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REVIEW

Infection and pubertal timing: a systematic review

J. A. McDonald[1]*, S. M. Eng[1], O. O. Dina[1], C. M. Schooling[2,3] and M. B. Terry[1,4]

[1]*Mailman School of Public Health, Columbia University, New York, NY, USA*
[2]*School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, People's Republic of China*
[3]*China and School of Public Health, The City University of New York and Hunter College, New York, NY, USA*
[4]*Herbert Irving Comprehensive Cancer Center, New York, NY, USA*

The decline in age of pubertal timing has serious public health implications ranging from psychosocial adjustment problems to a possible increase in reproductive cancers. One biologically plausible explanation for the decline is a decrease in exposures to infections. To systematically review studies that assess the role of infection in pubertal timing, Medline, Web of Science and EMBASE were systematically searched and retrieved studies were reviewed for eligibility. Eligible studies examined the association between infections, including microbial exposures, and physical pubertal characteristics (breast, genitalia and pubic hair development) or age at menarche. We excluded studies that were published in a language other than English, focused on precocious puberty, were case studies, and/or included youth with autoimmune diseases. We report on study design, population characteristics, measurement of infection and puberty and the main effects of infection on pubertal development. Based on our search terms we identified 1372 unique articles, of which only 15 human and five animal studies met our eligibility criteria. Not all studies examined all outcomes. Infection was associated with later breast development (4/4 human studies), with less consistent evidence for genitalia and pubic hair development. Seven studies assessed age at menarche with inconsistent findings (three supporting later, four no association). We conclude that a small but consistent literature supports that infection is associated with later breast development; the evidence for other pubertal events and age at menarche is less clear. Where fewer childhood infections coincide with the rise in incidence of hormone-related cancers.

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Key words: breast development, infection, menarche, puberty, review

Introduction

Pubertal maturation generally occurs sequentially, characterized by breast/genital development first, followed by pubic hair growth, with menarche for girls being one of the last markers of pubertal maturity.[1–3] Extensive evidence indicates that the age at pubertal timing has declined for girls with rising living standards and similar, but less well-documented, declines in boys.[1,4–6] Early maturation in the human population may be an indicator of chronic environmental exposures and a bioassay of energy availability during childhood.[4,7] Understanding contributors to early puberty is critical given its relationship to psychosocial adjustment and increased risk for adult chronic conditions including hormonal cancers[8–10] and possibly cardiovascular disease.[8,10,11]

While the age of menarche has fallen substantially since the 19th century,[12,13] recent secular trends for earlier age at breast development was observed starting in the 1990s in the United States and 15 years later in European countries; though the trend in Europe is less dramatic than the United States.[12] The US National Health and Nutrition Examination Survey[14] and the U.S. Pediatric Research in Office Settings (PROS) study[15] indicate that the median reported age of beginning breast development is ~0.8–1.2 years earlier than previous U.S. population-based studies.[16] U.S. trends of earlier breast development are most marked for racial and ethnic minorities, with African American girls developing the earliest, followed by Hispanic girls.[14,15,17–20] The Copenhagen puberty study reports breast development is occurring a whole year earlier over a 15-year period and other European countries are currently observing similar trends.[21–23] Whether similar trends have occurred elsewhere is less well documented.

Information on boys' puberty trends is less comprehensive than for girls. Measurement of boys' pubertal development can be subjective without the assessment of testicular volume through orchidometry, and U.S. population-based studies without volume assessments are therefore difficult to interpret.[1,24] The PROS study suggest that genital development is occurring 1.5 years earlier than a landmark UK study,[25] with stronger trends among African American boys; however, the trend is difficult to interpret due to differences in study methodologies and population characteristics.[26] European population-based studies suggest from the mid-1960s through 1990s there is no secular trend toward earlier age at genital development;[27,28] however, over a period of 15–30 years the age at attaining a testicular volume of >3 ml is ~3–5 months earlier.[28,29] Studies suggest earlier age at boys' puberty with economic development over the long term, although the earlier age at boys' puberty may be less marked in the short-term and less extreme than that observed in girls.[1,6,30]

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*Address for correspondence: J. A. McDonald, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th St, New York, NY 10032, USA.
(Email jam2319@cumc.columbia.edu)

Unlike breast development, there is less data to determine the trend for pubic hair development. According to an expert panel review of U.S. puberty from 1940 to 1994, the majority of the panel concludes that there is no secular trend over this time period, while a minority conclude that age at pubic hair development has declined for girls and boys by ~6 months.[1] European findings are varied; however, several studies indicate an earlier age at pubic hair development for girls and boys.[28,29,31,32]

The average age at menarche declined largely between the 1800s and 1900s in the United States and Western Europe with more recent declines in settings where economic development is more recent, such as Asia.[12,13] Although United States and Western European studies indicate that the age at menarche may have stabilized over the past 50 years, evidence still suggests that in the past 25 years, the median age at menarche has decreased by 2.5–4 months.[1,12] Stronger trends are observed in racial and ethnic minorities in the United States.[1,12,33–35]

The past several decades have seen a substantial increase in the prevalence of childhood obesity (Fig. 1).[3,24,41,42] Epidemiological studies have shown that girls with higher body mass index in their childhood years are more likely to undergo earlier pubertal development (i.e. breast development and menarche).[43–46] Body size changes may be a key driver in earlier puberty,[47] but the decline in the average age of menarche occurred before the childhood obesity epidemic, even in settings with lower childhood obesity (e.g. Hong Kong), suggesting that other factors are at play (Fig. 1).[21,48–54] Although several genes have been linked to the timing of menarche and height growth,[55–61] genes alone cannot explain the secular trends. To date, investigation of pubertal timing has focused on changes in (1) environmental exposures [e.g. endocrine disrupting chemicals (EDC)],[9,62–66] (2) differences in prenatal exposure and early infant growth[65,67–70] and (3) the social environment (e.g. childhood adversity).[7,9,65,66,71] Undoubtedly, all of these play a role, but other factors have also changed that may also explain recent trends.

Less attention has been given to examining infant and childhood exposures and pubertal timing in the context of other marked secular trends with economic development which maps closely to changes in pubertal timing. Major socio-economic changes and public health initiatives have resulted in vastly reduced exposure (e.g. improved sanitation, decrease in family size) and increased resistance (e.g. widespread antibiotic use, vaccinations) to infectious agents which may influence pubertal timing.[72,73] From a life history perspective, the energetics theory of pubertal timing postulates that in times of critical energy demands an individual will allocate resources for maintenance and survival.[7,71] The energetics theory has been indirectly assessed by examining the association of puberty with socio-economic status and nutrition.[7] The most common strategy to cope with energy demands is to reduce energy expenditure of non-essential physiological needs. Therefore, with more infections, there is greater energy investment in the immune system and less energy available for biological systems responsible for reproduction.[74,75]

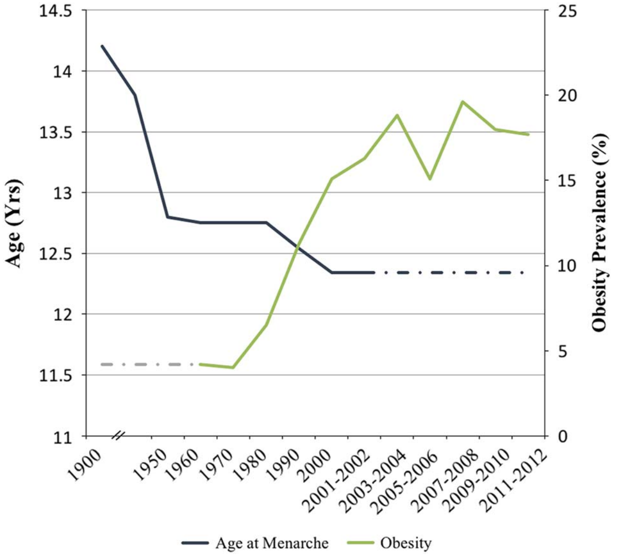


Fig. 1. Secular trends in age at menarche and childhood obesity (ages 6–11 years for boys and girls) in the United States from 1900 to 2012. The dark blue line represents trends in age at menarche and the light green line represents trends in childhood obesity from national data sources. The dashed lines are drawn to approximate trends. Sources: Tanner and Eveleth[36], Gould and Gould[37], Damon *et al.*[38], Anderson *et al.*[39], Anderson and Must[40], National Health and Nutrition Examination Survey II[151], Fryar *et al.*[41].

The biological basis for the association between infection and pubertal timing lies within the complex interaction between the immune and endocrine systems, where the immune system products modulate hormonal secretions and in turn regulates immune functioning.[76] This is evident in sex differences in immunological responses as females mount a stronger humoral immune response to infection compared with males who are generally more susceptible to infection.[77,78] Sex differences are partially attributed to differences in sex-steroids, which influence susceptibility and resistance to infection, most notably by altering host immunity.[77,78] Androgens are associated with immunosuppression.[78] Males with androgen deficiencies and gonadectomized mice have greater production of inflammatory cytokines.[78] Androgens also influence disease susceptibility genes (e.g. genes related to competent immune responses and pathogen clearance) and behavior.[78] Estradiol has dual effects, and at low concentrations is associated with proinflammatory activity and at high or sustained concentrations is associated with anti-inflammatory responses.[78] The dual effect makes the precise role of estrogen on immunity unclear.[78] The immune microenvironment in the stroma surrounding mammary gland epithelium is rich in immune cells and, via hormone-mediated communication, drives pubertal and adult mammary gland development.[79] Murine studies demonstrate that absence or deficiency in key immune cells leads to disruption in terminal end bud ductal branching.[79]

To clarify the potential role of exposure to infections in pubertal timing, we review the epidemiological literature and animal data examining the relationship between infection and pubertal timing – inclusive of breast, genitalia and pubic hair development, and age at menarche – with the hypothesis that infection is associated with later maturation.[80] As hypothesized previously, we would expect the greatest effect during periods when the hypothalamic–pituitary–gonadal (HPG) axis is active.[80] The HPG axis is active during fetal development and remains active during early infancy (first 12 months) then the HPG axis goes dormant.[81–84] HPG axis reactivation occurs at the onset of puberty.[85]

Method

Information sources and search criteria

We followed the PRISMA systemic review guidelines. Studies were identified by a systematic search of Medline, Web of Science and EMBASE up until 9 October 2014, with the earliest article identified in 1934.

Key words were identified by consulting the literature and using synonyms. Terms used included infection (without restrictions) and 'puberty,' 'pubertal,' 'menarche,' 'breast development' and 'thelarche' that were restricted to being listed in the title and/or abstract. We used the Boolean operator AND to combine infection and pubertal terms. We only included articles published in English.

Study selection

We included as eligible, primary articles that examined the association between infections including microbial exposures and physical pubertal characteristics (breast, genitalia, and pubic hair development) or age at menarche. We excluded studies that were either published in a language other than English; focused on precocious puberty, which is a diagnostic evaluation;[12,86,87] were case studies, and/or included youth with autoimmune diseases (including an anemia cohort) because of the difficulty discerning if the pubertal outcome is due to the autoimmune condition or the infection. Among 1372 non-duplicate articles, we excluded 1334 articles during the screening process and an additional 18 articles upon deeper review (Fig. 2).

J.A.M. performed all literature searches and the initial screening of article titles and abstracts for eligibility criteria. S.M.E. reviewed 10% of screened articles to validate inclusion and exclusion agreement with J.A.M. J.A.M. identified the full text articles eligible for extensive review and J.A.M. and S.M.E. independently reviewed articles with consensus reached by discussion and by an additional reviewer (M.B.T.).

Data extraction and synthesis

The type of data extracted for qualitative synthesis was decided by J.A.M., M.B.T. and S.M.E. J.A.M., S.M.E. and O.D. independently extracted data for qualitative synthesis and discrepancies between reviewers were resolved through mutual discussion and an additional reviewer (M.B.T.). The summary measures reported were differences in means and proportions, and relative risk ratios which represent hazard ratios or odds ratios depending on study analysis. J.A.M. assessed the quality of the epidemiologic studies using the Newcastle–Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), which uses a star system to judge study quality across three broad categories: selection of the study groups, the comparability of the groups and the ascertainment of the outcome (cohort study design) or the exposure (case–control study design).

Results

We identified 15 epidemiological studies for qualitative synthesis (Table 1) and five animal studies collectively from the Americas, Africa, Asia, the Caribbean and Europe; we organized these studies by infection type from 1372 screened articles (Fig. 2). Of the 15 epidemiology studies, outcomes were prospectively ascertained in five[80,88,89,91,92] and elicited in a cross-sectional manner at the same time as infection exposure status, in 10.[90,93–101] Physical pubertal characteristics were measured using Tanner and Marshall staging which uses line drawings showing five stages from Tanner stage T1–T5, with stage T2 marking the onset of pubertal development and stages T3–T5 marking increasing maturity.[102,103] With one exception where age at menarche was determined through medical records,[92] the start of menarche was recalled by study participants.[90,96,97,99–101] Infectious exposures were assessed diagnostically or through biospecimens, or reported through medical records or by guardian report. We identified four major categories of infection including viral (five studies[88–92]), bacterial (one study[99]), parasitic (10 studies[93–98,104–108]) and non-specific pathogenic infection, termed general infection (three studies[80,100,101]). For presentation, we have organized the summary of these results by outcome with the human results discussed first followed by the animal evidence.

Breast: all studies that assessed breast development suggested infection was associated with later breast development compared with girls without infection.[80,88,89,91] Three prospective studies suggested perinatal HIV infection was associated with later breast development in girls compared with controls,[88,89,91] with the difference ranging from 6 to 25 months (comparing breast Tanner stage 2, B2).[88,91] In one of the largest U.S.-based prospective studies of perinatal HIV infection, there was a difference in the mean age at breast development between HIV+ and HIV− exposed but uninfected (HEU) controls; the effect was strongest in girls born after 1997 compared with girls born before 1990.[91] HIV disease severity, defined by CD4 counts and viral load, was not associated with breast development.[91]

The association between infections and girls' pubertal development may start as early as the first few months of life. The Children of 1997 Hong Kong birth cohort collected

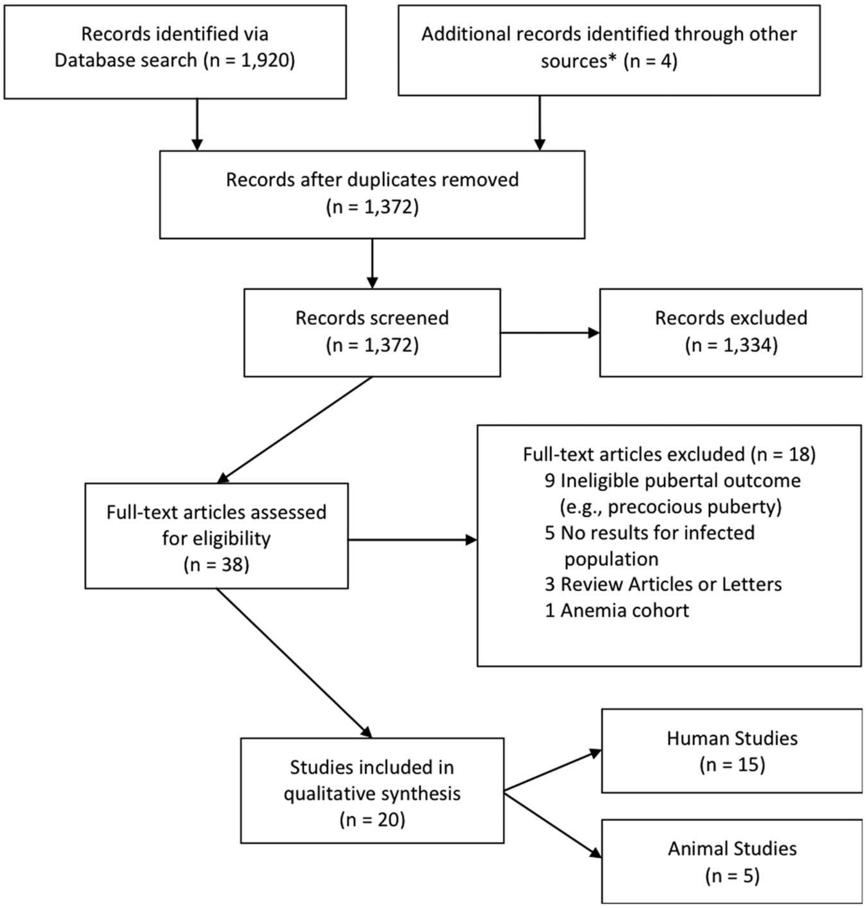


Fig. 2. Schematic of search protocol and results of systematic review. *Identified through review of references of selected papers.

information on the number of hospital admissions due to infection using hospital records from 9 days to 8 years of age.[80] In 3542 Chinese girls, two or more hospital admissions in the first 6 months of life was associated with later breast development; there was no association with hospital admissions in older ages.[80]

Genitalia: among the five human studies directly assessing genitalia development,[80,88,89,91,93] only the viral studies strongly suggested infection was associated with later development.[88,89,91] Perinatal HIV infection was associated with a 6–7 months later genitalia development in boys compared with controls (comparing genitalia Tanner stage 2, G2),[88,91] and as observed above with respect to girls and breast development, birth cohort effects were observed for the mean age at genitalia development.[91] Boys with greater HIV disease severity had later genitalia development ranging between 2 and 9 months.[91] Within a cross-sectional study of parasitic infection in 453 Egyptian boys, *Entamoeba hystolytica* infection was inconsistently associated with later genitalia development (observed in G2, G4 and G5 stages) compared with non-infected boys.[93] There was no association with overall parasitemia or other individual parasites whose prevalence ranged from 1 to 14% compared with *E. hystolytica* prevalence of 32–51%. Contrast to the findings with breast development, there was no association between the number of hospital admissions due to infection and genitalia development in 3985 Chinese boys.[80] However, one rodent study found that a tapeworm infection at 22 days of age was associated with later sexual development in male rats as defined by testicular and seminal vesicle weight.[105]

Pubic hair: while two studies suggested later pubic hair development in HIV-infected youth compared with controls,[88,89] these studies were limited to a cross-sectional control population and did not consider potential confounders. In contrast, there was no association between HIV-infected youth and pubic hair development compared with HEU controls in girls, with only a small, but not statistically significant, association observed in boys after controlling for confounders.[91] However, youth with greater HIV disease severity had later pubic hair development ranging between 3–8 months for girls (CD4 measures only) and 3–9 months later for boys (CD4 and viral load measures) compared with youth with lower disease severity.[91]

Combined measures of puberty: four studies used a sexual maturity rating (SMR) defined by a combination of Tanner staging for breast, genitalia, testes and/or pubic hair[95,98] or used Tanner staging without reporting the specific pubertal

Table 1. *Details of included epidemiological studies of puberty and infection*

							Newcastle-Ottawa Scale[a]		
Author, location, year	Study design	Study population	Pubertal measure	Infection measure	Main effects	Adjustments	Selection	Comparability	Outcome/exposure
Viral									
de Martino, Italy, 2001[88]	Prospective cohort	107 Girls 105 Boys Cross-sectional control population of 1664 youth (843 girls and 821 boys)	Tanner staging: breast (girls) Genitalia (boys) Pubic (girls and boys) Puberty defined as age at entry into stage 2 or higher	Perinatal HIV	Girls had a >21-month delay in breast and pubic hair development compared with control[b] Boys had a <15-month delay in genital and pubic hair development compared with control[b]	None reported	★★★		★★★
Buchacz, United States, 2003[89]	Prospective cohort	491 Girls 492 Boys Cross-sectional control population from NHANES III[c]	Tanner staging: breast (girls) Genitalia (boys) Pubic (girls and boys) Puberty defined as age at entry into stage 2 or higher	Perinatal HIV	The proportion of girls who begun breast development (B2 or higher) were consistently lower in comparison with NHANES III The proportion of boys who begun genitalia development (G2 or higher) were consistently lower in comparison with NHANES III The proportion of youth who begun pubic hair development (P2 or higher) were consistently lower in comparison with NHANES III	None reported	★★★★	★★	★★★
Ferrand, Zimbabwe, 2010[90]	Cross-sectional	130 Girls 171 Boys Hospital patients ages 10–18 years	Tanner staging: (higher value indicates more advanced development) Type unspecified (girls and boys) Menarche	HIV	The proportion of youth ages $\geqslant 14$ years old who were Tanner stage 1/2 were higher among HIV + (15%) compared with HIV − (2%) youths ($P < 0.001$). The proportion of girls who had attained menarche was lower among HIV + (28%) compared with HIV − (52%) girls ($P = 0.005$)	None reported	★★★★		
Williams, United States, 2013[91]	Prospective cohort	1253 Girls 1286 Boys Includes a prospective control population of HIV exposed but uninfected	Tanner staging: breast (girls) Genitalia (boys) Pubic (girls and boys) Puberty defined as age at entry into stage 2 or higher	Perinatal HIV	Girls' breast development was on average 5.55 months later compared with controls (95% CI 2.38, 8.72 months) Boys' genitalia development was on average 6.02 months later compared with controls (95% CI 2.15, 9.90 months) Compared with controls, there was no association with pubic hair development in girls (mean shift 1.48 months (95% CI −1.87, 4.83 months)), but a marginal association with later pubic hair development for boys (mean shift 3.92 months (95% CI −0.14, 7.98 months) Sensitivity analyses found no associations remained between HIV and Tanner stages after further adjustment for body mass index and height z-scores; however, these measures may be on the causal pathway	Race, ethnicity, birth cohort	★★★★	★★	★★★
Wu, Taiwan, 2014[92]	Prospective cohort	101 Women Positive for HBeAg	Menarche Earlier/later menarche defined as ±1 standard deviation than mean age of cohort	Hepatitis B	Women with earlier-onset menarche had a two-fold increased risk of earlier HBeAg seroconversion compared with women with later-onset menarche (RR 1.95, 95% CI 1.11–3.43)[d,e]	HBV genotypes and peak alanine aminotransferase levels before spontaneous HBeAg seroconversion[d]	★★★	★	★★★
Parasitic									
Cole, Egypt, 1982[93]	Cross-sectional	453 Boys School children ages 9–17 years	Tanner staging: genitalia	*Entamoeba histolytica*, *Hymenolepis nana*, *Ascaris*, *Giardia*	Overall parasitemia was associated with later genitalia development in the range of 1–6 months; however, the associations did not reach significance at $P < 0.05$ Boys who were *E. histolytica* + , genitalia development was about 0–7 months later compared with *E. histolytica* − boys, with stronger evidence for G2, G4 and G5 stages 7 Months later in G2, $P < 0.05$ 0 Months later in G3, $P \geqslant 0.05$ 5 Months later in G4, $P \leqslant 0.01$ 4 Months later in G5, $P \leqslant 0.01$	None reported	★★★	★	★

Ibrahim, Egypt, 1983[94]	Case–control	111 Cases[f] 64 Uninfected controls Boys only, ages 9–20 years	Tanner staging (higher value indicates more advanced development) Type unspecified (boys)	*Schistosoma haematobium*	Cases had a higher average chronological age at any stage of pubertal development than controls. Stronger evidence for stages III–V (*P* < 0.01) Mean age (standard error) Stage I: cases 10.98 (0.40); controls 10.6 (0.21) Stage II: cases 13.4 (0.61); controls 12.7 (0.23) Stage III: cases 15.00 (0.30); controls 13.70 (0.24) Stage IV: cases 17.20 (0.40); controls 14.50 (0.20) Stage V: cases 18.80 (0.35); controls 16.50 (0.47)	Controls matched to cases on age, education, socio-economic class, and freedom from systemic diseases (including those of the liver and biliary systems)	★	★★	★★
Aroke, Cameroon, 1998[95]	Case–control	100 Cases[g] (58 girls and 42 boys) 100 Controls School children ages 6–20 years	SMR defined by Tanner staging (higher value indicates more advanced development) Comprised of breast and pubic for girls Comprised of testes, genitalia, and pubic for boys	*Trypanosoma brucei gambiense*	Cases had a lower average SMR [mean (standard deviation (S.D.)] 2.80 (1.55)) compared with controls [mean (SD) 3.19 (1.50)] (*P* > 0.05)	Pair-matched for age at school entry and general exposure to learning opportunities, sex, place of residence, occupation of parents, level of formal education of parents, and cultural backgrounds (i.e. ethnicity, level of parental polygamy, household characteristics)	★★	★★	★
Bernhard, Tanzania, 2000[96]	Cross-sectional	404 Women[h] Ages ⩾ 15 years	Menarche	*Wuchereria bancrofti* (prevalence of circulating filarial antigen)	Circulating filarial antigen was not associated with age at menarche (no data shown)	None reported	★★★		
Braga, Brazil, 2005[97]	Cross-sectional	608 Girls[i] Ages 9–16	Menarche	*Bancroftian filariasis* (prevalence of microfilaraemia and circulating filarial antigen)	Filariasis was not associated with age at menarche [microfilaremia RR 0.65 (95% CI 0.16–2.68) and circulating filarial antigen RR 0.90 (95% CI 0.31–2.63)][e]	Bed net use and the presence of a microfilaraemic adult in the household (implied from text)	★★★	★	
Fox, Haiti, 2005[98]	Cross-sectional	95 Girls 97 Boys Ages ⩾ 7 years[j]	SMR defined by Tanner staging (higher value indicates more advanced development) Comprised of breast and pubic for girls Comprised of genitalia and pubic for boys	*Wuchereria bancrofti* (prevalence of circulating filarial antigen; ultrasound presence of adult worm infections in lymph node areas, breasts of prepubescent girls or scrotum of boys referred to as filarial dance sign)[k]	Youth who were positive for circulating filarial antigen had a two-fold increased risk of advanced pubertal staging (SMR3–5) compared with controls (RR 2.3, 95% CI 1.10–4.60)[e] Youth who had detectable adult worms had a two-fold increased risk of advanced pubertal staging (SMR3–5) compared with those with undetectable adult worms (RR 2.3, 95% CI 1.40–3.70)[e]	Inguinal lymph node pathology, crural lymph node pathology and severe interdigital lesions for circulating filarial antigen for circulating filarial antigen analysis None reported for filarial dance sign	★★★	★	
Bacterial									
Rosenstock, Denmark, 2000[99]	Cross-sectional	1419 Women	Menarche	*Helicobacter pylori*	Each additional year at age at menarche was associated with a 10% increase in being *H. pylori* + compared with negative controls (95% CI 1.02, 1.19 years)[e]	Socio-demographic factors (implied inclusion of age, marital status, housing density, social status, geographical residency and occupational energy expenditure), height, serum lipids, other chronic diseases (including heart condition and chronic bronchitis) and lifestyle practices	★★★	★★	
General infection									
Khan, Guatemala, 1996[100]	Prospective cohort	250 Women[l]	Menarche	Prospective collection for diarrheal and respiratory illness every 2 weeks between ages 3 months and 3 years by maternal or caretaker[m]	No correlation between menarche and diarrheal illness or menarche and respiratory illness Diarrheal illness was associated with a marginal later age at menarche (*P* < 0.10) but not respiratory illness (*P* > 0.10)	Skeletal matter for age <7 years, socio-economic status at 1975, height at age z-score, average daily energy from supplement and from diet	★★★	★★	★

Table 1. (*Continued*)

							Newcastle-Ottawa Scale[a]		
Author, location, year	Study design	Study population	Pubertal measure	Infection measure	Main effects	Adjustments	Selection	Comparability	Outcome/exposure
Blell, England, 2008[101]	Prospective cohort	276 Women Newcastle Thousand Families[n]	Menarche Earlier/later menarche defined as ± 1 S.D. than mean age of cohort	Respiratory infection, intestinal infection and overall infection reported between ages 0 and 8 years by health visitors, parents, general practitioners, and from hospital referrals and attendances	Age at menarche was not associated with rate per year of respiratory infections, intestinal infections or overall infections ($P > 0.50$)	None reported	★★★		★★
Kwok, Hong Kong, 2011[80]	Prospective cohort	3542 Girls 3985 Boys Children of 1997 birth cohort[o]	Tanner staging: breast (girls) Genitalia (boys) Puberty defined as age at entry into stage 2 or higher	Number of hospital admissions for infections using public hospital records from 9 days to <6 months, 6 to <24 months, 2 to <5 years and 5 to 8 years	Girls, but not boys, hospitalized at least two or more times during the first 6 months of life had pubertal development about 8 months later compared with those without hospitalization. The number of hospital admissions for infections between ages 6 months to 8 years was not associated with age at pubertal development for girls or boys	Birth weight, gestational age, birth order, breastfeeding, second hand smoke, maternal place of birth, maternal educational level, type of hospital at birth, income of household head and Rutter score at 7 years of age	★★★★	★★	★★★

NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; GSS, Gambian sleeping sickness; HBeAg, Hepatitis B e antigen; RR, relative risk; SMR, sexual maturity rating.

[a] We used the Newcastle–Ottawa Scale where a study can be awarded a maximum of 4 stars within the selection category, 2 stars within the comparability category and 3 stars within the outcome (cohort study design) or exposure (case–control study design) category based on the answers provided for each item within each category. For those studies with the assessment of multiple pubertal outcomes, the Newcastle–Ottawa Scale was applied to each outcome, independently. The number of stars allocated for each outcome independently was identical; therefore, we present the stars allocated to the outcome/exposure category as a representation of all the pubertal outcomes assessed within each study.

[b] Data are presented as the age at which 50% of HIV + girls and boys reached each Tanner stage (stages 2–4) compared with the median (50% percentile) ages of control girls.

[c] The NHANES III 1988–1994.

[d] HBeAg seroconversion defined as the spontaneous clearance of serum HBeAg and appearance of anti-HBe for >6 months.

[e] RR ratios are presented and represent hazard ratios or odds ratios depending on study analysis.

[f] Criterion for cases was infection with *Schistosoma haemotobium* only as confirmed by repeated urine and stool analyses. Subjects with other parasitic infections were excluded from study.

[g] School children were recruited during a campaign against GSS. Cases had school records showing that they had been treated for GSS. Controls were re-tested with the Testryp-CATT to confirm sero-negative status.

[h] Women recruited from two adjacent villages in northeastern Tanzania and includes women untested for microfilaria.

[i] Data collected via door-to-door survey in northeastern Brazil.

[j] Pediatric cohort from the Léogâne Commune that had participated in longitudinal filariasis studies for ⩾10 years. Study represents cross-sectional diagnostic evaluation that took place in November 2002.

[k] Ultrasound assessment performed to detect adult worm infections ($n = 45$ girls and 57 boys). Adult worms identified by motility referred as the filarial dance sign.

[l] Community-based nutritional intervention study carried out between 1969 and 1977. Age at menarche collected between 1991 and 1992.

[m] Data only includes children where at least 360 days of illness data available.

[n] Birth cohort was born in 1947 and traced at age 49–51 years where menarche reports were collected.

[o] Children of 1997 birth cohort recruited from all 49 governmental Maternal and Child Health Centers in Hong Kong. Passive follow-up via record linkage was performed in 2005 and active follow-up with direct contact performed in 2007.

characteristic assessed.[90,94] Among the one study of viral infection[90] and the three studies of parasitic infection,[94,95,98] none provided information on the role of infection on independent physical pubertal characteristics and some did not provide information on initiation of puberty. One study showed a null effect,[95] two studies found later timing,[90,94] and one earlier pubertal development.[98] A cross-sectional Haitian study was the only identified study to observe that infection, defined as having circulating *Wucheria bancrofti* antigen and the presence of adult worms, was associated with advanced SMR (stages 3–5), compared with those without infection.[98] However, of 102 youth examined for presence of adult worms, only 11 children had adult worms ($n = 10$ boys) which could be a reflection that detection of adult worms is easier in post-pubertal youth.

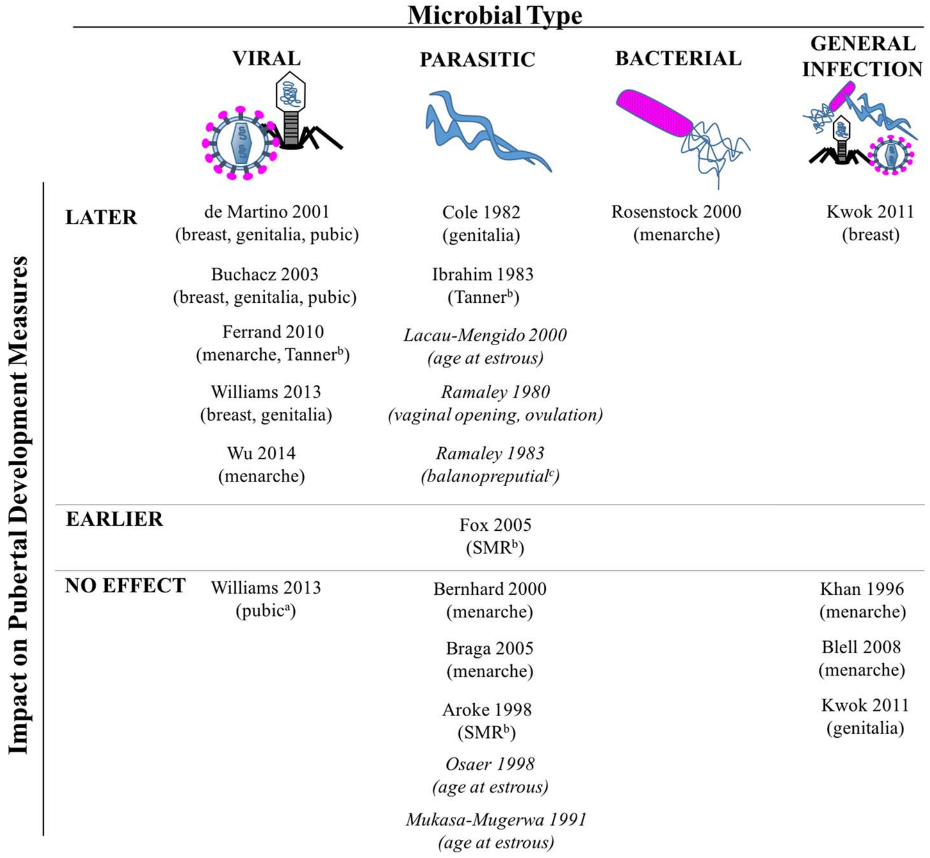
Age at menarche: the impact of infection on age at menarche was inconsistent. Three studies suggested infection was associated with later start of menarche.[90,92,99] A Taiwanese cohort [mean (S.D.) age at recruitment 4.6 (3.1) years] that was followed for an average of 24 (3.8 S.D.) years examined Hepatitis B viral infection and menarche.[92] Hepatitis B antigen seroconversion was associated with earlier age at menarche after controlling for viral pathogenic covariates. The two cross-sectional parasitic studies did not show an association with menarche.[96,97] *Helicobacter pylori* positivity was associated with a 10% increased risk in later age at menarche, compared with *H. pylori* negative women, after controlling for sociodemographic, metabolic, lifestyle factors and chronic conditions.[99] Two prospective cohort studies assessed general infection and menarche, including a Guatemalan study where diarrheal and respiratory illness were reported every 2 weeks by maternal or caretaker recall from age 3 months to 3 years and age at menarche was retrospectively collected at approximate ages 15–30 years.[100] There was no association with respiratory illness ($P > 0.10$), but marginally ($P < 0.10$), later age at menarche was associated with diarrheal illness after adjusting for confounders.[100] The Thousand Family study in the United Kingdom found that infection rate between birth and 8 years of age was not associated with later age of menarche.[101] Respiratory and intestinal infection were notified by health providers and parents with retrospective recollection of age at menarche by subjects at age 50 years old.[101] The findings for infection and puberty are also inconsistent among animal studies, while puberty is defined as the first behavioral estrous.[109] In a Argentinian study of heifers ($n = 40$), those treated with an anti-helminthic reached puberty 3.7 weeks earlier than heifers not treated with an anti-helminthic (statistical significance not reported).[104] In two independent ewe lamb studies ($n = 24$ and 112), there was no association between parasitic infections and age at first estrous.[107,108]

Discussion

Infection is associated with later breast development, with less consistent evidence for genitalia and pubic hair development and age at menarche (Fig. 3). The consistent association with breast development may be attributed to the fact that secular trends for breast development are more marked than for other pubertal measures. The differences by gender and pubertal marker may be biological or due to measurement issues. The literature is emerging and careful consideration of study design, including exposure and outcome measurements (Table 2), is needed to understand some of the existing inconsistencies and major gaps in the evidence base. Nevertheless, the data are intriguing, particularly given the overall consistency between infections and later breast development as childhood infections have declined over time[52,53] and average age at breast development has also declined.[15,16,19,21,24,39,110–112] The evidence also supports our hypothesis as the strongest effect between infection and puberty was with infections acquired in early life (perinatal and early infancy), presumably during HPG axis activity.[80,88,89,91,100]

Differences by gender: the inconsistencies observed between infection and pubertal timing may be influenced by sex differences. For example, compared with youth with lower HIV disease severity, there were stronger pubertal trends observed for boys with greater disease severity than with girls.[91] As discussed above, sex differences may be due to differences in initial immunological response, where males generally mount a weaker response compared with females, or to differences in levels of circulating sex-steroid hormones.[77,91] The endocrine system impacts the functioning of the immune system.[76] Immune cells express sex steroid receptors; therefore, sex steroids may modulate activity, expression, and function of immune cells important to cellular and humoral immunity[113] and drive mammary gland development.[79,114–116] Parasitic and bacterial infections cause dysregulation of the HPG axis by downregulating sex-steroid hormone production or sex-steroid hormone receptors.[94,117–123] Thus, greater childhood infectious exposures may result in lower sex-steroid production that results in later age at breast development and menarche. The weaker evidence with genitalia and pubic hair development may be explained because they are more affected by androgens rather than estrogens.[34,124,125]

Challenges in epidemiologic study interpretations: in seven prospective studies,[80,88,89,91,92,100,101] three had inadequate or no control population[88,89,92] and few explicitly report lost to follow-up.[80,89,101] In studies that report, the lost to follow-up ranged between 5 and 14%, which could affect small associations through selection bias.[80,89,101] The six cross-sectional studies can only infer associations,[90,93,96–99] not causation, and selection bias may be an issue in the two case–control studies based on the control selection.[94,95] Of the five studies that solely concluded that infection had no association with pubertal development, the NOS quality assessment of the outcome was low (0–2 stars), which stems from the nature of cross-sectional studies lacking follow-up assessments and self-reported menarche introducing recall bias. In contrast, some of the highest quality studies were the viral studies, which consistently found that viral infections resulted in later pubertal development. The viral studies had a high-quality assessment



Impact on Pubertal Development Measures	Microbial Type: VIRAL	PARASITIC	BACTERIAL	GENERAL INFECTION
LATER	de Martino 2001 (breast, genitalia, pubic) Buchacz 2003 (breast, genitalia, pubic) Ferrand 2010 (menarche, Tanner[b]) Williams 2013 (breast, genitalia) Wu 2014 (menarche)	Cole 1982 (genitalia) Ibrahim 1983 (Tanner[b]) *Lacau-Mengido 2000 (age at estrous)* *Ramaley 1980 (vaginal opening, ovulation)* *Ramaley 1983 (balanopreputial[c])*	Rosenstock 2000 (menarche)	Kwok 2011 (breast)
EARLIER		Fox 2005 (SMR[b])		
NO EFFECT	Williams 2013 (pubic[a])	Bernhard 2000 (menarche) Braga 2005 (menarche) Aroke 1998 (SMR[b]) *Osaer 1998 (age at estrous)* *Mukasa-Mugerwa 1991 (age at estrous)*		Khan 1996 (menarche) Blell 2008 (menarche) Kwok 2011 (genitalia)

Fig. 3. Results of studies examining infections and pubertal development, 1980–2014. Later refers to studies that the observed infection was associated with a later age of development of the pubertal outcome (indicated in parentheses). Earlier refers to studies that the observed infection was associated with an earlier age of development of the pubertal outcome (indicated in parenthesis). No effect refers to studies that observed no association between infection and the pubertal outcome (indicated in parenthesis). (*a*) Pubic hair development was later with HIV disease severity in boys. (*b*) Tanner staging with type unspecified. (*c*) External sign of puberty in the male rat that is accompanied by testicular and seminal vesicle weight. Animal studies are in italics. SMR; sexual maturity rating.

for selection (3–4 stars) and outcome (3 stars, with one study having 0 stars). In contrast, the most heterogeneous findings related to the role of parasitic infections on pubertal development. The heterogeneity within parasitic infections may be attributed to the low quality assessment for both the comparability between groups (0–2 stars) and the outcome (0–2 stars). In the general infection category, the one study that found an association with later pubertal development had the highest NOS assessment ratings.

Challenges in measurement of outcomes: a major challenge to interpreting the existing literature is heterogeneity in measurement of outcomes. With respect to breast development measurement, palpation assessment is important to avoid misclassification given the rise of childhood obesity[102,103] but no study reports this method.[80,88,89,91] The gold standard of measuring boys' puberty includes a visual assessment supplemented by an estimation of testicular volume.[6] The latter provides greater accuracy and less variability across observers; although, the testicular volume threshold indicating pubertal onset is not consistent.[6] One study implied the use of an orchidometer[95] and three out of nine studies reported orchidometer use,[80,91,94] with one of these reporting use on a subset of the cohort.[91] Misclassification in Tanner staging can be minimized by training, but studies that provide details on training are scant.[89] In addition, Tanner stage 2 marks the onset of development; therefore, studies that combine Tanner stages 1/2 are failing to capture initiation.[90,98] Many of the studies examining age at menarche rely on self-reported age at menarche that may result in misclassification, or at the very least, loss of power if the recall of menarche is in years rather than capturing months.

Challenges in measurement of exposures: potential measurement errors for assessing infectious exposures include the type of measurement and the timing of collection. The majority of studies diagnostically assessed infection measures with only four studies assessing infection before the onset of physical pubertal characteristics.[88,89,91,92] Infection measures were also assessed through health provider and guardian reports.[100,101] Retrospective collection of exposure data, though more feasible, is limited by maternal recall bias. Though bias

Table 2. *Measurement of pubertal outcome and infection exposure measures and associated challenges*

Common measures across studies		Measurement	Challenges
Outcome	Breast	Tanner visual and palpation	Without palpation, misclassification possible; requires invasive examination
	Genitalia	Tanner visual and orchidometer	Orchidometer provides greater accuracy but discrepancy on the threshold volume marking the initiation of puberty; requires invasive examination
	Pubic	Tanner visual	Requires invasive examination
	Combined Tanner staging (e.g. sexual maturity rating)	Tanner staging comprised of a combination of girl and boy physical pubertal characteristics (e.g. breast, genitalia)	Physical characteristics cannot be assessed independently; stages commonly occur sequentially, but not always; pubertal staging is influenced by different sources and levels of sex steroids; requires invasive examination
	Menarche	Self-reported; medical records	Retrospective collection of exposure data may result in recall bias
Exposure	Viral	Viral markers and antibodies	Blood measures required
		Measures for immune response include detection for chronic disease using disease-specific markers or measuring seroconversion	Blood measures required
		Disease severity by immune markers such as viral load	Blood measures required
	Parasites	Presence of microfilaria or circulating filarial antigen	Blood measures required
		Ultrasound detection of adult worms	Medical equipment required
		Hydrocele or spermatic cord thickening (boys only)	Medical equipment and a physical examination needed
		Stool or urine	Biological samples required
		Records (e.g. medical, school)	The infrastructure to obtain these records may not be in place and may require considerable manpower; records may only capture serious infections
	Bacteria	Antibody detection	Blood measures required
	General infection	Records (e.g. medical, school)	The infrastructure to obtain these records may not be in place and may require considerable manpower; records may only capture serious infections
		Health practitioner reports	Retrospective collection of exposure data may result in recall bias
		Guardian reports	Retrospective collection of exposure data may result in recall bias

is expected to be non-differential, this may be of greater consequence in studies of childhood illness where mothers of babies with defects may recall information differentially than mothers of babies without infections.[126] Medical reports are a valuable alternative. The strength of the Hong Kong cohort was that hospital discharge records accounted for 81.4% of all hospital admissions.[80] However, a limitation of medical reports is that they capture serious infections that require hospitalization and physician intervention, missing milder infections. A reduced risk of young adult Hodgkin's lymphoma has been associated with daycare attendance and a greater number of siblings,[127,128] suggesting the importance of non-medical and early-life infectious exposures for the maturation of cellular responses.

Challenges in temporality: the temporal sequence of acquired infections and puberty is critical to understand causality. In a scenario where infection occurs before pubertal development, there are limitations in data interpretation as there are other factors that affect pubertal timing, such as body size and physical activity. Therefore, prospective studies of infection and pubertal timing should include repeat measures of these relevant constructs. Cross-sectional studies, where the timing of infectious exposure relative to the pubertal outcome is unclear, also presents data interpretation challenges. For example, during pubertal development, the body will focus energy on the endocrine system; thereby, the body may exert less energy on the immune system resulting in greater vulnerability to infection. In this scenario, the infection is subsequent to the pubertal outcome.

Challenges in defining infection and a microbial life cycle: infection is a dynamic process involving a varying degree of immunomodulation during the course of a microbial life cycle – which may range to include an exertion of pathogenesis to a commensal state; whereby, the commensal state can be short lived or prolonged.[129] Parasites and bacterial communities are prime examples of microbes living in a commensal state within the human host.[129] The literature is limited in examining the relationship between the microbial life cycle and the hosts' life course relative to puberty. For example, the life cycle of parasitic helminthes, such as schistosomes, are dynamic and within the mammalian definitive host can drive both a proinflammatory and an anti-inflammatory immune response; therefore, eliciting different host responses and host health outcomes.[130,131] Our literature review observed inconsistent findings between parasitic infections (e.g. filarial, trypanosome, schistosome, protozoan) and pubertal outcomes. In addition to the studies collectively having a low-quality assessment via the NOS scale (discussed above), inconsistency could be due to a simplified definition of *infection* that does not delineate phases of the microbial life cycle. Methodologically, the effect between high parasitic infection burden and pubertal development may be real, albeit small, and thus require a robust sample size. Moreover, observed effects may require a robust sample of individuals who are experiencing a phase of the microbial life cycle that garners host immune reactivity that would incite changes in hormonal activity.

While we did not include precocious puberty within our eligibility criteria, of the over 80 studies identified in our search that pertained to infections among populations experiencing either constitutionally delayed puberty or precocious puberty, three studies met our criteria for inclusion in the current review.[132–134] The single study[134] examining the natural history of premature breast development among U.S. girls found no association between this condition and frequency of prenatal general infections. The remaining two studies investigated the prevalence of infections among boys and girls in Turkey[133] and India[132] with delayed puberty. Büyükgebiz *et al.* found an increased prevalence of *H. pylori* infection among children with constitutional delay in growth and puberty ($n = 16$ out of 24, 66%) compared with healthy, age-matched control children with normal pubertal development ($n = 12$ out of 32, 37.5%)[133], and Bhakhri *et al.* observed that the highest etiologic proportion (38%) of pubertal delay in their study population was attributable to functional hypogonadotropic hypogonadism owing to chronic illnesses, including chronic infections.[132] Both of these latter study results are consistent with our hypothesis that the burden of chronic infection delays puberty.

A way forward: in summary, given the intriguing, but limited epidemiological and animal data, we propose suggestions for future studies to explore the role of infection and puberty.

(1) *Studies that carefully measure anthropometry*: teasing apart factors that contribute to earlier pubertal maturation is difficult because childhood obesity exists alongside the changing environment[3,135] and emerging evidence is examining the role of infection as a cause of obesity.[136–138] Epidemiologic studies will need to examine these associations in pubertal cohorts that span the continuum of body size.

(2) *Studies that have measures of additional exposures that are also changing with time*: EDCs and the immune system interact with the endocrine system affecting hormone production;[62–64] therefore, EDCs and infectious exposures could interact synergistically or antagonistically depending on the EDC. Future studies should consider the interaction between exposures to EDCs and infection on pubertal timing.

(3) *Studies that measure home and community environment that may impact both infection exposure and pubertal outcomes*: psychosocial factors contribute to pubertal timing[7] and mounting evidence links the immune and neuroendocrine system.[76] Animal and human studies suggest adaptation to the social environment leads to a complex interaction between immune and reproductive functioning.[114,139] Future studies should examine the complex interaction between the home and social environment (e.g. familial relationships, stress), infection and puberty.

(4) *Studies able to assess multiple pubertal outcomes*: large prospective studies with wide age ranges are most desirable for the study of infections and pubertal timing where the timing of pubertal outcomes and infection are known or adequately approximated and confounders can be ascertained.[1] Including more studies on the association of infection with pubic hair development, pubertal tempo (time between maturational stages) and childhood height would be valuable. Given that shorter adult stature has been associated with later pubertal timing[140] and childhood infections have been shown to impair height,[141–144] future studies should examine infection and pubertal height.

(5) *Studies that assess multiple common infections through diverse measures across windows of susceptibility*: future studies should include a variety of infectious exposures with pre-pubertal measures including diagnostic and biospecimen assessment, medical records and prospective and retrospective health provider and/or guardian reported data. When collecting infectious exposure data, three factors should be considered. First, infection severity should be captured biologically or by infection frequency. Second, timing and type of infection should be considered within windows of susceptibility from birth throughout childhood, including acute and chronic infections and if possible the microbes life cycle, given the different factors that determine infant, childhood and pubertal growth.[145] Third, in populations where infectious exposures are limited, measures should be carefully selected to represent a range of prevalence to adequately test hypotheses.

(6) *Studies that assess the interactions between the endocrine and immunoregulatory systems*: sex steroids not only underlie the physical manifestations of puberty, they also increase years before physical signs that may be attributed to differences in centrally or peripherally produced hormones.[124,146] Studies need to investigate the intersection between the complexities of the endocrine system (with comprehensive sex-hormone measures) and the plausible influence of the

immunoregulatory system. A key consideration here is the use of measures which capture sex hormones comprehensively.

(7) *Animal studies*: the animal literature is scant but generally consistent with the human evidence. Pending results of human epidemiological studies, consideration of animal models to disentangle exposure effects will be needed.

If large studies replicate the intriguing findings that exposure to childhood infections may delay pubertal timing, the impact on public health is clear. There should not be changes to public health policies like vaccinations and sanitation improvements that have reduced the spread of infectious disease, but rather there may be a greater need to discourage excessive environmental sterility and use of antibacterial lotions and products.

Understanding infection across the continuum of maturation can inform whether infant/childhood public health policies, such as vaccinations, or other practices, such as use of antibacterial product use, may affect long-term risk of breast cancer and other hormone-related diseases.[8,9,80,147] The incidence of late-stage breast cancer risk is rising in young women (<40 years)[148] and there is a rise in incidence of testicular cancer, for which pubertal timing is a risk factor.[149] With rapid declines observed in age at onset of breast development and age at menarche remaining relatively stable, pubertal tempo is increasing that may be related to breast cancer.[150] Globally, as countries develop and infectious agents decrease, the age of puberty declines; thus, future research that explores common childhood microbes and the underlying biological mechanisms (i.e. endocrine system) are important to mitigate population-level health risks.[8]

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Conflicts of Interest

None.

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