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What is in our environment that effects puberty?

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Abstract

Recent studies indicate that the onset of puberty is occurring at increasingly younger ages. Many etiologies have been hypothesized to be involved, but environmental exposures are among the most worrisome. Multiple organizations have endorsed the need to study and provide clinical awareness regarding the effect of a child's environment on pubertal timing. This review article summarizes the current understanding of the major environmental influences on pubertal timing, focusing on factors for which the most scientific evidence exists. The research reviewed addresses *intrinsic factors unique to each individual, naturally occurring endocrine disruptors and chemical endocrine disruptors*. In each category, evidence was found for and against the involvement of specific environmental factors on pubertal timing. Ultimately, an individual's environment is likely comprised of many aspects that collectively contribute to the timing of puberty. The need for research aimed at elucidating the effects of numerous specific yet disparate forms of exposures is emphasized.

Keywords

Puberty timing; Endocrine disrupting chemicals; Phytoestrogens; Phthalates; Bisphenol-A; Pesticides

1. Introduction

Puberty is a time of dramatic developmental changes during which a child's body progresses through a sequential set of stages to reach mature adult reproductive function. Although the stages of puberty delineated by Tanner et al. in 1969 have not changed, the timing of puberty has become dramatically altered over the last several hundred years. Pubertal maturation begins with increasing GnRH pulses from the hypothalamus that stimulate the production of sex steroids and the progression of secondary sex characteristics resulting in the adult phenotype and reproductive capabilities [1,2]. These pulses herald the end of the dormant hypothalamic–pituitary–gonadal (HPG) axis period of childhood. Breast development, also known as thelarche, was identified by Tanner as the first sign of puberty

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in girls whereas testicular enlargement and thinning of the scrotum were noted to be the first signs of puberty in boys [3]. Recent research has identified key players involved in triggering puberty such as leptin, kisspeptin, genetics, nutrition and the presence of environmental stimuli [1,2,4,5]. However, precisely what ultimately starts puberty remains enigmatic.

1.1. Secular trends

Historical data have demonstrated a definite decrease in the age at puberty initiation from the 1800s to the mid 1900s [6]. More recent studies show a questionable continual decrease in the age at the start of puberty. These studies have been flawed by issues related to participant selection, poor comparison between groups and a lack of uniform methodology for the assessment of pubertal development [7]. An expert panel in 1994 concluded that there was sufficient evidence to establish a secular trend of earlier thelarche, but not menarche for girls and that there was insufficient evidence for earlier puberty in boys [7]. Indeed, thelarche occurred one year earlier in 2006 as compared to 1991 in a study of 2095 girls in The Copenhagen Puberty Study which was not explained by BMI or hormone levels, leading the researchers to postulate that other factors were involved [8]. These findings have been corroborated in multiple other studies leading to the question of why the onset of thelarche is continuing to decline [9–13]. An alteration in the tempo of pubertal progression has also been noted as thelarche is occurring earlier but the age of menarche appears to be constant. There are fewer studies evaluating pubertal timing in boys making it harder to form conclusions. In addition, there is no seminal event in boys that is analogous to menarche that allows for retrospective studies on puberty timing. However, pubertal onset in boys was recently brought into question by a large national study examining timing of secondary sexual development in relation to ethnic background [14]. Although boys were observed to develop a pubertal testicular size from 6 months to 2 years earlier than previous norms, some of the study's findings are internally inconsistent and the age at achievement of Tanner V development was virtually identical to historical reports and unaltered by ethnicity. Nonetheless, these data are intriguing and require further investigation prior to declaring a younger puberty trend in boys. Despite the observations of earlier pubertal onset, most pediatric endocrinologists still adhere to the traditional lower age limits of normal, which are 8 years in girls and 9 years in boys.

1.2. Role of environmental exposures

Multiple studies and cross-sectional reviews have identified environmental exposures and endocrine disruptors as likely contributors to the international secular trend in earlier pubertal development. Evidence for a central role of the environment has included the contemporaneous rapid increase in obesity rates over the last fifty years, geographical differences in pubertal timing, epidemics of earlier puberty concurrent with specific exposures, an increase in manufacturing during this time period and the identification of endocrine disruptors in pollutants and industrial compounds [15–17]. Due to heightened concern, a 2008 expert panel was convened by the US Environmental Protection Agency (EPA), the National Institute of Environmental Health Sciences and the Serono Symposia International to examine the relationship between environmental influences and pubertal timing and identify crucial research needs [18]. Endocrine disruptors and body weight were

identified as the most concerning factors involved. Although existing data were felt to be highly suggestive of a link between endocrine disruptors and pubertal timing, it has also been readily acknowledged that association does not prove causality [18]. For example, although higher phthalate levels have been found in girls diagnosed with central precocious puberty (CPP) compared to age matched controls without CPP, this does not establish that phthalates cause CPP. Particular areas targeted for future investigation include etiologies of earlier puberty, critical exposure times and mechanisms of disrupting agents [19].

The EPA defined an endocrine disrupting chemical (EDC) as “an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes” [20]. The Endocrine Society published a scientific statement in 2009 regarding EDCs and the evidence that they potentially impact many aspects of endocrinology including male and female reproductive organ formation and the HPG axis [20]. The FDA and EPA are in charge of controlling the risk of environmental substances, which is a significantly daunting task in light of how little is known regarding the effects of the numerous chemicals we are exposed to every day [21]. In addition to the Endocrine Society, the European Society for Pediatric Endocrinology and the Pediatric Endocrine Society have also endorsed position statements calling for basic and clinical research, epidemiologic studies and the recognition of EDCs in clinical practice [20,22,23]. These statements highlight the need to examine the consequences of EDCs and other types of environmental exposures during critical periods of development including the prenatal period, infancy and throughout childhood. In addition to post-natal exposures, fetal programming has also been proposed as a possible mechanism for reproductive effects seen later in life due to endocrine disrupting agents. Other mechanisms are thought to be direct effects of environmental exposures on hypothalamic, pituitary or gonadal hormones [17]. Other factors may also be at play as recent scientific advances have brought the relatively young field of epigenetics to attention as a key process that is impacted by environmental EDCs [24]. Epigenetics is the study of changes to the DNA code that do not alter the underlying sequence but induce silencing or activation of gene transcription utilizing DNA methylation and histone deacetylation [24]. The DNA changes can be environmentally induced and inherited by multiple generations independent of subsequent individual exposures [25]. Interestingly, genome wide methylation studies have suggested that epigenetic mechanisms are intrinsically involved in the neuroendocrine control of female puberty [26]. Moreover, both human and animal studies have implicated epigenetic changes resulting from exposures to different types of EDCs in the genesis of altered pubertal timing, as will be discussed in a later section of this review [27,28]. Collectively, there is resounding unanimity among governmental agencies and the scientific community regarding the importance of exploring the link between environmental exposures and human health. This article will summarize the current understanding of the major environmental influences on pubertal timing with a focus on physiologic HPG axis activation rather than variants such as premature adrenarche. We have organized these as *intrinsic factors unique to each individual, naturally occurring endocrine disruptors and chemical endocrine disruptors*. While an exhaustive description of every purported modifier is beyond the scope of this

article, we have aimed to delineate factors within each of these categories for which the most scientific evidence exists.

2. Intrinsic factors unique to individuals

An individual's genetics have been identified as the primary determinant of the timing of pubertal onset and the tempo of progression. However, it is known that many other aspects of an individual's life and environment will affect this developmental stage [15,29]. Many association studies examining a host of factors ranging from the intrauterine environment to psychosocial and nutritional exposures have been conducted. As discussed below, these have reported earlier puberty, later puberty or no effect.

2.1.1. Body weight

One of the most enduring observations is that being overweight is associated with earlier puberty in girls. However, these findings have not been substantiated in boys [30–33]. In fact, there are actually conflicting data with one study showing slightly earlier puberty in obese boys [34] and others finding precisely the opposite [32,35]. Proposed physiologic mediators of the link between obesity and pubertal timing include leptin, adipocytokines and gut peptides [31,36]

2.1.2. Prenatal growth

There has been increasing interest in the effects of intrauterine growth, birth weight and the pace of early weight gain on fetal programming and subsequent pubertal development. In one study, small for gestational age (SGA) status was found to be an independent risk factor for idiopathic CPP in girls [37]. This effect has been explained through the concept of increased metabolic efficiency imparted by low weight in infancy and evidenced by greater insulin resistance and higher IGF-1 levels in SGA infants who have subsequent rapid weight gain [38,39]. The “thrifty gene” hypothesis states that SGA children are born with the need to take advantage of calories and therefore will gain weight more easily promoting increased BMI and earlier puberty. However, another study reports that girls with a longer and leaner size at birth, not just SGA status, achieve menarche earlier than their shorter and heavier counterparts [40]. The observation that a lower birth weight alone does not increase a child's chance for earlier puberty but that being longer and lighter at birth does, suggests that under nutrition and possible rapid postnatal weight gain may establish metabolic dysregulation.

2.1.3. Diet

Besides the ingestion of known endocrine disruptors such as phytoestrogens, which are reviewed in the next section, the impact of specific dietary exposures on the timing of puberty has also been examined. Infant nutrition is thought to be optimal when it consists exclusively of breast milk. One large study showed that a one month increase in exclusive breastfeeding reduced the risk of attaining early menarche (<12.1 years) by 6% [41]. However, a subsequent study did not substantiate this and found no association with breastfeeding or childhood milk consumption and an alteration in pubertal timing [42]. Other studies have investigated multiple dietary factors with varying influences on the age of pubertal onset and/or menarche. The 1999–2004 NHANES data found a slight

statistically significant negative association between cow's milk intake during childhood and menarchal age [43]. Women who reported daily milk intake from 5 to 12 years of age experienced menarche 0.317 years earlier than non-milk drinkers [43]. Interestingly, higher animal protein intake was also associated with earlier puberty in both boys and girls in yet another study, although fiber intake had no effect [44]. Finally, vitamin D deficiency in girls has been implicated in shifting the age of menarche downward by ~10 months compared with controls [45]. Additional purported nutritional effects have been nicely reviewed elsewhere [44]. As evidenced by these studies, there are many possible nutritional factors associated with the timing of puberty. It is likely that none of these factors acts alone but rather that a combination of nutritional influences partially directs pubertal timing.

2.1.4. Maternal considerations

In addition to its obvious impact on fetal growth, other aspects of the intrauterine environment are felt to have important implications for future health and development. Two independent studies have found maternal smoking to be associated with earlier puberty [46,47]. This is interesting as maternal smoking is also a known cause of SGA status. Abnormalities in pubertal timing have also been noted in several animal models of neonatal stress felt to be analogous to pre-eclampsia [48]. While this generated interest in the human correlate, no effect of exposure to pre-eclampsia on timing of human puberty has been identified thus far [49]. Reassuringly, the first study to examine reproductive function in children of *in vitro* fertilization also failed to find any association with altered puberty timing [50]. Studies evaluating *in utero* exposures are unquestionably important in evaluating future health concerns. Currently this is an open field for further research to identify causality of prenatal exposures on puberty timing.

2.1.5. Psychosocial features

Social stress and deprivation are known to adversely affect psychological as well as physical health in children. Several studies have examined the role of family disruption, particularly a fathers' absence, on pubertal timing. It is hypothesized that a stressful environment interrupts neuroendocrine control and that this may alter the start of puberty. International adoption and immigration have received significant attention due to an association with earlier puberty hypothesized to be secondary to stressful life events. One study showed a 10–20 times higher risk of CPP in adopted children with decreased risk if the child immigrated with their family and increased risk if adoption occurred after age two [51]. Other studies have demonstrated that a father's absence and family stressors are independently associated with earlier puberty [37,52,53]. The association of sexual abuse and earlier menarche was explored using data from the Black Women's Health Study [54]. Women with a history of sexual abuse had a relative risk of 1.27 of menarche prior to age 12 compared with women without a history of abuse. The relative risk increased with increasing episodes of abuse. There was also a slight association of menarche prior to age 12 with physical abuse. Stressful life events impart many health concerns and the evidence for promoting earlier puberty appears to be increasing. This emphasizes the need for improved psychological treatment of children who are victims of abuse or high stress environments.

Based on a significant body of literature, which is summarized in Table 1, there appear to be many aspects of one's intrinsic environment that are associated with earlier puberty and/or menarche. Differentiating the importance of any single intrinsic factor is daunting given the presence of multiple variables, genetic heterogeneity and inherent recall bias. Although the existing studies are by no means absolute or indicative of causality, they nevertheless demonstrate the need for further investigation.

3. Naturally occurring endocrine disruptors

Endocrine disruptors can be naturally occurring or synthetic. This section reviews current knowledge regarding the effects of natural endocrine disruptors on pubertal timing. The most notorious of these are plant derived phytoestrogens such as those found in soy. Phytoestrogens share a chemical structure with estrogen and have the ability to be both stimulatory and inhibitory at the level of the estrogen receptor [55]. The prototypes of soy derived phytoestrogens are the isoflavones, daidzein and genistein, which are present in high concentrations in infant soy formula. There has long been concern about potential deleterious effects of a high intake of soy formula on child development [55,56]. Studies show conflicting evidence regarding exposure to soy in infancy and an effect on timing of puberty. While earlier menarche was reported in infants fed soy formula in one study, others found no association between soy formula intake and reproductive outcomes [57]. Similarly, higher serum and urine isoflavone concentrations have been associated with earlier breast development and peak height velocity (a marker of pubertal timing) as well as CPP in some studies, while others have indicated opposite effects with later breast development in girls [58–60]. Thus, the true impact of soy ingestion on pubertal timing is far from clear. Other examples of naturally occurring endocrine disruptors include lavender oil, tea tree oil and fennel, all of which have been linked to breast development in prepubertal children presumably due to estrogenic effects [61,62]. These reports have involved oral intake or systemic absorption from topical exposure. Ultimately, other than anecdotal case reports, the relationship between natural endocrine disruptors and pubertal timing remains inconclusive and in need of further study. Table 2 summarizes the major publications devoted to this area of investigation.

4. Chemical endocrine disruptors

Although there are a multitude of chemical toxins in our environment, a few in particular have been implicated as having endocrine disrupting attributes. The classic example was an accidental exposure of over 4000 individuals in Michigan in the early 1970s to polybrominated biphenyls (PBBs) thru cattle feed contamination [63]. The exposed women and their offspring have been extensively studied. The maternal cohort had serum PBB levels measured providing the ability to calculate future serum concentrations using the half life, and therefore allowing precise association studies to be performed. Girls exposed to high PBB levels *in utero* reached menarche at 11.6 years compared to 12.2–12.6 years in girls with low exposure [63]. Many other studies have examined the relationship between chemical EDCs and the timing of puberty, and several extensive reviews have now been published [15–17,64]. The impact of epigenetics on the field of chemical EDCs has increasingly been investigated in animal studies. In one study, multiple environmental

pollutants were given to gestating female rats at a time point when sex differentiation occurs in the fetus [28]. Notably, no toxic effects were seen in the gestating females and the sex ratios of their litters were unchanged. However, first and second generation offspring exhibited marked alterations in pubertal timing depending on the gender and the specific exposure involved. Most intriguing was the finding that the third generation females also experienced earlier puberty after exposure to BPA/phthalate mixture, dioxin and jet fuel. This demonstrates a transgenerational inherited effect as the third generation had no direct contact with the initial EDCs. Thus, although epigenetic changes appear to be dependent on the timing of the environmental exposure that induces them, the evidence suggests that they are also heritable and persist for generations without further exposure [65]. Experts in this field believe that we are also on the brink of confirming the existence of this phenomenon in humans, not only as it relates to pubertal timing but to a whole host of adverse human secular trends and diseases as well. This section will specifically focus on three of the most widely studied chemical EDCs which are phthalates, bisphenol-A (BPA) and pesticides.

4.1.1. Phthalates

Phthalates are chemicals that are used in plastics to add flexibility [66]. They are found in toys, construction materials and clothing as higher molecular weight compounds and in solvents, cosmetics and pharmaceuticals in low molecular weight forms [64]. Human exposure can occur through oral, inhaled, IV and topical routes and is extremely prevalent [64]. A Danish study found urine samples from 129 healthy children to be nearly universally contaminated by 11 different phthalate metabolites [67]. The metabolites identified with the highest measured levels were dibutyl phthalate and di-(2-ethylhexyl) phthalate. Although the endocrine disrupting mechanism of phthalates is not fully understood, studies indicate possible anti-androgenic effects as well as estrogen agonistic and antagonistic activities [68–72]. Multiple association studies have evaluated the effect of phthalates on pubertal timing in humans. In general, phthalates have been associated with earlier puberty, but some studies are not in agreement. Higher urine and serum phthalate levels in girls have been linked to both isolated early breast development [73] as well as CPP in a study in Puerto Rico where the incidence of premature thelarche is the highest in the world [74]. In contrast, several other studies have found no association between phthalate levels and the timing of thelarche or central puberty [67,68,75]. A recent study evaluated phthalate effects in boys. Forty boys diagnosed with pubertal gynecomastia showed significantly higher serum phthalate levels than controls although no association was seen between the phthalate level and serum hormone concentrations [71]. Studies reporting an association between phthalates and puberty are summarized in Table 3. Further exploration is clearly warranted in order to draw definitive conclusions.

4.1.2. BPA

BPA is a compound used in epoxy resins and polycarbonate plastics [76]. It can be found in Tupperware™, plastic bottles, food cans and medical products and at high temperatures escapes from its solid material into the containers contents [64]. The main source of human exposure is through food contamination from plastic packaging [76]. BPA was incidentally found to interact with the estrogen receptor when an interfering substance (BPA) was identified in *Saccharomyces* culture in polycarbonate flasks [77]. A headline article

published in Nature in 1999 read: “Exposure to bisphenol A advances puberty” [78]. This study demonstrated premature first estrus in mice that were born to mothers fed BPA. However, human studies are sparse and have yet to fully identify BPA as a cause of earlier puberty. In one study of 1151 girls, the effects of 5 different phenol environmental toxins were examined [79]. Although BPA had no influence on breast development, another phenol compound, benzophenone 3, was associated with earlier onset of secondary sexual characteristics, yet no evidence for a dose response effect was found. Another study found significantly higher serum levels of BPA in girls with CPP which were also correlated with increased uterine and ovarian volumes [80]. Reviewed studies are described in Table 3. Given these inconsistent results, more human studies are needed to definitively implicate BPA in the alteration of pubertal timing. Nonetheless, many plastic products are now being marketed as BPA-free as the consumer becomes increasingly aware of health concerns from exogenous chemicals.

4.1.3. Pesticides

Humans are exposed to numerous pesticides through everyday activities and occupations. Over 100 pesticide compounds have been identified as endocrine disruptors and human consumption of them has nearly quadrupled in the last 40 years [81]. Several excellent reviews describe a multitude of different chemicals in pesticides [16,81]. This section focuses on dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyl dichloroethane (DDE), the most studied EDC in pesticides. Even though DDT was banned in the US in the 1970s, it is still used in developing countries today [82]. Additionally, it can still be found in humans across the world as it is stored in adipose tissue with an average half life of 10 years [82,83].

Several studies have found that exposure to DDT and its metabolite DDE are associated with a younger age of puberty as evidenced by earlier menarche or thelarche [37,83]. One such study evaluated children diagnosed with CPP and found higher plasma levels of DDE in those who were adopted or immigrated from foreign countries compared with ones native to the country [84]. This led the authors to infer that the children were exposed to higher environmental pesticides in their prior countries resulting in CPP. Another study has evaluated extrapolated maternal DDT levels and the association with menarchal timing in exposed female offspring. Women who were exposed to higher levels of DDE *in utero* (by 15 mcg) reached menarche at younger ages than women with lower levels of exposure [85]. However, the association’s significance disappeared when weight at menarche was controlled for. As increased weight is known to contribute to earlier puberty in females it is unknown whether DDT induces pubertal changes intrinsically or through causing increased weight gain.

Other studies have refuted the above findings and shown no association of DDT exposure with earlier pubertal development. These have included studies of serum DDE levels in girls in farming and urban areas as well as those living near the St Lawrence River in New York, Ontario and Quebec where animals have been found with levels of DDE that exceed the FDA’s upper limit for human consumption [86]. Similarly, girls in New York City were evaluated at 9 years of age for stage of breast development and no association was found

with DDE levels [59]. Lastly, the impact of prenatal DDT exposure on pubertal development in boys was examined using stored maternal serum. No association between prenatal maternal DDT levels and height, BMI, skeletal age, serum testosterone or DHEAS was found [87]. Studies reporting the effects of DDT and DDE on puberty are reviewed in Table 3.

As the available studies investigating the effects of pesticides on pubertal timing are inconsistent it is difficult to make any sound conclusions. This is also the case for many other worrisome observations pertaining to human health in which exposure to EDCs has been implicated as having a potential causative effect. These include the current epidemics of obesity and diabetes, increasing rates of cryptorchidism in infant boys as well as declining fertility rates, semen quality and birth weight in the US and elsewhere [88–90]. Further factors complicating this area of research are that EDCs likely have different endocrine disrupting abilities at different concentrations, exposure amounts, developmental time periods and precise chemical make-up. Despite these formidable obstacles, further study is imperative.

5. Conclusion

In summary, multiple lines of evidence exist to suggest a central role of environmental exposures in the modulation of human pubertal timing. From *in utero* to nutritional to environmental factors, there are many potential avenues for endocrine disruptors to affect the timing of puberty in girls and boys. However, with the possible exception of obesity in girls, the overall effects of any one factor have been reputed and disputed in different studies which have often reported conflicting results. Therefore, it would be naive to propose that any one factor solely changes the timing of puberty. It is much more likely that many factors have small individual effects acting in concert with one another and that the combination of influences in each individual is what determines pubertal timing. As described earlier in this article, several international societies have put forth position statements on the importance of future research into the effect of environmental exposures on pubertal timing. Prospective studies should also focus on the burgeoning field of epigenetics where we may be able to identify mechanisms for polygenic control of not only puberty but of other aspects of the reproductive endocrine system as well. It will be imperative to investigate which specific exposures and at what points in an individual's development the effects are the most harmful. These studies are difficult to carry out in humans and initial information may still need to come from animal studies that pave the way for targeted evaluation in humans. The most important conclusion is that further study is needed to address the question of what environmental factors affect puberty and how we can best eliminate relevant exposures with the goal of maximizing the health and well-being of today's children and future generations to come.

Abbreviations

HPG	hypothalamic–pituitary–gonadal
EDC	endocrine disrupting chemical

EPA	environmental protection agency
FDA	food and drug administration
SGA	small for gestational age
CPP	central precocious puberty
PBB	polybrominated biphenyls
BPA	bisphenol-A
DDT	dichlorodiphenyl-trichloroethane
DDE	dichlorodiphenyl dichloroethane

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Table 1

Effects of intrinsic exposures on puberty timing.

Environmental factor	Year	Subjects	Effect on puberty
Body weight	2008 [30]	8080 women, Canada	Older age at menarche (one year older) associated with lower BMI (0.5 less)
Body weight	2009 [32]	156,835 children, Denmark	BMI at 7 years of age is inversely correlated with the start and peak of a child's growth spurt as indicators of puberty timing
Body weight	2012 [33]	2127 girls, Croatia	Girls who achieved menarche prior to 11.98 years were of higher BMI than girls who had not
Body weight	2009 [36]	98 children, Netherlands	Peak leptin levels occurred prior to peak LH and FSH levels in girls but not in boys
Birth weight	2006 [91]	156 girls, Australia	Infants >49.3 cm and <3.325 kg achieved menarche 1 year earlier than shorter, heavier infants
Birth weight	2006 [92]	187 girls, Spain	Infants with BW -2 SD or below had earlier menarche, girls with premature adrenarche and BW -2 SD were three times as likely to reach menarche prior to 12 years
Birth weight	2001 [40]	997 girls, Philippines	BW alone did not affect timing of menarche, but being long (>49 cm) and lean (<3 kg) at birth predicted menses 6 months earlier than the opposite regardless of BMI at 8 years
Birth weight	2012 [37]	78 girls, China	SGA status was significantly associated with CPP
Social	2012 [37]	78 girls, China	Father's absence between ages 4 and 6 in a girl's life was significantly associated with CPP
Social	2006 [51]	655 children, Denmark	10–20 times increased risk of precocious puberty in internationally adopted boys and girls, with even higher risk if adopted after age 2
Social	2008 [52]	161 girls, New Zealand	Sisters who were premenstrual prior to familial dysfunction achieved menarche 11 months earlier than older sisters
Social	2011 [53]	120 children, Wisconsin	Earlier menarche was associated with higher family stress and sympathetic nervous system activation
Social	2009 [54]	35,330 women, USA	Positive association between earlier menarche and history of sexual abuse
Intrauterine environment	2011 [46]	3486 boys, Denmark	Maternal smoking during pregnancy was associated with earlier puberty
Intrauterine environment	2011 [47]	3169 girls, Denmark	Menarche occurred 2.8–4.1 months earlier in girls who were exposed to prenatal maternal smoking (10+ cigarettes/day)
Intrauterine environment	2001 [49]	589 women, Sweden	Exposure to pre-eclampsia had no effect on puberty timing
Intrauterine environment	2011 [50]	166 young adults, USA	No association of <i>in vitro</i> fertilization with puberty timing
Diet	2011 [41]	994 girls, Philippines	Girls who were exclusively breast fed longer had later onset of menarche
Diet	2011 [45]	242 girls, Columbia	Vitamin D deficient girls reached menarche 0.8 years earlier than vitamin D sufficient girls
Diet	2011 [43]	2657 women, NHANES	Increased milk intake from 5 to 12 years of age was weakly associated with earlier menarche
Diet	2010 [60]	227 children, Germany	No association with fiber intake and puberty timing (Dortmund study)
Diet	2012 [82]	112 children, Germany	Children with higher vegetable intake reached puberty 7 months later than average and ones with higher animal protein intake reached puberty 7 months earlier than average

Table 2

Effects of natural exposures on puberty timing.

Environmental Factor	Year	Subjects	Effect on puberty
Skin lotion	2007 [61]	3 boys	Boys with gynecomastia had exposure to lavender and tea tree oils which resolved after stopping oils and <i>in vitro</i> studies confirmed estrogenic properties of both oils
Soy formula	2012 [57]	2922 girls, UK	Infant girls fed soy formula at <4 months reached menarche earlier (4 months) than girls not fed soy or fed soy later than 4 months
Soy formula	2001 [93]	811 adults, Iowa	In recall, no difference in timing of menarche or breast development in women fed exclusive soy vs. cow's milk formula in infancy
Soy formula	2004 [94]	48 children, Italy	No effect of >6 months of soy formula feeding on precocious puberty, gynecomastia, bone age, estradiol levels
Fennel	2008 [62]	4 girls, Turkey	Premature thelarche occurred in girls given <i>goeniculum vulgare</i> tea and resolved when stopped
Isoflavones	2011 [58]	108 girls, Korea	Girls with CPP showed significantly higher serum isoflavone (daidzein, genistein and total isoflavone) concentrations than controls
Phytoestrogens	2008 [59]	192 girls, New York	Higher levels of phytoestrogens (daidzein, genistein, enterolactone) were associated with later onset of breast development
Phytoestrogens	2010 [60]	227 children, Germany	Girls who had the highest urinary markers of phytoestrogen intake achieved breast development (0.7 years) and peak height velocity (0.6 years) later than girls with less phytoestrogen intake (Dortmund study)

Table 3

Effects of chemical endocrine disruptors on puberty timing.

Agent	Year	Subjects	Effect on puberty
Phthalates	2009 [73]	89 girls, Taiwan	Higher phthalate metabolite levels were seen in girls with premature thelarche
Phthalates	2000 [74]	76 girls, Puerto Rico	Premature thelarche was associated with higher phthalate levels
Phthalates	2007 [95]	210 girls, Shanghai	Higher phthalate levels are in girls with CPP
Phthalates	2010 [71]	61 pubertal boys, Turkey	Higher phthalate metabolite levels associated with pubertal gynecomastia in boys
Phthalates	2012 [68]	750 girls, 25 with precocious puberty, Denmark	No association of phthalate levels and precocious puberty
Phthalates	2010 [75]	56 girls, USA	No association with phthalate levels and CPP
Phthalates	2011 [74]	300 women, New York	Association between hair oil use and perms with earlier menarche
Bisphenol-A	2010 [79]	1151 girls, New York, Ohio, California	No effect of BPA on breast development
Bisphenol-A	2010 [80]	210 girls, Shanghai	Higher BPA levels in girls with CPP
DDE	2004 [85]	151 girls, Michigan	Increase in serum DDE of 15 mcg/l associated with decreased age at menarche by 1 year
DDE	2012 [37]	78 patients, China	Higher DDE levels slightly associated with CPP
DDT	2005 [83]	446 women, China	Higher DDT serum levels associated with earlier menarche
DDE	2001 [84]	145 children, Belgium	CPP patients who had immigrated to Belgium had higher DDE levels
DDE	2008 [59]	192 girls, New York	No association of DDE urine levels and breast advancement
DDE	2005 [86]	138 girls, New York, Canada	No association of DDE with menarche timing
DDE	2012 [96]	94 girls, Italy	No association of DDE with precocious puberty