Title: Adverse effects of early puberty timing in girls and potential solutions

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ABSTRACT

Given the global secular declining trends of the age at puberty and its relevant mechanisms, as illustrated in the first part of this series, the present part will discuss the public health implications of early puberty, and potential clinical and public health measures. Although the major effect of earlier maturation impacts the adolescent's mental health and likelihood of engaging in risky behaviors, there are also effects in adulthood on cardiometabolic health, especially type 2 diabetes, and an increased risk of certain cancers, especially hormone-related cancers, such as breast cancer. The paper ends with recommendations for clinical management, especially those girls who should receive further evaluation, and closes with recommendations for the patient and her family, as well as for public health considerations.

Introduction

The timing of pubertal development has been extensively examined in relation to a wide range of health outcomes. Available studies have been predominantly limited to recalled age at menarche in women. In this second of the two-part manuscript, we have appraised existing findings on the associations between puberty timing on key health outcomes. These include greater likelihood of cardiometabolic disorders, such as higher body mass index (BMI) and adiposity, type 2 diabetes, and ischemic heart diseases; cancer, especially breast cancer; mental illness; and risk behaviors. This paper closes with implications for clinical management.

Cardiometabolic disease risks

A systematic review in 2013 found that 30 out of 34 studies, mostly performed in Western settings, reported associations between earlier puberty timing (age at peak height velocity or menarche) and higher adult BMI in women.[1] In a meta-analysis, early menarche (<12 years) was associated with 0.34 kg/m^2 higher BMI (based on 10 studies) and two times higher risk of obesity (≥30 kg/m^2) (based on 5 studies).[1] Similar associations were observed in subsequent large studies in China and the United Kingdom (UK).[2, 3] Nevertheless, these findings were not adjusted for prepubertal childhood adiposity, likely due to their retrospective study design. In Brazilian birth cohort studies that incorporated childhood size in their analyses, early menarche (≤ 11 years) was associated with higher adiposity at 30 years in the Pelotas 1982 cohort but not with adiposity indicators at 18 years in the Pelotas 1993 cohort.[4] This discrepancy is likely explained by differential adjustment, where the former was adjusted for weight-for-height at 4 years which precedes puberty and correctly represents potential confounding by prepubertal adiposity, but the latter was adjusted for BMI at 11 years, i.e. after puberty onset and is thus a mediator or part of the outcome.[4] Besides

these phenotypic observational findings, one Mendelian randomization (MR) study suggested that earlier age at menarche may be causally associated with higher adult BMI.[5] However, another MR analysis added that the inverse association between genetically predicted age at menarche and BMI at 18 years was fully attenuated after adjustment for BMI at 8 years.[6] Therefore, it appears that the causal effect of puberty timing on subsequent BMI or obesity risk among women remains inconclusive.

Evidence for the associations of puberty timing with cardiometabolic risk factors and diseases in adulthood among women are emerging. Results from meta-analyses of five and eight studies showed that early (≤13 years) (versus later) menarche was associated with higher insulin resistance (measured by homeostatic model assessment) and fasting serum insulin levels, respectively, in both Western and Asian populations.[7] Also, meta-analyses of 17 studies reported that early menarche (mainly ≤11 years) was associated with higher systolic and diastolic blood pressure, and higher hypertension (>130/85 mmHg) risk among women,[8] and these associations may be causal and independent of childhood BMI, as supported by a recent MR analysis.[9] Similarly, meta-analyses of 28 studies showed that earlier age at menarche (as a continuum) and early (<14 years) versus later menarche were associated with higher risk for Type 2 diabetes and/or impaired glucose tolerance.[10] These associations were only partially attenuated when adult adiposity was additionally adjusted for,[10] suggesting that there may be both adiposity- and non-adiposity-related pathways linking early puberty timing to Type 2 diabetes. Furthermore, in a systematic review, eight of twelve identified studies reported associations between early menarche with higher risks for cardiovascular diseases including coronary heart disease, ischemic heart disease, ischemic stroke and hemorrhagic stroke.[11] Overall, each one-year earlier age at menarche was associated with a 2-3% higher relative risk of death from all causes and from ischemic heart disease.[12] These potential causal effects of earlier age at menarche on higher risks for

cardiometabolic outcomes, including Type 2 diabetes, ischemic heart disease and cerebral infarction, are substantiated by a recent MR study that explored the impacts of puberty timing on a wide range of health-related traits.[13]

Risk of cancers

Earlier puberty timing has been linked to increased risk for several cancers. Data from the nationally representative Brazilian Health Survey showed that early age at menarche (≤11 years) was associated with a higher risk (odds ratio 2.45) for any cancer [14]. Using a genetic MR approach, earlier menarche (as a continuum) appeared to be causally associated with higher risks for several sex-steroid sensitive cancers, such as breast and endometrial cancers, and these associations were independent of BMI.[15] Specifically, in MR studies the increased risk of ovarian cancers with earlier age at menarche, may affect certain ovarian cancer subgroups such as invasive epithelial ovarian carcinoma.[16]

The best-described relationship of pubertal timing with cancer is with breast cancer. In a pooled analysis, the relative risk of pre- and post-menopausal breast cancer were 7% and 3%, respectively, lower for each year later age at menarche.[17] Overall, the risk of breast cancer in girls with age at menarche at 15 years or after was only 84% of that in girls with menarche before 12 years of age.[17] There is a greater effect on premenopausal breast cancer, where the risk is 66% if age at menarche is at or greater than 15 years, contrasted to age menarche under 12 years.[17] There are several potential underlying mechanisms, including duration of sex steroid exposure and other growth factors. In the longitudinal LEGACY study, girls with a family history of breast cancer had earlier breast development and slower pubertal tempo, independent of body size and race/ethnicity, suggesting in part a broadened window of susceptibility.[18] In analyses incorporating growth parameters, the age at the peak pubertal growth spurt, and age at reaching adult height, were identified as risk factors for breast cancer,

independent of age at menarche.[19, 20] Another longitudinal cohort study reported that the links between earlier age at puberty (e.g. onset of breast development, age at peak height velocity, and age at menarche) with later breast cancer risk may be explained through higher Insulin-like Growth Factor-1 (IGF1) concentrations, higher lifelong estrogen exposure (with a higher estrogen to testosterone ratio), and an expanded pubertal window of susceptibility.[21]

Mental health and risk-taking behaviors

In addition to disease outcomes in later life, earlier pubertal maturation in girls has been associated with multiple adverse mental health outcomes, greater engagement in risky behaviors and poorer educational achievements during adolescence and early adult life. Reported mental health outcomes include higher risks of depression, anxiety, eating disorders, and antisocial behaviors; risky behaviors include earlier onset of sexual activity, higher number of sexual partners, and higher likelihood of substance use, delinquency, and low academic achievement.[22-25] Some studies have noted that these concerns may be limited to adolescence, although there is also evidence for 'selective persistence' into adulthood and links to adult depression.[3, 23]

Ge and Natsuaki suggested several potential mechanisms to explain the effects of early pubertal timing in girls on psychological and social behaviors, including hormonal exposures, maturation disparity (differences in physical, social, and psychological maturation), contextual amplification (that is, earlier age at the pubertal transition places the girls in a contextual social disadvantage) and accentuation (preadolescent vulnerability and challenges occurring simultaneously with the pubertal transition).[26] Earlier maturation in white girls has been associated with lower self-esteem, in part related to the higher BMI that is typical of early maturing girls.[27] In addition, functional Magnetic resonance imaging (MRI) studies have shown an interaction between relative timing of puberty (early, on-time, late) with stage

of puberty on brain development, including portions of the brain associated with reward processing, possibly mediated by earlier exposure to sex hormones, or by affiliation with peer group.[28] Earlier maturing girls have increased interactions with deviant peers, enhancing their likelihood of risky behaviors.[22, 24] Sexual harassment was one the factors that mediated the association between greater engagement in problem behaviors and depression in early maturing girls.[29] A recent longitudinal study examined pubertal timing in relation to mental health, and found differing relationships by race and ethnicity; white participants had higher rates of depression if maturing early, whereas Latinas had higher rates of anxiety with early maturation.[30] Conversely, Asian participants, who matured later than the other groups, had higher rates of depression and anxiety if they matured late.[30] These findings indicate a complex interplay between puberty timing, race/ethnicity and cultural factors on mental health outcomes. Not all studies have reported adverse outcomes with earlier onset of puberty, and one study suggests that treatment of central precocious puberty may minimize the impact of earlier onset of puberty.[31]

Implications for clinical management

The secular trends towards earlier puberty onset have led to large increases in numbers of girls referred to specialist pediatric endocrine clinics with concerns about early puberty timing.[32] With no change in the incidence of pathological causes, the likelihood of finding such organic causes has decreased and an increasingly large majority of cases have been diagnosed with non-organic (i.e. 'idiopathic') central puberty. Hence, there is a need for a more individualized specialist assessment pathway to avoid very large numbers of normal healthy 6 to 7-year-old girls having to undergo typical invasive and costly investigative procedures (dynamic hormone stimulation tests and MRI brain scans). Instead, in this age group, he more extensive assessments might be better targeted to girls presenting with

unusual features of early puberty (e.g. disconsonant appearance of physical pubertal milestones, such as variance between breast and pubic hair changes by two or more stages or rapid progression of puberty), or with associated neurological symptoms or signs, rather than those with common risk factors for physiological early puberty timing (e.g. overweight/obesity, low birth weight, family history of early puberty timing, or history of immigration from a developing setting).

In addition to evaluating the cause of early puberty, Pediatric Endocrinologists often offer to girls with idiopathic early puberty timing treatments to suppress their reproductive hormonal axis using depot gonadotrophin-releasing hormone agonists (GnRHa). Even when these are appropriately indicated (in young girls with predicted short adult height and/or severe psychological distress), they do not address the underlying drivers for early puberty – as reviewed in our accompanying article – and indeed adiposity and insulin resistance often worsen during such treatment.[33] Recent evidence on the potentially modifiable lifestyle determinants of early puberty timing should inform more holistic approaches, either together with or instead of GnRHa therapy. Such approaches may include dietary changes (to reduce intakes of total energy and protein), promotion of physical activity (regardless of intensity) and insulin sensitization therapy. Their effectiveness would need to be evaluated, especially to understand if any effects on avoiding early puberty or delaying pubertal progression might be independent of changes in BMI.

In a longitudinal study of puberty, Knight et al. noted that a mother's report of anxiety in their pre-pubertal daughters was associated with a greater likelihood of earlier thelarche, although they could not exclude an effect of earlier hormone exposure on the developing brain.[34] The authors suggested a possible intervention by primary care providers through screening for anxiety in childhood. A recommendation for parents of early-maturing girls could be increased parental monitoring (parents accurately knowing where their adolescent is,

with whom, and when they will return). For example, a study reported that greater parental monitoring moderated the association of pubertal timing and alcohol experimentation.[22] Similarly, greater baseline parental monitoring in adolescents with both substance use and psychiatric disorders led to greater improvement in depressive symptoms as well as suicidal ideation.[35]

We noted in the previous article the data supporting earlier onset of puberty with consumption of polyunsaturated fatty acids (PUFA).[36] The cardiometabolic benefits of substituting saturated fatty acids with PUFAs through lowering low-density lipoprotein are recognized, but different types of fatty acids differentially influence the metabolic and physiologic processes due to distinct biochemical properties and pathways.[37] Large-scale studies do not support an increased risk of breast cancer with omega-3 consumption. In separate meta-analyses, increased consumption of omega-3 relative to omega-6 PUFA was associated with lower risk of breast cancer;[38] particularly with marine sources of omega-3 PUFA.[39] Hence, further studies are needed to distinguish the potential differing effects of omega-3 and omega-6 PUFA on puberty timing.

Finally, while the promotion of physical activity and avoidance of excessive total energy intakes are existing public health strategies, most children do not meet the recommended levels for diet and exercise. Future studies should assess whether understanding of their potential impacts on avoiding early puberty timing, regardless of effects on weight and BMI, might increase the motivation of children and their families to achieve recommended levels of lifestyle behaviors.

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