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A systematic review on maternal and perinatal factors influencing breast development

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ABSTRACT

Background: A secular trend towards earlier age at menarche has been reported, but the trend in breast development is less clear. We reviewed the evidence on the relationship between in utero and early life events and breast onset/development.

Methods: Eligible studies were identified in PubMed and Embase databases. We selected studies in which female human exposure during fetal or the first years of life was measured or estimated, and associations with breast onset or development were evaluated.

Results: Of the 49 cohort studies and 5 cross-sectional studies identified, 43 provided sufficient data to assess associations. High maternal weight, primiparity, and early weight gain, were related to an increased risk of early breast onset/development in most of the studies that analysed these associations, whereas late breast onset/development was associated with preterm birth.

Results were inconsistent for smoking in pregnancy, maternal hypertensive disorders, breastfeeding, diabetes, and small for gestational age. No association emerged for maternal age at delivery, alcohol drinking, and selected drug use during pregnancy, and low birth weight.

Conclusions: The results of this review show that high maternal weight, primiparity and early weight gain were associated with an increased risk of early breast onset/development. Late breast onset/development was associated with preterm birth.

Breast development is a key physical marker of puberty onset, and early puberty development is linked to consequences that can reverberate throughout life. Answering the questions about the interconnections between pre/postnatal environmental exposures and their impact on puberty, represents an important area of multidisciplinary research.

1. Introduction

Puberty is the developmental process through which reproductive competence is attained. It is characterized by rapid growth and changes in body composition, attainment of secondary sexual characteristics, behavioural changes, and marks an important period in the dynamics of the individual development from childhood to adolescence.

Assessing puberty is challenging because hormonal processes are already underway when physical changes occur. Nevertheless, most of the studies assessing pubertal maturation have used the 5-point Tanner staging system for breast, genital, and pubic hair growth [1].

Breast development is considered a better indicator of the onset of puberty than pubic hair growth because it is linked to gonadal function [2]. The appearance of glandular breast tissue is called thelarche and is defined as B2 stage on the Tanner scale. Menarche is a late marker of female puberty and is the endpoint of a complex sequence of developmental steps. Menarche typically occurs within 2–3 years after thelarche (breast budding), at Tanner Stage IV breast development, and rarely

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before Tanner Stage III development [3].

Since the mid-19th century, a secular trend towards earlier menarcheal age has been reported in many European and North American countries [3]. This trend appears to have leveled off during the last 50 years in some countries, while a moderate decrease continues in others [4]. With regard to thelarche, Eckert-Lind et al. recently reviewed systematically the literature. They concluded that "the age at thelarche decreased by 0.24 years (95% CI, −0.44 to −0.04) (almost 3 months) per decade from 1977 to 2013". [5].

The developmental origins of health and disease hypothesis suggest that exposure to certain environmental factors during critical periods of human development may have important short- and long-term health consequences [6], including pubertal programming as an adaptive mechanism to early environmental stressors. Energy availability in fetal/early life and timing of weight gain, as well as maternal constitution and exposure to diseases, may play a role in influencing pubertal onset, in addition to the exposure to endocrine disrupting compounds (ECDs) [5,7].

Several studies have analysed the influence of environmental factors acting during the prepubertal period on the timing of breast development, of which girl's weight and exposure to ECDs are considered to be the most important [5].

In this paper we have reviewed the available evidence on the impact of intrauterine exposures, breastfeeding and early growth on breast development. We have not consider exposure to endocrine-disrupting chemicals.

2. Methods

2.1. Study question and selection criteria

The current study was conducted according to the PRISMA guidelines for the reporting of systematic reviews.

The study question was: "What is the effect of prenatal and early life maternal-child factors on breast onset and development in girls?". Supplementary Table 1 reports the PECO – participants, exposure, comparator and outcomes – statement.

We selected studies in which female human (i) exposure during fetal or starting during the first year of life (only breastfeeding and early life growth) (ii) was measured or estimated (iii), and associations with breast onset or development were evaluated (iv). We did not require breast development to be the main outcome of the study (Table 1).

We excluded studies if they i) targeted breast development under 2 years of life, ii) were based on subjects with diseases related to pubertal development (e.g., McCune Albright, Turner syndromes) or neoplasms, and iii) did not use the Tanner scale to assess the outcome. We also excluded iv) conference abstracts, letters or notes to editors, v) case reports, and vi) studies not published in English.

The procedure of study selection is reported in Fig. 1.

2.2. Search method

We identified relevant literature from PubMed (http://www.ncbi.nlm.nih.gov/pubmed/, 20 May 2023) and Embase (http://apps./online-tools/embase, 20 May 2023) databases, with no limitation by language or publication date.

We developed a search string by using a combination of the following keywords: puberty, pubertal, timing, tanner, 'breast size', 'breast development', 'breast growth', nipple, areola, thelarche, B2, 'breast stage', 'breast stages', girl, woman, female, child, adolescence. Our search term list did not include terms for exposures, giving the explorative aim of identifying any putative risk/protective factor influencing breast development. We also hand-searched the reference list of 1) included studies, 2) pertinent reviews identified by the search.

2.3. Data extraction, risk of bias and certainly of evidence assessment

Two authors (MD and SC) extracted the data from all the included studies, under the supervision of a third author (EN). We collected details on the study characteristics (i.e., population, study design, period of assessment, and type of assessment), type of exposure and assessment, type of outcome measure (i.e., age at a point on the Tanner scale, position on the Tanner scale, Tanner scale progression, type of pubertal onset), type of analysis, and effect estimates. Where possible, we converted effect estimates in months as reported in the studies or calculated from time ratios. Two authors (MD and GE) independently assessed the risk of bias and the certainty of the evidence using the Newcastle-Ottawa assessment tool [8]. Disagreements were resolved by consulting a third author (EN). An adapted version of the assessment tool was used for cross-sectional studies, by omitting the evaluation of follow-up.

In the qualitative synthesis of the results, we did not include studies that did not report enough information to assess the association or that presented potential risk of bias.

We categorized the studies in: "association/no association" according to the p-value reported in the original paper (association $p < 0.05$).

3. Results

3.1. Study characteristics and risk of bias assessment

Characteristics of the 54 [9–62] included studies, with a detailed description of each of them, are reported in Supplementary Table 2.

Twenty-seven studies were conducted in Europe or the UK, 15 in the Americas, and 12 in Asia. Forty-nine were cohort studies, and 5 were cross-sectional studies. The findings of some cohort studies were reported in more than one paper, addressing different exposures or outcome specifications: in particular, 15 studies were conducted using data from the Puberty Cohort and/or the Danish National Birth Cohort (DNBC).

The assessment of the outcome of interest and follow-up varied markedly between the studies. Most of the studies included clinical visits

Table 1
Summary description of studies characteristics.

		Nr. of studies	References
Location	Europe	27	[10–12,14,17–19,22,33,36,40,41,44–57,60]
	Asia	12	[9,13,15,21,23–27,35,37,62]
	The Americas	15	[16,20,28–32,34,38,39,42,43,58,59,61]
Study design	Cohort	48	[9–14,16–19,24–37,39–61]
	Case-control nested in cohort	1	[22]
	Cross-sectional	5	[15, 20, 21, 23, 62]
Period of exposure	In pregnancy (Tot. number of potential risk factors = 10)	28*	[17–19,22,24,30,32–34,36,38–41,43–46,48–52,56,57,60–62]
	In neonatal period (Tot. number of potential risk factors = 3)	23	[9–16,19–21,23–25,28,29,32,37,47,52,53,55,59]
	In early life (Tot. number of potential risk factors = 2)	15	[16,19,26–28,31–33,35,43,47,54,55,58,59]
Total		54	

* Some paper reported information on different periods.

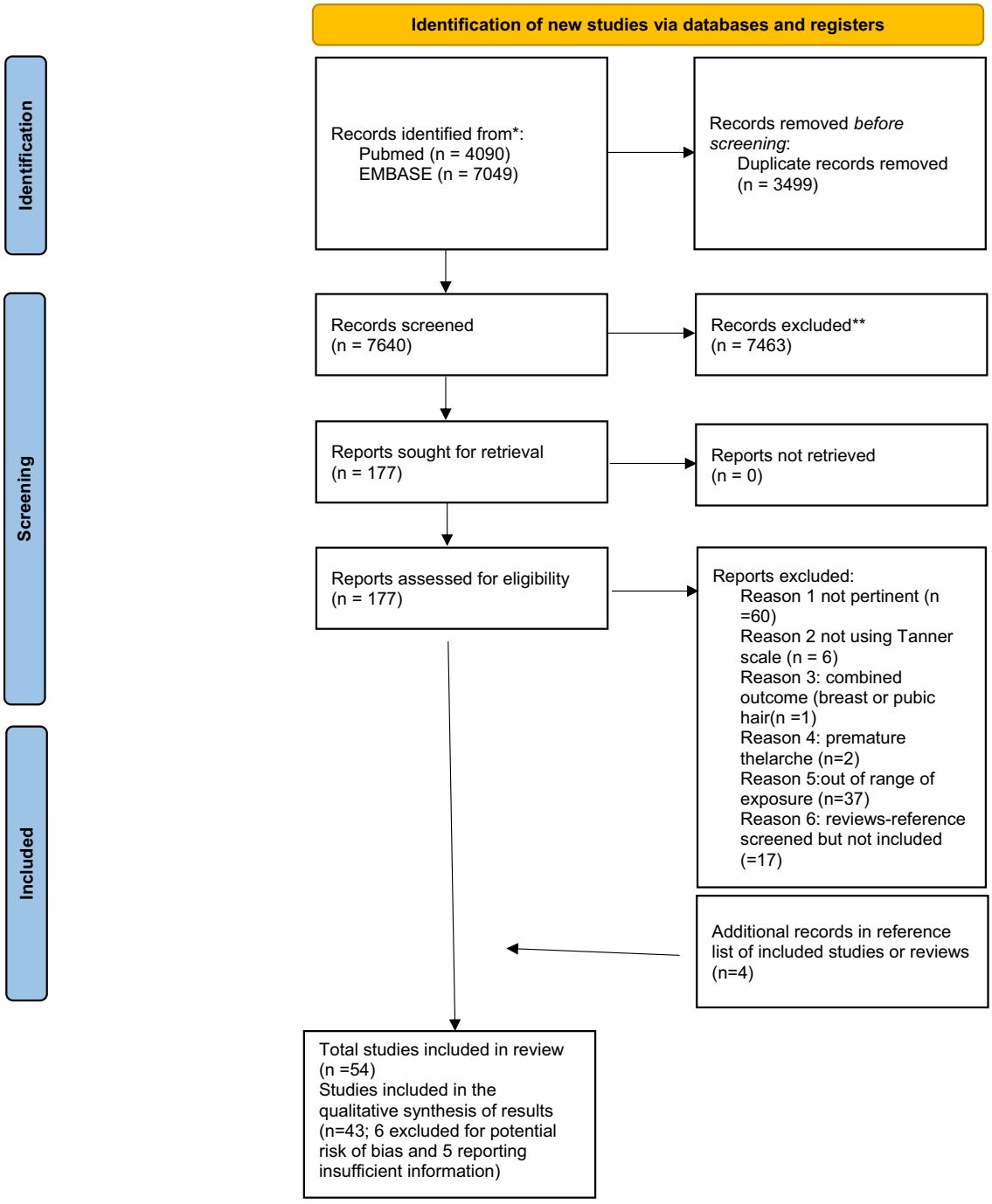

Fig. 1. PRISMA flowchart.

with breast assessment performed by medical professionals, whereas in 24 studies breast assessment was self-performed or reported by the child caregiver via questionnaire. Among the studies that assessed the outcome with a clinical visit, 16 included a visual and palpation assessment, 7 included a visual inspection only, and the remaining did not report assessment details.

Nine studies performed only one assessment between the ages of 6 and 18 years, while the other studies reported at least two clinical evaluations. A few of the studies followed girls periodically from birth, while most of the studies addressed breast and pubertal assessment during the peripubertal age. In particular, the age at which pubertal assessment began varied from 6 to 15 years, while the end of follow-up varied from 8 to 20 years or until full maturity.

The studies were generally of good quality (i.e., quality score > 6) (Supplementary Tables 3a–3b), with lower quality mainly in the cross-sectional studies.

The representativeness of the exposed cohort/group and the selection of the non-exposed cohort/group were appropriate in the majority of the studies. One study presented appropriate selection of exposed/not exposed group only for the main exposure assessed with potential risk of bias for the others [30]. Comparability was generally ensured by appropriate adjustments for the main potential confounders. A frequent reported limitation was self-assessment of the outcome, but this may not affect differently exposed and non-exposed groups given their satisfactory comparability in those studies. Among studies where the analysis was longitudinal, in 6 studies the age at end of follow-up (or the age

range for cross-sectional studies) was <12 years, which is unlikely to cover the transition to B2 of most of the participants. In general, where described, the follow-up was complete; only in 3 studies the 50 % of subjects or more dropped out. Finally, some cohort studies started when some girls already transitioned to Tanner B2+, performing analysis that did not account for this limitation (5 studies).

3.2. Study results

Breast development was studied using as outcomes, either breast onset (attainment of thelarche or B2 Tanner stage), or age at thelarche attainment, or breast development through the different Tanner stages, and type of puberty initiation (thelarche vs pubarche vs synchronous). For studies considering the same risk factor, exposure measurement was generally not consistent across studies.

Among the 54 identified studies, 11 did not report sufficient information to assess association or presented potential risk of bias, while 1 study was eligible only for one exposure, according to risk of bias assessment. Supplementary Tables 3a-b reports reasons for exclusion.

Table 2 (and Supplementary Table 4) summarizes the results for the remaining 43 studies.

3.3. Pregnancy period

Studies analyzing the effect of age at delivery did not find any significant effect, for any type of analysis, categorization of the exposure, consideration of potential confounders, and parent considered (i.e., mother or father). Being first-born was associated to a significant earlier breast onset/progression in 2 studies out of 3.

Seven out of the 8 studies considering the effect of mother's pre-pregnancy weight or body mass index (BMI) found significant and coherent effects. High maternal pre-pregnancy BMI was associated with a higher risk of early breast development in daughters and thelarche initiation of puberty (vs synchronous).

Moreover, higher gestational weight gain (GWG) and higher gestational BMI were associated to earlier thelarche or breast development in all the related studies.

One study found a delaying effect in breast development with the exposure to maternal preeclampsia only among exclusively breastfed girls, while two studies reported a lower risk of thelarche initiation of puberty (with a consequent later age at thelarche).

No association emerged in one study between nausea in pregnancy and age at thelarche.

Two studies out of 3 found an association between maternal smoking in pregnancy and early breast onset/progression.

No association emerged between maternal alcohol drinking during pregnancy and daughter breast development.

No significant effects were found for maternal use of medicines such as folic acid, paracetamol, antibiotics, or glucocorticoids.

3.4. Neonatal period

Four out of 6 studies found a delaying effect of preterm birth/low gestational age.

As regards small gestational age (SGA), 4 studies did not find any association, while one study reported different effects according to the type of adjustment.

No association emerged between birth weight and breast onset and development, except for one study which also reported a similar delaying effect for birth length.

Table 2
Summary of the associations between in utero and early life exposures and breast onset/development.

	No association	Earlier onset/development	Delayed onset/development
In pregnancy			
Maternal age at delivery	3 studies [19,32,56][a]		
Maternal primiparity	1 study [24]	3 studies [17–19][a]	
Maternal high pregravid body mass index	1 study [34]	7 studies [17,18,19,41,44,52,61][b]	
Maternal high gestational weight/body mass index		4 studies: 1 on gestational body mass index [39]; 3 on gestational weight gain [41,43,61]	
Maternal gestational diabetes	3 studies [34,39,40]	1 study [36][b]	
Maternal hypertensive disorders	1 study on hypertension/HELLP syndrome/preeclampsia [51][c]		2 studies on preeclampsia [22,33][d]
Maternal smoking	1 study [38]	2 studies [19,45]	
Maternal alcohol drinking	3 studies [19,30,49]		
Maternal drugs use	3 studies: 1 on antibiotics [50]; 1 on glucocorticoids [48]; 1 on paracetamol use [46]; 1 on folic acid [60]		
Nausea in pregnancy	1 study [57]		
Neonatal			
Daughter's preterm birth/ gestational age	2 studies [52,59]		4 studies [24,32,37,55][b]
Daughter born small for gestational age	4 studies [19,47,53,55]	1 study [25][b,e]	
Daughter's low birth weight	5 studies [19,20,28,32,62][f]		1 study [55]
Daughter's low birth length	1 study [19]		1 study [55][b]
Early life			
Maternal breasfeeding	3 studies [27,33,54]		3 studies [31,32,42][b]
Daughter's early weight gain	1 study [55][g]	8 studies [19,26,28,35,47,58,59][b]	
Daughter's early height gain		1 study [55][b,h]	

[a] Paternal age was also assessed and not significantly related to breast onset.
[b] Suggestive associations.
[c] Only one anticipating effect for type 2 diabetes and B5 was reported.
[d] Results among exclusively breastfed girls.
[e] Study reported an anticipating effect when adjusting for child height and a delaying effect when adjusting for linear growth.
[f] Cross-sectional studies.
[g] Only faster progression between B2 and menarche was reported.
[h] Anticipating effect for B4, faster progression between B2 and B4/menarche were reported.

3.5. Early life period

Three studies out of 6 reported protective effects for breastfeeding against early breast onset and development. Studies investigating early weight gain considered dissimilar reference periods, confounding factors and categorization of the exposure variable. Nonetheless, a positive association between early weight gain and early breast development emerged almost uniformly across studies. Only one study reported no association with early weight gain but a significant anticipating effect for early height gain.

4. Discussion

The results of this review show that high maternal weight, primiparity, and early weight gain were related to an increased risk of early breast onset/development in most of studies which have analysed these associations. Conversely, late breast onset/development was associated to preterm birth.

Results for smoking in pregnancy, maternal hypertensive disorders, breastfeeding, diabetes and small for gestational age were inconsistent. No association emerged for maternal age at delivery, alcohol drinking, and selected drug use in pregnancy and low birth weight.

Most of the negative or inconclusive findings, however, were based on a limited number of studies or the study design did not provide the opportunity to analyse separately effect of different risk factors. For example, studies showed mild associations with GDM [39]: this finding may be due at least in part to the indication for weight gain monitoring given to women with GDM [40].

Before discussing these results, we have to consider strengths and limitations. Strengths include the comprehensive search strategy with no time and independent screening of studies and risk of bias. Among limitations, we underline that the different measures of the outcome and exposures impeded the application of meta-analytic methods to calculate summary measures across studies.

The first major finding emerging from this review is the observation that maternal pre-pregnancy overweight/obesity and GWG were generally associated with earlier breast development, by about four months [19,34,39,41,43]. Studies that performed a combined analysis of these two variables suggested an independent effect of maternal BMI and a synergistic effect with GWG [43]. Daughters of overweight/obese mothers are at higher risk of childhood obesity. Nevertheless, studies that accounted for daughter's BMI showed that the effect of mother's weight was slightly attenuated but generally still significant and thus not fully mediated by the daughter's body mass [34,39,41,43,44,52]. Maternal adiposity may act directly, for example through fetus/child exposure to leptin or other hormones, but may also share a common genetic determinant with the daughter's age at onset of puberty.

Another maternal characteristic associated with earlier attainment of breast Tanner stages was parity, with the first-born child having a higher risk in 3 out of 4 studies. The reported risk estimates were about 4 months before breast onset [19], and associations were also found for progression to later stages or for thelarche versus synchronous pubertal onset [17,18]. Higher exposure to maternal sex hormones has been suggested as an explanation for this effect, as their concentration in umbilical cord blood is higher in firstborn children. In addition, firstborns have a higher risk of low birth weight and subsequent rapid weight gain. However, it should be stressed that this association was based on a limited number of studies.

Preterm birth was associated to a later onset of breast development [24,32,37,55] and shorter duration of puberty (i.e., interval between thelarche and menarche) [37]. However, the effect sizes for preterm birth were small (<1 month delay), so the significance of the effects for gestational age was less consistent [24,32,37,52,55]. A role of lower estrogen exposure in utero in down-regulating the gonadotrophic axis has been suggested: as plasma levels of estrogen appreciably drop from the prenatal to the postnatal period, preterm birth reduces the overall exposure to estrogen from the maternal placenta [37].

Measures of fetal growth restriction, such as placental z-score or SGA, as well as low birth weight, were linked to the earlier onset of menarche [28,53]. Regarding breast onset and development, most studies did not report evidence of an association with intrauterine growth status and birth weight. Interestingly, an association between low birth weight and menarche was observed in the same studies that found no significant association with thelarche [28]. Although we have to consider cautiously these findings, due to the limited number of studies, it has been suggested a differential impact of genetic loci on age of thelarche and menarche. In particular it has been speculated: "that factors predominantly involved in the reactivation of the hypothalamic-pituitary-gonadal axis at a central level, i.e., hypothalamic level, may be associated with timing of all pubertal milestones, whereas this might not be the case for more peripherally acting target-tissue specific factors. In line with this theory, LIN28B, presumably centrally acting, and FSHB/FSHR, peripherally acting, appear to exert their effect independently, as they did not interact significantly" [63].

In contrast, more coherent evidence emerged across studies of the influence of early weight gain on early breast onset/progression. The largest variation in weight gain rates usually occur in the first 2 years of life, when infants show accelerated or diminished growth to compensate for intrauterine restraint or enhancement of fetal growth [19,28]. We, therefore, focused on this period. However, one study analysed increments up to 36 months [55]. Rapid early weight gain is associated with the development of insulin resistance and excessive adrenal androgen secretion. One study that did not find a significant association with early weight gain [55], suggested that postnatal catch-up may be more associated with this effect rather than activation of the HPG axis. This may explain the results for all pubertal markers (i.e., while a not appreciable effect emerged for breast, a significant anticipating effect emerged for pubic hair onset and development). Moreover, low birth weight followed by rapid early weight gain is associated with an increased risk of central fat deposition and later obesity.

One study [55] performed a mediation analysis to disentangle the relationship between birth weight, early weight gain, and breast onset. The study supported that birth weight and postnatal growth play independent roles. Thus, this combination of hormonal and metabolic changes may affect the progression of puberty in a complex, multifactorial way. Further cohort studies considering prospectively these potential confounding factors may help to better understand this association.

In conclusion, many environmental influences can affect puberty onset. However, given the heterogeneity in the studies reviewed, inference on causality is complex. Moreover, disaggregating these effects into closed areas (such as diet or pregnancy characteristics), or closed periods (such as prenatal vs neonatal) may be misleading because of the evident interconnection between various factors, making it important that future cohort studies begin to collect data from before pregnancy to thelarche.

Breast development is a key physical marker of puberty onset, and early puberty development is linked to consequences that can reverberate throughout life. Answering questions about the interconnections of environmental exposures in pre/postnatal period and their impact on puberty represents an important area of multidisciplinary research.

Registration information

The systematic review was registered with PROSPERO (ID=CRD42016046146). Review protocol is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=270530. No amendment was required.

CRediT authorship contribution statement

Michela Dalmartello wrote the draft, participated to studies

selection, data extraction and risk of bias and certainty of evidence assessment and filled PRISMA checklists and flow chart. Francesca Chiaffarino participated to studies selection and reviewed the manuscript. Sonia Cipriani participated to data extraction and reviewed the manuscript. Giovanna Esposito participated to risk of bias and certainty of evidence assessment and reviewed the manuscript. Fabio Parazzini designed the study, supervised studies selection and reviewed the manuscript. Elena Ricci and Carlo La Vecchia and Luca Persani reviewed the manuscript. Eva Negri supervised data extraction, risk of bias and certainty of evidence assessment and reviewed the manuscript.

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Consent statement

Patient consent was not required.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2023.105816.

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