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Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): The European trend

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Abstract

Ever since the publication of the first textbook on human growth by Johann Augustin Stoeller in 1729, temporal changes (or secular trends) in growth and pubertal maturation have been observed throughout the world. Data covering the longest time span are often reported from European populations. For example, in Norway and Denmark the age at menarche has fallen rapidly since the 19th century, by up to 12 months per decade. These changes have broadly paralleled increases in adult height in most European countries over the last century, with rates of around 10–30 mm per decade.

These secular trends are influenced by background ethnic, geographical and socio-economic factors, and clearly nutritional changes have an important role as reflected by positive correlations between age at puberty onset or age at menarche and childhood body size. Changes in height, pubertal maturation, and childhood body size have all also been related to rate of weight gain in infancy, and there is growing evidence to suggest that this early postnatal period may represent an early window of susceptibility to long-term 'programming' of various outcomes in humans.

There is debate as to whether the secular trends in pubertal maturation are continuing or have reached their limit. Even where temporal changes are overall clearly significant, they are most marked in the more nutritionally deprived sub-groups. Whether over-nutrition and increasing childhood obesity will continue to lead earlier puberty is uncertain. The confirmation of an estimated advance in the age at menarche of 6–12 months per 100 years will require a long-term perspective on behalf of current investigators, and new consideration of methodological approaches in an age of increasing recognition of children's rights for privacy.

Keywords: Pubertal maturation; Secular trends; Childhood maturation; Childhood growth

1. Introduction

Wide variations in the tempo of childhood maturation and timing of puberty have important relevance not only for social, behavioural and educational development of the individual, but are also predictive of their longer-term health risks, including obesity, breast cancer, and even mental health (Johansson and Ritzen, 2005; Group, 2004). Therefore, in light of the increasingly described close links between nutrition and the reproductive system, a major question is whether or not the current epidemic in childhood overnutrition and obesity will continue to fuel the population trends towards earlier pubertal onset and progression.

2. Heterogeneous secular trends in puberty

European populations have some of the oldest records of age at menarche, which is the most robust historical marker of the timing of puberty. Those data have shown marked trends towards younger age at menarche over the last 150 years, from mean ages at menarche of around 16–17 years in the mid 19th century (Tanner, 1973). In various countries these advances have occurred at a surprisingly consistent rate of around 3 years for every hundred years (3.6 months/decade).

More recent European data from the last 50 years have showed variable rates of advance in age at menarche (Fig. 1). In several eastern European countries, and in the relatively older data from North-West European countries, rapid rates of advance are seen, similar to the historical rates of 3.6 months per decade. In contrast, for the majority of North-West European countries the trends have slowed or even stopped, as in for example Norway, Belgium and Italy. However, in several of these coun-

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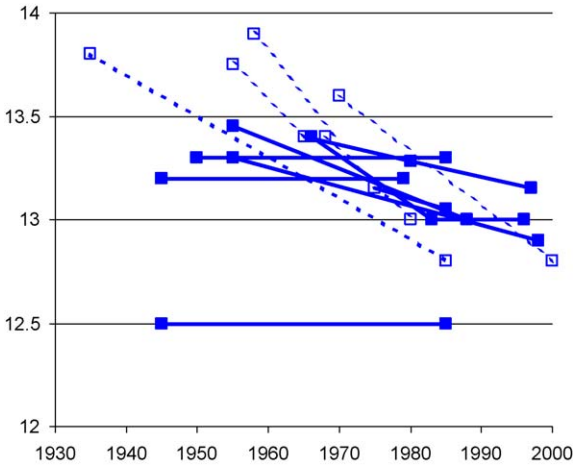

Fig. 1. Heterogeneity in secular trends in age at menarche in Europe. Faster rates of decline (∼3.6 months per decade) were seen in Germany 1958–1975, Netherlands 1955–1965, Hungary 1935–1985, Israel 1968–1980, and Turkey 1970–2000 (open squares and dotted lines) (Ersoy et al., 2005; Chodick et al., 2005; Bodzsar and Zsakai, 2002; Wyshak and Frisch, 1982). Slower rates of decline (∼1.0 or less months per decade) were seen in Germany 1975-, Netherlands 1965–1997, Spain, UK, Denmark, Belgium, Norway, Sweden and Italy (solid squares and solid lines) (Sanchez-Andres, 1997; Mul et al., 2001; Hauspie et al., 1996; Whincup et al., 2001; Liestol and Rosenberg, 1995; Helm and Grolund, 1998; Vercauteren and Susanne, 1985; Lindgren et al., 1991).

tries the data still show relatively slow, non-statistically significant advances in age at menarche of around 1.0 months/decade (roughly 1 year for every 100 years; Fig. 1), which may be significant on meta-analysis, and may also be compatible with current data from the US (Anderson et al., 2003).

Overall, there is much heterogeneity in the more recent European data, with both faster and slower rates of advance in menarche, and this heterogeneity is related to social class, income, urban versus rural background, education, and family size. These are factors that reflect differences in general health and nutrition, and they are also associated with cross-sectional differences in age at menarche, particularly in developing or transforming countries (Parent et al., 2003). Lower socio-economic class or poorer nutrition is associated cross-sectionally with later age at menarche, and also, if nutrition is improving, with faster secular trends or longitudinal rates of decline in age at menarche. For example, across the political and economic transformation of 1989 in Poland faster rates of decline in age at menarche were seen in rural (fell from a mean of 13.88–13.42 years) than in urban populations (13.18–13.04 years) (Laska-Mierzejewska and Olszewska, 2004). Similarly a faster decline was seen among girls with less-educated fathers in Brazil (3.6 months per decade) than in those with better educated fathers (1.2 months per decade) (Junqueira Do Lago et al., 2003), and the fastest rates world-wide are seen in those countries with more recent economic transformations, e.g. in South Korea where the decline from 1920 to 1988 was 4.1 years (7.5 months per decade) (Hwang et al., 2003).

Interestingly, within North-West Europe, these differences were also still present in Denmark between 1950 and 1960, with later age at menarche in poorer textile workers compared to other women, and a strong suggestion that the difference was starting to close in the 1970's (Olesen et al., 2000). A recent report from the large European Prospective Investigation into Cancer and Nutrition (EPIC) study, with individual data on almost 300,000 women aged 35–70 years, showed significant but variable rates of decline ranging from 1 to 4 month per decade in all the nine western European countries studied in women born from 1935 onwards (Onland-Moret et al., 2005). In addition to these between-country differences, within each country the trends often varied with nutritional circumstances, as in France, Germany, and The Netherlands, a sharp increase in the mean age at menarche was seen in women born between 1920 and 1934, corresponding to age at puberty during the second world war, after which steady declines were seen (Onland-Moret et al., 2005). It is likely that wide heterogeneity in the rates of advance in puberty has long existed even among the historical European data, with slower rates seen among those sub-groups with long-standing improved nutrition.

These observations therefore suggest that more rapid rates of decline in age at menarche are currently still seen among less advantaged populations, or population sub-groups, where the mean age at menarche is higher. In addition to average age at menarche, these studies report that variance in the distribution has also become much narrower, and there is some evidence that intra-familial correlations, or the genetic contribution to age at menarche have increased with time (Sanchez-Andres, 1997). The current question is therefore whether all of these trends are leading towards a common target, or so-called genetic limit, beyond which age at menarche will no longer reduce further? And if so, what is the target lower age limit of menarche?

3. A genetic lower limit to age of puberty?

One would predict that in those populations where the secular trends in puberty have slowed, and mean age at menarche is near to the genetic limit, we would no longer see significant cross-sectional associations with socio-economic influences, or 'environmental' factors. In support of this hypothesis, in a large UK-based population study, the Avon Longitudinal Study of Parents and Children (ALSPAC) (Golding et al., 2001) there was no correlation at all between mother's age at menarche, reported by recall questionnaire with replies from over 5000 women, and either social class or mother's highest educational achievement (unpublished data). The mean age at menarche in these mothers, who were born in 1960–1970, was 13 years. However, even among this contemporary UK population with largely 'genetically-determined' pubertal development there was wide individual variation around a normal distribution with standard deviation of 1.7 years. Therefore the concept of a single lower genetic limit of puberty is inappropriate, as the distribution of age at menarche suggests that timing of puberty is determined by a large number of genetic factors, each contributing to a small degree. Similarly, the geography-related decline in mean age at menarche 13–12 years following a North-to-South gradient within Europe (Parent et al., 2003) could relate to variable distribution of these genetic factors. Furthermore, if we consider the large normal range of puberty within each population, a significant proportion of South European girls maybe have menarche at

ages 8–10 year old simply according to their genetic predisposition. This has obvious implications for clinical interpretation of early pubertal development, and the likelihood or pathological causes of early puberty (Kaplowitz and Oberfield, 1999; Viner, 2002), which will likely vary according to the child's population, socio-economic and genetic backgrounds.

4. Secular trends in puberty related to body size?

There is a strong biological basis for links between weight gain, growth and age at pubertal development. Frisch and McArthur hypothesised that there is a lower weight limit below which the reproductive system becomes inactive (Frisch and McArthur, 1974), and several studies have described leptin as a strong candidate link between nutritional status and the onset of puberty (Farooqi, 2002). Both puberty onset and leptin levels are positively related to body size, and body fat mass, however both associations show wide variation, and there are no specific cut-offs for pubertal progression that are generally applicable (Ong et al., 1999). While, other factors are clearly also necessary, 'sufficient' levels of body fat and leptin are likely to be important to 'permit' reproductive development to progress.

It is not surprising therefore to find that childhood growth and body weight are positively correlated with rate of pubertal development in many population surveys (Mul et al., 2001; Davison et al., 2003), and historical trends in puberty often appear to occur at times of increasing childhood and adult height (Hwang et al., 2003). However a recent critical analysis of the historical European data in Europe concluded that there were striking differences in the secular trend in menarche, which has slowed or stopped, and the secular trend in height, which continues (Cole, 2000), as indeed does the trend in childhood overweight (Lobstein et al., 2004; Herpertz-Dahlmann et al., 2003). One explanation given is that the secular increase in adult height is determined only during the first two years of life, as changing socio-economic and nutritional factors resulted in more rapid infancy growth (Cole, 2000).

Cross-sectional studies of the association between childhood overweight and pubertal development are open to potential confounding by reverse causality, i.e. those children could be larger simply because they are in early puberty, or have a more rapid tempo of growth. Temporal associations require much more long-term observations in longitudinal cohorts, and some have been reported (Davison et al., 2003; He and Karlberg, 2001). However, again the association between higher adiposity and pubertal advancement does not prove a causal link; rather both outcomes could be consequent to accelerated maturation of the neuroendocrine system. Even with long-term longitudinal data it may still be difficult to prove the direction of cause and effect, for example if the genetic determinants of puberty also had some early manifestation on the tempo of pre-pubertal growth. He and Karlberg described that rapid gain in BMI between age 2 and 8 years predicted earlier puberty; however children in this group had already shown the fastest gains in length between birth to age 2 years (He and Karlberg, 2001), suggesting that the underlying increase in tempo of growth may already be manifest in the first 1–2 postnatal years.

5. Reproductive brakes and accelerators

The above observation that the pubertal trends are slowing down just at the time when childhood overweight and obesity are increasing could be explained by the concept that current nutritional status or energy balance can only slow down, or apply a brake, to the genetic rate of development, but cannot accelerate it. This brake would be lifted in times of adequate nutrition, to reveal the genetic potential of that population or individual. A strong candidate mechanism for this brake is through central neuropeptide Y (NPY) neurones, which promote appetite and are inhibited by leptin, but also project to the hypothalamus to influence GnRH secretion (Sawchenko et al., 1985; Li and Ritter, 2004). This same mechanism underlies adult hypothalamic amenorrhoea due to eating disorders or intense exercise training; i.e. the brake may be subsequently reapplied during adult life in times of chronic negative energy balance, and recent studies show that leptin administration may lift this brake (Welt et al., 2004).

In contrast to current nutrition status, which can slow down but not advance the free-running reproductive system, it is possible that optimal nutrition during early postnatal life could act as an accelerator of later pubertal development. In population cohort studies rapid early postnatal growth predicts a faster tempo of childhood maturation and earlier puberty (dos Santos Silva et al., 2002), and the chapters by Dunger and Ibanez herewith describe a number of hormonal mechanisms that could mediate this link. There is some epidemiological evidence that markers of more rapid infant weight gain, such earlier birth order and formula milk feeding, are associated with subsequent earlier menarche (Novotny et al., 2003; Padez and Rocha, 2003). Therefore it is possible that current trends towards faster infant weight gain could be the accelerator for continuing, though slower, population advances in age at pubertal maturation.

6. Potential selection and reporting bias

The confirmation of an estimated advance in the age at menarche of 6–12 months per 100 years, as currently seen in Europe and the US, will require a long-term perspective on behalf of current investigators, and accurate methodology in an age of increasing consideration of children's rights for privacy. In addition to age at menarche, there is much data on onset and rate of progression through puberty, based on assessment of physical features. For example the Dutch National Surveys reported an early decline in age at early, mid, and late puberty, followed by more recent stabilisation (Mul et al., 2001). However, even in such large, nationally representative surveys it is difficult to persuade the majority of children to undergo investigator assessment of puberty. In the Dutch National Surveys, only around 50% agreed to puberty examinations. While such data may be very valuable for identifying factors related to pubertal onset and development, the poor response rates makes it difficult to judge whether differences between each survey may be real or due to selection bias. One could imagine that young subjects with relatively early onset puberty, or older children with absent features of

puberty, could be particularly embarrassed, and decline to participate.

Selection bias, where the reason for selection or drop-out is directly related to the outcome measure, is a potential major, and probably undetectable, concern. Even with self-reported menarche, Artaria and Henneberg found that more educated girls showed a reporting bias against premenarcheal status, possibly in order not to appear to immature, and this was only detected by comparison with their future reassessment (Artaria and Henneberg, 2000). Differences in local geography and migration could also introduce selection bias due to differences in frequency of common genetic factors.

One method that overcomes the issue of selection bias is to study differences in reported age at puberty development or menarche between parent-offspring pairs. Interestingly all three published contemporary studies of age at menarche using this method, from Spain, Turkey, and South Africa, found a similar significant decline in age at menarche, at an 'intermediate rate' of around 2.4 months per decade, which is half-way between the historical and the more recent rates of decline reported from the longitudinal surveys (Sanchez-Andres, 1997; Ersoy et al., 2005; Cameron and Nagdee, 1996). Ideally, further and more widespread studies using such intra-familial comparison would be needed to confirm whether secular trends in age at menarche have indeed stopped.

In addition to selection bias, there are well-known difficulties in the assessment of physical markers of puberty status. In particular, in boys non-palpation or self-rated assessments are complicated by the lack of clear physiological demarcations between stages. Similarly in girls it may not be possible to differentiate between early puberty and simple obesity without palpation of breast buds, nor to distinguish between true puberty and isolated thelarche. It is therefore necessary to develop and validate other robust and acceptable markers of pubertal development.

Blood levels of sex hormones is one possibility to confirm or complement self-rated assessment of puberty in both boys and girls. In the Chard, UK longitudinal study, normal schoolchildren had pubertal status assessed 6-monthly by medically trained observers using non-palpation (Ahmed et al., 1999). Unpublished data from that study show that there was a strong correlation between sex hormone levels and puberty stage, and in particular in boys there was a reasonably clear demarcation between Tanner stages 1 and 2 in testosterone levels, and in girls with estradiol levels (Fig. 2). Difficulties for more widespread use of sex hormone levels for comparison of population studies may include differences or temporal drift in assays and the specificity of the antibodies used.

Finally, reported voice breaking could be an alternative assessment in boys. Formal assessment of boys' speaking voice using laryngography shows a sudden drop in frequency between Tanner stages 3 and 4 (Harries et al., 1998) and assessment of frequency combined with intensity of the singing voice (or phonetogram) showed a significant relationship with SHBG levels in a small pilot study (Pedersen, 1993).

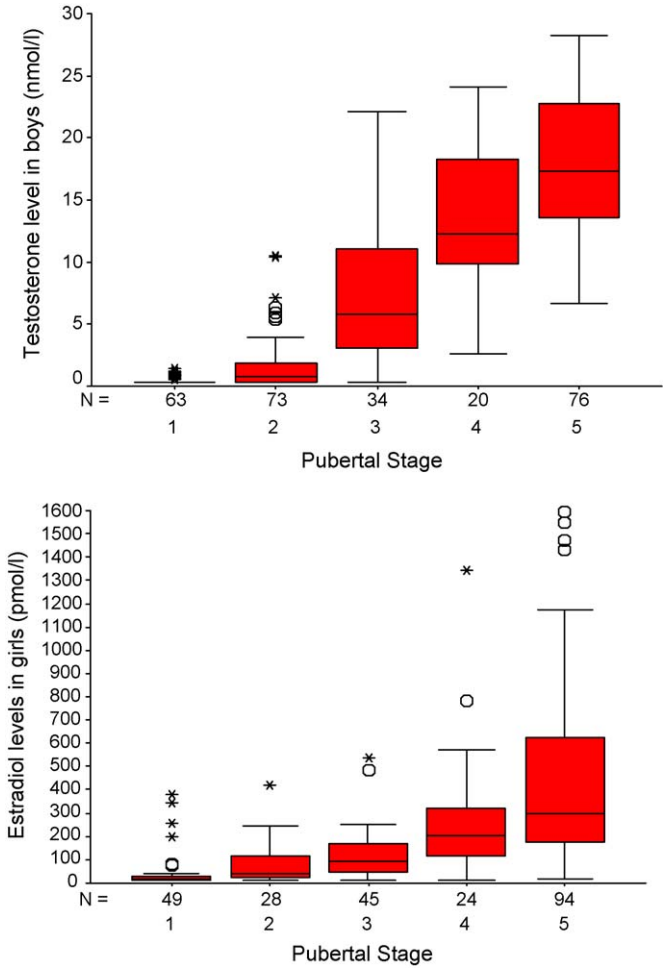

Fig. 2. Plasma testosterone levels in boys and estradiol levels in girls, by pubertal stage, in the longitudinal Chard study, UK. Boxes represent the inter-quartile range for each category; the median line, whiskers (the largest and smallest observed values that are <1.5 box lengths from either end of the box), outliers ("O": between 1.5 and 3 box lengths from the end of the box), and extremes (>3 box lengths from the end of the box) are also displayed. We thank Dr Les Perry, Dept of Clinical Biochemistry, St. Bartholomew's Hospital, London, UK for performing the hormone assays, and Professor Michael Preece, Institute of Child Health, University of London, for providing the data.

7. Conclusions

Change in the timing of puberty remains an area of great interest, not only to clinicians and research biologists, but it also impacts social and educational policies. Broad statements that trends have stopped in Europe are unhelpful, as trends appear to continue in many populations wherever nutrition and socio-economic conditions have been sub-optimal, but have recently improved. There is no single physiological lower limit of puberty, but rather a wide normal distribution in age at menarche is seen, likely reflecting the effects of multiple common genetic factors. Identification of a 'population average' lower limit of menarche will require ongoing long-term analysis, including consideration of early growth data in order to explore the potential promotional effects of infant nutrition on programming of puberty and longer-term health risks. Future identification and validation of specific genetic factors related to timing of puberty

could allow the development of individual-specific genetic normal ranges for puberty; and gene-environmental interactions could raise the possibility that some individuals could be more susceptible than others to the inhibitory or promotional effects of nutrition on puberty.

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