

# A systematic review on the effects of environmental exposure to some organohalogenes and phthalates on early puberty

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**Background:** Early puberty is a common worldwide problem. Different parameters as genetics, metabolic diseases, obesity, as well as environmental factors may affect the age of puberty. This systematic review aims to survey the related literature on the effects of environmental pollutants and especially organohalogenes and phthalates on early puberty. **Materials and Methods:** A systematic review of papers published in the English language was completed in January 2014. Studies on the associations of organohalogenes and phthalates with the puberty time were included. A literature search was conducted in EMBASE, PubMed, Scopus, ISI Web of Science, and Cochrane Library from 1995 to January 2014; moreover manual search through references of relevant manuscripts was considered. The literature search identified 212 papers, of which 13 papers fulfilled the inclusion criteria of the current study. Two reviewers independently identified relevant papers for potential inclusion and assessed the methodological quality. **Results:** This review included 6572 participants in nine countries from three continents (Europe, North America, and Asia). Different studies determined the effects of pollutants on maturation signs and pubertal stages and confirmed the association of organohalogenes and phthalates with early puberty. **Conclusion:** Based on the studied literature, environmental pollutants surround and accumulate in human societies and their adverse health effects are well documented. It can be concluded that organohalogenes and phthalates are disturbing the normal process of puberty timing; especially their influence on early maturation in girls should be underscored.

**Key words:** Early puberty, organohalogenes, phthalates, systematic review

**How to cite this article:** Poursafa P, Ataei E, Kelishadi R. A systematic review on the effects of environmental exposure to some organohalogenes and phthalates on early puberty. *J Res Med Sci* 2015;20:613-8.

## INTRODUCTION

Puberty is an important landmark that occurs in the transition from childhood to adulthood.<sup>[1,2]</sup> Human puberty consequences for health and wellbeing are thoughtful and contradictory. In addition to obtaining physical maturation with enhanced strength, speed, and fitness, puberty is also accompanied with emotional and cognitive changes.<sup>[3]</sup>

Puberty onset has specific signs, which differs in terms of gender.<sup>[4]</sup> Timing of puberty may be important in expecting longitudinal health risks like obesity and cancers

in adulthood.<sup>[2]</sup> Longer exposure to steroidal hormones might increase the risk of steroidseries dependent cancers such as breast and ovarian cancers in women, and possibly prostate cancer in men. Furthermore, increased rates of obesity in early developers might amplify oxidative stresses that in turn would exacerbate the risks for a range of cancers.<sup>[3]</sup> True precocious puberty in girls is typically defined as the appearance of secondary sexual characteristics before the age of 6 years.<sup>[5]</sup> During the past decades, secular trends of earlier age at onset of puberty have been observed.<sup>[4]</sup> Different research studies have reported the reduction in the age of puberty around the world.<sup>[6-10]</sup> Precocious puberty in boys is generally defined as the appearance of secondary sexual characteristics before the age of 9 years.<sup>[11-13]</sup>

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10.4103/1735-1995.165971

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**Received:** 09-01-2015; **Revised:** 15-06-2015; **Accepted:** 28-07-2015

Different factors are contributed in the decreasing age of puberty in the recent years. Genetic factors play a main role in the timing of maturation. However, the rapid worldwide decrease in pubertal timing over the past decades clearly indicates that it should have an environmental etiology. Significant diversities in the age of pubertal stages of girls living in various regions with different ethnicity and geographic characteristics are documented. Moreover, obesity as an epidemic event has received special attention and is related both to early puberty and environmental factors. Furthermore, changes in nutrition and dietary habits, physical activity, and exposure to endocrine disrupting chemicals (EDCs) are possible factors influencing the maturation time of the reproductive system.<sup>[2,3,14,15]</sup> EDCs are natural and synthetic chemicals that would disturb the normal function of the endocrine system. These compounds interfere with normal hormonal function through influence on the activity of estrogen receptors.<sup>[16]</sup> EDCs are exogenous chemicals that usually imitate hormones, block hormonal action sites or trigger inappropriate hormone activity.<sup>[17]</sup> Different studies determined the role of some pollutants as polychlorinated biphenyls (PCBs), polybrominated biphenyl (PBB), dioxins, phthalates, etc., on pubertal growth and its signs.<sup>[14,18,19]</sup> Of important groups of these compounds are organohalogenes and phthalates. These compounds are usually highly lipophilic and hydrophobic; they accumulate sometimes to a high concentration in lipid-rich tissues.<sup>[20]</sup> This study aims to systematically review the literature that assessed the associations of organohalogenes and phthalates with the timing of puberty.

## MATERIALS AND METHODS

### Literature search

We attempted to explore papers in which the associations of organohalogenes exposure on pubertal signs have been reported. A literature search was done in following databases: EMBASE, PubMed, Scopus, ISI Web of Science, and Cochrane Library from 1995 to January 2014, with the major concentration on latest papers. The following keywords or their combinations were used: Early puberty, precocious puberty, menarche, organohalogenes, PCBs, dichlorodiphenyltrichloroethane, dichloro diphenyldichloro ethylene, organochlorine, dioxin, phthalates, girl, boy, children, adolescents. Further studies were observed by a manual search through references of relevant manuscripts, relevant reviews, and consultation with experts in this field. Search evaluation was done randomly by two independent researchers, and it was confirmed that all relevant studies were considered.

### Study design

Two independent reviewers (PP and EA) determined the appropriateness of the study according to the prearranged criteria and subsequently extracted characteristics: Related

data of participants (number, age, type of disorder), study features (type, duration, applied intervention), measured parameters (first menarche, breast development, testicular development, Tanner stage signs, body size) and outcomes. Differences in judgments were solved via discussion and consensus. Paper language selection was limited to English.

### Data collection

#### *Inclusion criteria for data collection were as follows*

1. Exposure to one or more than one organohalogenes during childhood or adolescence.
2. Measurement of related criteria as first menarche, breast development, testicular development, Tanner stage signs, body size.
3. No history of using drugs or other determined compounds with the effects on endocrine systems.

Studies without above mentioned criteria were not included in this systematic review.

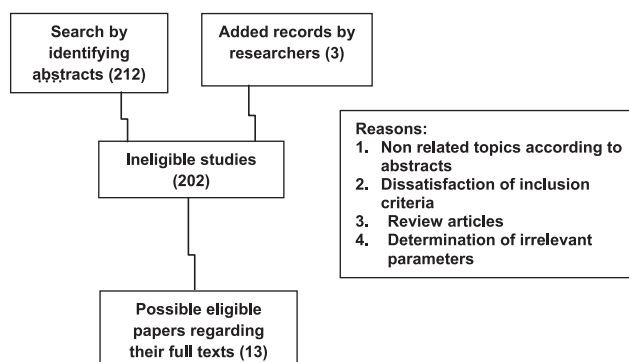
## RESULTS

### Study selection

The flowchart of the search is depicted in Figure 1. At first, 215 likely relevant articles were found. Of those, 202 articles were removed by evaluating abstracts, and it was cleared that those papers could not meet the inclusion criteria of the current study. Finally, 13 articles were selected to read their full texts and to determine the eligible articles to be included in this systematic review.

### Study features

As aforementioned, 13 articles were selected according to the inclusion criteria. This review included 6572 participants in nine countries from three continents (Europe, North America, and Asia). Of these, seven studies had a cohort design, two were cross-sectional, one was retrospective, and three were case-control. Details of the studies are presented in Table 1.



**Figure 1:** Flowchart and characteristics of studies included/excluded for review

**Table 1: Summary of studies on the association of exposure to organohalogenes and phthalates with puberty time**

Author (year)	Location, gender (girl, boy)	Sample size	EDC type	Methods	Results
Blanck <i>et al.</i> (2000)	Canada (girl)	327	PBB	Cohort study	The associations observed lend support to the hypothesis that pubertal events may be affected by pre- and post-natal exposure to organohalogenes <sup>[21]</sup>
Denham <i>et al.</i> (2005)	Canada (girl)	138	PCB DDE	Cross-sectional study	By testing several PCB congener groupings, it was determined that specifically a group of potentially estrogenic PCB congeners affected the odds of reaching menarche and no relationship with DDE was observed <sup>[22]</sup>
Gladen <i>et al.</i> (2000)	USA (girl)	316	PCB	Cohort study	Prenatal exposures at background levels may affect body size at puberty <sup>[23]</sup>
Vasiliu <i>et al.</i> (2004)	USA (girl)	151	PCB DDE	Cohort study	Using linear regression models analysis indicates that DDE ( $P=0.038$ ) but not PCB ( $P=0.76$ ) lowered age at menarche with statistical significance <sup>[24]</sup>
Axmon (2006)	Sweden (girl)	3202	Organochlorines	Cohort study	The present study did not indicate a relationship between a high persistent organochlorines pollutants exposure in utero and through breast milk or food intake during childhood and age at menarche <sup>[25]</sup>
Karmaus <i>et al.</i> (2002)	Germany (girl)	343	DDE PCB	Cohort study	Background level concentrations to DDE, but not PCB, during childhood are associated with a small reduction in growth for girls evident through the age of 8 years <sup>[26]</sup>
Krstevska-Konstantinova <i>et al.</i> (2001)	Belgium (girl)	41	DDE	Retrospective study	A possible relationship between transient exposure to endocrine disrupters and sexual precocity is suggested and deserves further studies in immigrant children with nonadvanced puberty <sup>[27]</sup>
Deng <i>et al.</i> (2012)	China (girl, boy)	175	DDE	Case-control	A significant relationship was observed in children with high concentration of DDE and early puberty <sup>[28]</sup>
Ozen <i>et al.</i> (2012)	Turkey (girl)	94	DDE	Case-control study	Between pesticides, the concentration of DDE may be the related to early puberty <sup>[29]</sup>
Wolff <i>et al.</i> (2010)	USA (girl)	1151	Phthalate	Cohort study	Weak hormonally active xenobiotic agents investigated in this study had small relationship with pubertal development, mainly among those agents detected at highest concentrations <sup>[30]</sup>
Chou <i>et al.</i> (2009)	Taiwan (girl)	89	Phthalate	Case-control study	Significantly higher monomethyl phthalate in the premature thelarche girls revealed that phthalate may be one of the environmental causes of early puberty in Taiwanese girls <sup>[31]</sup>
Lomenick <i>et al.</i> (2010)	USA (girl)	56	Phthalates	Cross-sectional study	Although phthalates may be associated with certain other toxicities in humans, this study suggests that their exposure is not connected with precocious puberty in female children <sup>[32]</sup>
Humblet <i>et al.</i> (2011)	Russia (boy)	489	Dioxin and PCB	Prospective cohort study	Maternal PCB serum concentrations measured 8 or 9 years after sons' births which may reflect sons' prenatal and early-life exposures were associated with acceleration in some, but not all, measures of pubertal onset <sup>[33]</sup>

EDC = Endocrine disrupting chemical; PCB = Poly chlorinated biphenyls; PBB = Poly-brominated biphenyls; DDE = Dichloro diphenyldichloro ethylene

## DISCUSSION

This review confirmed the effects of pollutants on maturation signs and pubertal stages and confirmed the association of organohalogenes and phthalates with early puberty, notably in girls. Such an effect may have short-term and long-term health effects, and warrants interventions to reduce these pollutants.

Puberty time is a transition step between childhood and the adult reproductive stage. It is an important stage of life with elevated increased risk of health and psychosocial problems.<sup>[34-38]</sup> It is documented that an independent relationship might exist between early puberty and adult metabolic syndrome-related derangements both in males and females. This finding underlined that the mechanisms accelerating puberty may also contribute to adult metabolic disorders.<sup>[38]</sup>

We reviewed several articles from different areas of the world, and it is unanimous that variation in puberty timing trends is a global issue, both in developed and developing countries. Though the age of puberty is related to different parameters including genetic factors,<sup>[39]</sup> disorders and malformations of central nervous system,<sup>[13]</sup> and some metabolic diseases,<sup>[40]</sup> the important role of environmental pollutants and EDCs should be taken into account.

Environmental pollutants including PBC, PBB, dioxin, and phthalates are widespread in different societies and have several adverse health effects.<sup>[28,29,33,41]</sup> One of the important consequences of EDCs is disturbing the normal process of puberty timing, especially their influence on early maturation in both sexes, particularly in girls. In boys, pollutants exposure is associated with reaching to genital stages earlier than normal time.<sup>[28,33]</sup> In girls, a higher concentration of EDCs in the body is associated with early menarche and breast development with or without growth of pubic hair.<sup>[21,32]</sup>

A recent review studied the trends of puberty and its relationship with environmental pollutants and concluded that the age at pubertal onset has been declining in the last two decades in USA and Europe. Thus, age at breast development is now going on 1-2 years earlier in comparison with previous studies. Prominently, the age at menarche has changed by 0.3-0.6 years in the same period, signifying a prolonged duration of the pubertal transition and found that development of glandular breast tissue at much younger ages at short period of time are highly suggested to have environmental origins.<sup>[19]</sup>

Weight status is associated with the pubertal age, given that environmental pollutants may increase the risk of overweight,<sup>[42-44]</sup> therefore the decline in the age of puberty may be explained, at least in part, by excess weight due to exposure to some environmental pollutants.

It should be acknowledged that in original studies included in the current review, the exact time and the duration of exposure were not considered; moreover recall bias may exist in reporting the age of puberty. Chronic diseases origin in early life, and it is well documented that exposure of children and adolescents to environmental pollutants is related with risk factors of noncommunicable diseases.<sup>[45-48]</sup> Furthermore, the age of puberty, which in turn might be related to exposure to environmental factors, is associated with chronic diseases.<sup>[49,50]</sup>

## CONCLUSION

The findings of this review propose that organohalogenes and phthalates are disturbing the normal process of

puberty timing with special influence on early maturation in girls. The current decline in the age of puberty might be related, at least in part, to exposure to some environmental chemicals, and in turn it might increase the risk of noncommunicable diseases in the future. These findings underscore the necessity of implementing wide-ranging interventions to reduce the pollution burden for health promotion and disease prevention at the global level.

## Financials support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## AUTHOR'S CONTRIBUTION

All authors contributed in the study concept and design, in conducting the literature search, in drafting the paper and its revision. All authors approved the final version for submission, and accept the responsibility for the paper content.

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