence (49); likewise the direction of the effect can only be postulated. Additionally, four of the studies were from the same cohort (35-38), and three of these described similar outcomes (all assessed with different scales), which risks over-representation of their data. Only four of the twelve cross-sectional studies controlled for potential confounders such as socio-economic status.

Brooks-Gunn *et al.* estimated only 1% of variance in negative emotional expression was due to estradiol (41) in their study. Environmental and social factors or determinants in an individual may mediate or amplify susceptibility to behavioral or affective changes as a result of pubertal hormone change (49). Angold *et al.* postulated that hormonal influences on mood and behavior are less causative than sensitizing – that is, pubertal increases in sex hormones surpass a threshold that would render one more likely to alter affect or behavior (27). That one-fifth of samples had hormone levels that fell below assay limits of detection and timing of sample collection was not as rigorous as other studies should be viewed as specific study limitations.

The studies appraised in this systematic review are both observational and primarily cross-sectional. Longitudinal cohort studies would provide the best

evidence for an effect, if any, of estradiol on adolescent mood and behavior and this was the finding in the large longitudinal study from Angold et al (27).

None of the studies in the systematic review addressed mechanisms for a putative relationship between estradiol and behavior and/or mood. Such mechanisms are likely primarily central. Estrogens, especially estradiol, have been shown to modulate genetic expression in neural monoamine systems (such as the dopaminergic, serotonergic and noradrenergic systems) (17, 18). These systems are commonly targeted by psychotropic drugs such as monoamine oxidase inhibitors and selective serotonin re-uptake inhibitors, which support at least a role for estradiol in the onset or progression of mood or behavioral disorders. Pubertal hormone changes are often thought to modulate mood and behavior by activating previously organized neuroarchitecture (see Introduction). It would be anticipated that these changes persist into adulthood, but given the limited follow-up in the studies reviewed, we cannot postulate as to whether estradiol's effects in this regard are persistent. Regardless, it is important to consider how sex hormone changes might affect adolescent mood and behavior, especially given the salient increase in psychopathology during and after adolescence and the importance of earlier intervention.

This systematic review has several strengths. Our methodology included comprehensive searches of many databases of potential relevance to this review, as well as detailed data extraction and quality analysis. Of the fourteen included studies, seven included over 100 girls.

There are a number of limitations. The studies included in the systematic review used a range of measurement tools to assess behavior and affect, and meta-

analysis or quantitative analysis of the collected study data was not possible. There may be a bias in that only published manuscripts were included in our final analysis, but as a counter to this argument, published studies had mainly negative findings. Information about the quality of the environment and early-life stresses experienced by the participants were not offered in the majority of the studies. These factors might well contribute to any aberrant moods or behaviors, and are thus important confounders.

The irregular nature of menstrual cycles for some time after menarche makes control for menstrual cycle difficult in any study, and was only done in one of the retained studies. Failing to control for menstrual cycle may be a limitation of the review. Alternatively selecting a specific phase of the cycle (follicular, mid or luteal) may also skew the findings – if samples were not collected in the mid-follicular phase, progesterone may be a confounding factor. The most important methodological limitation of every study is the method of estradiol measurement. The American Endocrine Society's consensus statement on estradiol measurement (26) concludes that even current assays are inadequate for pre-pubertal estradiol measurement, indicating that the methodologies of the reviewed studies may lack sufficient sensitivity to detect estradiol, especially at low levels or indeed to measure with enough specificity mid puberty levels. In older, less sensitive assays especially estradiol-mediated effects will be underestimated if too many estradiol levels are below limits of quantification.

In conclusion, this systematic review has found that there are insufficient longitudinal data of high methodological quality to confirm that the rise in estradiol during puberty plays a causative role in adolescent mood and behavioral changes,

though the current evidence clearly suggests such a relationship exists. Future studies would require sufficient duration and frequency of sampling of biological markers, adequate statistical power and the use of mass spectrometry techniques to clarify the role of estradiol. However, given the intra- and inter- individual variability of estradiol levels from the beginning of puberty onwards, and the variation in timing and tempo of puberty it is possible that even with careful longitudinal studies, the assignation of a causal role may prove elusive.

We believe that it is important for health professionals to take care when attributing adolescent psychopathology to puberty hormones, as the current data supporting these assertions are limited. Both timing and tempo of puberty may contribute to vulnerability in certain adolescents, particularly if other adverse psychosocial circumstances exist. Such adolescents may require supportive intervention during their adolescence in order to ensure that health trajectories are optimized. To this end, further understanding on how the dramatic rise in estradiol during puberty affects adolescent girls' mood and behavior has important public health repercussions.

Acknowledgements

The authors would also like to thank Monica Cooper, Faculty Liaison Librarian, University of Sydney Medical Library, for her assistance in database search optimisation.

Contributors' statements

Ben W.R. Balzer: developed search strategy, performed literature search, extracted data, drafted the initial manuscript and revised subsequent drafts. Approves final manuscript as submitted.

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Supplement A: Search Strategy

MEDLINE

1. Adolescent/
2. schools/ or students/
3. exp Puberty/
4. (adol* or teen* or juvenile* or youth* or student*).tw.
5. pubert*.tw.
6. 1 or 2 or 3 or 4 or 5
7. Adolescent Psychology/ or Adolescent Psychiatry/
8. behav*.tw.
9. adolescent behaviour/ or Behaviour/ or behavioural symptoms/ or affective symptoms/ or aggression/ or agonistic behaviour/ or bullying/ or depression/ or self-injurious behaviour/ or self mutilation/ or stress, psychological/ or drinking behaviour/ or alcohol drinking/ or drug-seeking behaviour/ or impulsive behaviour/ or risk reduction behaviour/ or risk-taking/ or social behaviour/ or Risk-Taking/ or Accidents/ or accidents, home/ or accidents, traffic/ or Dangerous Behaviour/ or impulsive behaviour/ or compulsive behaviour/ or behaviour, addictive/
10. (Social* adj3 (behav* or conform* or adjustment or dominan*)).tw.
11. (Behav* adj3 (competitive or cooperative)).tw.
12. (Risk adj3 (taking or behav*)).tw.
13. (impulsiv* or dangerous* or dangerous behav* or hazardous or delinqu* or antisocial behav* or conduct disorder* or oppositional defian*).tw.
14. exp Substance-Related Disorders/
15. (drug taking or drug abuse or smok* or tobacco or alcohol or addiction* or substance abuse or drug dependenc*).tw.
16. (accident* or crash* or traffic accident*).tw.
17. exp Self Concept/
18. Body Image/ or personal autonomy/
19. (Self adj3 (concept* or image* or esteem or perception*)).tw.
20. exp aggression/ or bullying/
21. Violence/ or Juvenile Delinquency/ or Student Dropouts/ or Social Behaviour Disorders/
22. (aggress* or violen* or bully* or bullies).tw.
23. mental disorders diagnosed in childhood/ or "attention deficit and disruptive behaviour disorders"/ or child behaviour disorders/ or "feeding and eating disorders of childhood"/ or Antisocial Personality Disorder/ or Conduct Disorder/
24. social behaviour/ or aggression/ or competitive behaviour/ or cooperative behaviour/ or helping behaviour/ or shyness/ or social dominance/ or social identification/ or social isolation/ or social stigma/
25. exp Self-injurious behaviour/
26. exp Suicide/
27. emotions/ or affect/ or irritable mood/ or anger/ or rage/ or anxiety/ or apathy/ or boredom/ or happiness/ or hate/ or hostility/
28. (emotion* or mood* or bored* or hostil* or apath* or frustrat*).tw.

29. exp mood disorders/
30. mental disorders/ or Depression/ or anxiety disorders/ or eating disorders/ or mood disorders/ or sleep disorders/ or substance-related disorders/
31. (depress* or suicid* or parasuicid* or self harm* or self injur* or self destruct* or self mutilat*).tw.
32. (anxiet* or nervous* or anxious).tw.
33. motivation/ or achievement/ or "conflict (psychology)"/ or drive/ or goals/ or "power (psychology)"/
34. (motivat* or ambition*).tw.
35. exp Sleep Disorders/
36. sleep/ or sleep disorders/ or dyssomnias/ or sleep deprivation/ or sleep disorders, circadian rhythm/ or sleep disorders, intrinsic/
37. (sleep* or insomnia or sleep disorder or late waking).tw.
38. or/7-37
39. exp Estrogens/
40. exp Oestradiol/
41. (estrogen or oestradiol or ?oestradiol or ?estrogen*).mp.
42. 39 or 40 or 41
43. 6 and 38 and 42
65. limit 64 to humans

Supplement B: Table of Excluded Studies

Author	Year	Reason for Exclusion
Attie *et al.* (1)	1989	No oestradiol measurement
Avgoustinaki *et al.* (2)	2012	Subjects outside of age range; no methodology for hormone measurement provided
Baker *et al.* (3)	2007	Oestradiol was combined with other markers of pubertal development meaning no analysis of oestradiol's effects in isolation were given
Balada *et al.* (4)	1993	Outside age range
Barrack *et al.* (5)	2010	Subjects were a small number of elite runners and thus not a representative community sample
Benjet *et al.* (6)	2001	No oestradiol measurement
Benjet *et al.* (7)	2002	No oestradiol measurement
Blyth *et al.* (8)	1985	No oestradiol measurement
Boettinger *et al.* (9)	2010	Outside age range
Brambilla *et al.* (10)	2001	Outside age range
Brooker *et al.* (11)	2012	No oestradiol measurement
Bruinsma *et al.* (12)	2006	No oestradiol measurement
Chandrashekhar *et al.* (13)	2001	No oestradiol measurement
Colzato *et al.* (14)	2012	Outside age range; assessed cognitive, not behavioural outcomes
Cotrufo *et al.* (15)	2000	Outside age range
Culbert *et al.* (16)	2011	Review article
Daitzman *et al.* (17)	1980	Male only
de Water *et al.* (18)	2013	Females on oral contraceptive pill included (continuous contraception e.g. Mirena excluded)
DeBruine *et al.* (19)	2005	No oestradiol measurement
Deng *et al.* (20)	2011	Outside age range; looking at menstrual cycle changes
DeRose *et al.* (21)	2011	No oestradiol measurement
Dick *et al.* (22)	2001	No oestradiol measurement
Dorgan *et al.* (23)	2003	Oestradiol was a dependent variable
Drapela *et al.* (24)	2006	No oestradiol measurement
Dubas *et al.* (25)	1991	No oestradiol measurement
Duncan *et al.* (26)	1985	No oestradiol measurement
Durante *et al.* (27)	2009	Assertive mating is not a relevant behaviour
Edelstein *et al.* (28)	2012	Oestradiol was a dependent variable
Edelstein *et al.* (29)	2010	One third of females on oral contraceptive pill; behaviour is sexual
Edwards *et al.* (30)	2011	No oestradiol measurement
Ehrhardt *et al.* (31)	1981	No oestradiol measurement
Finkelstein *et al.* (32)	1997	Exogenous oestradiol used
Fujisawa *et al.* (33)	2012	Outcome of interest, loneliness, was not considered a behaviour or mood
Ge *et al.* (34)	2002	No oestradiol measurement
Ge *et al.* (35)	2001	No oestradiol measurement

Ge *et al.* (36)	2001	No oestradiol measurement
Gearing *et al.* (37)	2009	No oestradiol measurement
Goddings *et al.* (38)	2012	Neuroimaging study without validated behavioural or affective measure
Hayward *et al.* (39)	2002	No oestradiol measurement
Inoff-Germain *et al.* (40)	1988	Subjective assessment of behaviour
Joinson *et al.* (41)	2012	No oestradiol measurement
Klump *et al.* (42)	2006	Outside age range
Klump *et al.* (43)	2008	Outside age range
Lazaro *et al.* (44)	1996	Eating disorder cohort with no controls (oestradiol is affected by malnutrition)
Llewellyn *et al.* (45)	2012	No oestradiol measurement
Mendle *et al.* (46)	2012	No oestradiol measurement
Pahlen *et al.* (47)	2005	Review
Paikoff *et al.* (48)	1991	Oestradiol and behaviour not contemporaneous
Pajer *et al.* (49)	2006	Some subjects on oral contraceptive pill
Reynolds *et al.* (50)	2011	No oestradiol measurement
Reynolds *et al.* (51)	2012	No oestradiol measurement
Riecher-Rössler *et al.* (52)	1994	Outside age range
Schelleman-Offermans *et al.* (53)	2011	No oestradiol measurement
Schiefelbein *et al.* (54)	2005	No oestradiol measurement
Schiller *et al.* (55)	2012	Outside age range
Schwartz *et al.* (56)	2012	Outside age range
Smiarowska *et al.* (57)	2002	No control group
Soldin *et al.* (58)	2011	Outside age range
Susman *et al.* (59)	1996	Oestradiol was a dependent variable
Swarr *et al.* (60)	1996	No oestradiol measurement
Vermeersch *et al.* (61)	2008	Male only

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