

W Adolescent Health 1

Pubertal transitions in health

George C Patton, Russell Viner

Lancet 2007; 369: 1130–39

Published Online

March 27, 2007

DOI:10.1016/S0140-

6736(07)60366-3

See [Comment](#) page 1057

See [Perspectives](#) page 1075

This is the first in a [Series](#) of six papers about adolescent health

Murdoch Childrens Research Institute, Department of Paediatrics, University of Melbourne, Melbourne, Australia (Prof G C Patton); and General and Adolescent Paediatric Unit, Institute of Child Health, University College London, London, UK (R Viner)

Correspondence to:

Prof George C Patton, Centre for Adolescent Health, William Buckland House, 2 Gatehouse Street, Parkville, Victoria 3052, Australia
george.patton@rch.org.au

Puberty is accompanied by physical, psychological, and emotional changes adapted to ensure reproductive and parenting success. Human puberty stands out in the animal world for its association with brain maturation and physical growth. Its effects on health and wellbeing are profound and paradoxical. On the one hand, physical maturation propels an individual into adolescence with peaks in strength, speed, and fitness. Clinicians have viewed puberty as a point of maturing out of childhood-onset conditions. However, puberty's relevance for health has shifted with a modern rise in psychosocial disorders of young people. It marks a transition in risks for depression and other mental disorders, psychosomatic syndromes, substance misuse, and antisocial behaviours. Recent secular trends in these psychosocial disorders coincide with a growing mismatch between biological and social maturation, and the emergence of more dominant youth cultures.

Puberty is initiated in late childhood through a cascade of endocrine changes that lead to sexual maturation and reproductive capability. Human puberty is accompanied by major physical growth and substantial brain maturational changes, features that are unique in the animal world.¹ Its consequences for health and wellbeing are profound and paradoxical. On the one hand, physical maturation propels an individual into adolescence with peaks in strength, speed, and fitness. Yet puberty also triggers emotional, cognitive, and behavioural changes. Aristotle's comment that "Youth are heated by nature as drunken men by wine" has been echoed through the ages. Today, these changes lie behind the increased mortality and morbidity from accidental and intentional injuries, suicide and mental disorders, substance abuse, and eating disorders in young people.

Puberty

Puberty begins with the poorly understood activation of a complex neuroendocrine network, quiescent since neonatal life.² Sexual maturation (gonadarche) is initiated with the pulsatile nocturnal release of gonadotrophin

releasing hormone from a small number of specialised hypothalamic neurones that in turn leads to the pituitary release of follicle-stimulating hormone and luteinising hormone. The resulting gonadal growth and production of gonadal sex steroids bring about the development of secondary sexual characteristics.²

Preceding and independent of the hypothalamo-pituitary-gonadal axis, the production of adrenal androgens increases from around age 6–8 years in a process known as adrenarche, unknown in species other than human beings and chimpanzees.³ These androgens have a role in the development of axillary and pubic hair and contribute to the emergence of acne. The evolutionary significance of adrenarche is unclear, but evidence suggests that its timing might affect risk of physical and mental health problems.⁴

In this paper we will use the term puberty to encompass the changes following gonadarche and adrenarche, as well as less well-characterised biological changes. These include the maturation of the growth hormone-insulin like growth factor and thyroid axes that lead to the pubertal growth spurt and achievement of adult height, maturation of many organ systems, and changes in blood lipids, haematological indices, and enzyme systems, including liver cytochrome P-450 systems. Changes in the regulation of oxytocin and vasopressin are associated with altered patterns of social interaction and attachment.

Puberty can therefore be considered as an interconnected suite of changes with wide individual variations in the sequence and timing of its components.⁵ A system of reliable staging of the external signs of puberty was developed by Marshall and Tanner in the 1960s.^{6,7} The earliest external changes—breast buds in girls and enlargement of testicular volume to greater than 4 mL in boys—appear at the mean ages of 11.0 years and 11.1 years, respectively, in the UK (figure 1). Despite the similar age of gonadarche in both sexes, these early changes have greater visibility in girls than in boys, coupled with an earlier onset of the growth spurt.

Search strategy

The aims in this review were to consider the role of puberty and pubertal timing on the course of pre-existing childhood health problems, the initiation of adolescent health problems, and risk for illness later in life. We searched the MEDLINE, PsychLit, and Embase databases (1996 to December, 2005 for each). We used the terms "puberty", "menarche", and "age factors" in combination with: "depression", "mental disorders", "substance-related disorders", "child behavior disorders", "obesity", "anorexia nervosa", "bulimia nervosa", "attention deficit with hyperactivity", "headache", "migraine", "asthma", "constipation", "enuresis", "asthma", and "chronic illness". We selected publications from the past 10 years but also included commonly cited and seminal papers published earlier.

Menarche, often seen as the defining element of female puberty, occurs in late puberty, about 2·0–2·5 years after breast budding. In boys, no such easy signifier exists, although spermaturia and first ejaculation occur from about age 13–14 years. Puberty is generally complete over the 2–4 years after gonadarche, but other changes induced by sex steroids, including sexually dimorphic patterning of fat and muscle, continue throughout adolescence. For boys, puberty-initiated physical changes, such as androgenic patterns of hair growth and loss, continue well into old age.

Pubertal timing

The 4–5 year variation in age of onset of puberty among healthy individuals is a physiological peculiarity of man and is observed even where living conditions are similar for all members of a group.⁸ This variation reflects a strong genetic component, with nutrition, psychological status, and socioeconomic conditions having additional effects.^{8–10} Pathological pubertal delay is most commonly associated with chronic illness, stress, and undernutrition. Precocity is more commonly reported in females and is generally a consequence of premature activation of the hypothalamo-pituitary-gonadal axis, sometimes secondary to neoplasia.⁸ It can also arise from autonomous gonadal hormone production. Premature adrenarche in girls can be a forerunner of the polycystic ovary syndrome and its associated metabolic consequences.¹¹

Change in pubertal timing, as indicated by a falling mean age of menarche during the twentieth century in most developed and developing countries, has attracted much attention.^{8,12} The mean menarcheal age is now 12–13 years in most developed countries, with minor variations.⁸ This secular trend ceased in most developed countries after the 1960s, but concerns were re-ignited in the late 1990s with the publication of American studies^{13,14} that suggested a sudden fall in the age of onset of puberty in girls and boys. A possibility loomed of ever-younger children entering puberty, exacerbating the modern pattern of young people developing biological reproductive capability well before psychosocial maturity.¹⁰ However, little evidence exists to support claims of a recommencement of the secular trend outside the USA in developed countries.^{2,8,15,16} Indeed, studies done after 1960 show a modest increase in menarcheal age in northern European countries including the UK, Sweden, and Belgium (0·14, 0·05, and 0·03 years per decade, respectively).⁸ Well-observed studies of large Dutch¹⁷ and Danish¹² cohorts show no change in the age of puberty or menarche from the 1960s to 1990s, despite a substantial increment in height over this period. The published US findings might well reflect selection and misclassification bias in studies not specifically designed to assess trends in pubertal timing.^{2,15} In short, the mean age of menarche seems to have stabilised at around 12–13 years in well-nourished populations, an age that evolutionary theorists suggest is biologically appropriate, because it is about the

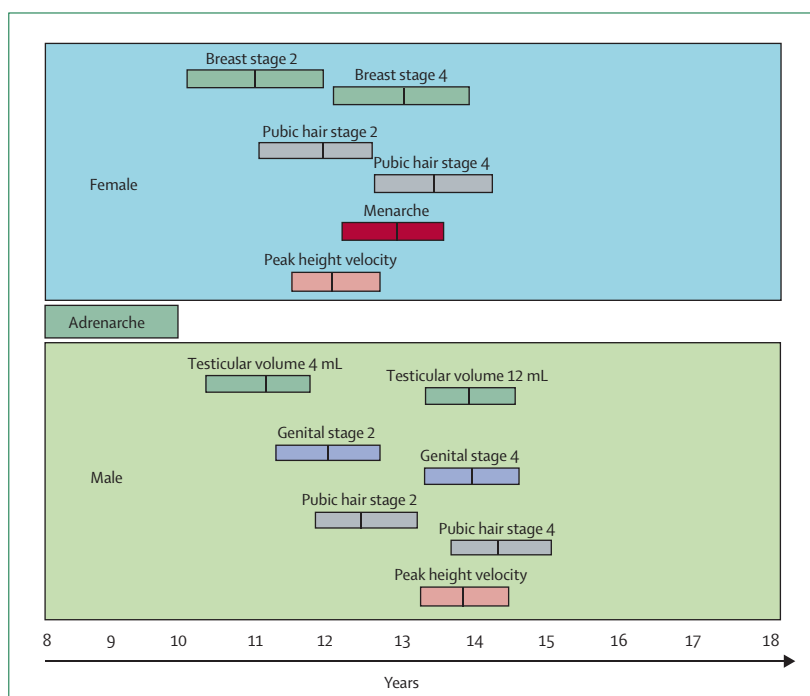


Figure 1: Pubertal timing in UK adolescents (1990)

Bars show 75th and 25th centiles for entry into pubertal stages.

same as that estimated for that of early hunter-gatherer *Homo sapiens* (figure 2).¹⁰ The much later menarche seen in the more recent past may be an artifact of poor nutrition as a result of population growth that followed agricultural settlement.

Puberty and adolescent development

Early adolescent theorists built on Haeckel's view that individual development (ontogeny) recapitulates evolutionary development (phylogeny). Puberty was typically considered as the trigger to a biologically driven phase of inevitable emotional turmoil¹⁸ with biology driving psychological and social development.^{19,20} It is now clear that broader social processes define adolescence, not least because its form varies so widely across societies and cultures. In pre-industrial societies the adolescent transition from puberty to adult roles, as defined by the onset of sexual activity, marriage, and parenthood, ranged from around 2 years in girls to 4 years in boys.¹⁰ In today's developed economies, longer periods in education, increased affluence, and the availability of effective contraception means that adolescence commonly persists for well over a decade.¹⁰

Current concepts of adolescence typically encompass a biological onset at puberty and highly variable social transitions that mark its completion. The biological processes initiated at puberty interact with the social context to affect an individual's emotional and social development.^{21–23} The modern pattern for mature reproductive capacity, as well as sexual activity, to

precede role transitions into parenthood and marriage by more than a decade is exceptional in human history (figure 2).^{24,25} An accompanying rise in number of sexual partners prior to marriage has been linked to changing patterns of sexually transmitted diseases. So, too, the delay in taking on mature social roles and responsibilities in marriage, parenthood, and employment, tied with earlier initiation of substance use, has been linked to rises in mental disorders and substance abuse in young people.²⁶

Although emotional turmoil is a far from inevitable consequence of puberty, there is evidence that puberty affects early psychosocial development.²⁷ Male individuals who reach puberty later than their peers are often less assertive and popular.^{28,29} and late in engaging in sexual activity.³⁰ By contrast, early puberty in females is associated with emotional and behavioural problems and early sexual activity.³¹

The effects of puberty on behaviour are evident in findings from animal studies, particularly in primates. They include altered social interactions with peers, sometimes accompanied by conflicts with parents as well as behaviours characterised by sensation-seeking and risk taking.^{32,33} Pubertal changes in the regulation of oxytocin in females and vasopressin in males have been linked to social attachment, pair-bonding, and parental behaviour across species.³⁴ Such cross-species conservation of adolescent typical behaviours³⁵ suggests their relevance for reproductive success, perhaps by facilitating migration away from genetically related adults and building a social network to support offspring.³⁶ However, no other species shows the

complexity of changes in brain seen in humans nor the repertoire of behavioural changes. These behavioural changes are in turn greatly affected by the socio-cultural and economic milieu in which humans mature.¹ For these reasons findings from the study of rodents and even non-human primates may be less applicable to humans.

Brain changes

Many brain changes take place during adolescence. Some precede and initiate puberty. Others continue for around a decade beyond. Yet gonadal hormones affect a wide range of neuronal processes: neurogenesis, dendritic growth, synapse formation and elimination, apoptosis, neuropeptide expression, and sensitivity of neurotransmitter receptors.³⁷ Sex differences in brain development during puberty might reflect the different effects of male and female gonadal hormones. Frontal lobes, which are involved in planning, organising, and executive functions, reach a peak thickness at 11·0 years in girls and 12·1 years in boys.³⁸ These changes result from increased dendritic branching rather than increasing neuronal numbers. Similarly, parietal lobe grey matter reaches a peak at 10·2 years in girls and 11·8 years in boys.

Early studies of the effects of gonadal hormones on brain function focused on the hypothalamus and other regions directly involved in reproduction. Later studies, however, also showed effects on the hippocampus, striatum, cerebellum amygdala, and cerebral cortex. Three known oestrogen receptors mediate effects on cholinergic, noradrenergic, serotonergic, and dopaminergic neurotransmitter systems. The functions affected include cognitive abilities, aggression, affect regulation, learning, and memory.^{37,39}

Gonadal hormones affect many pubertal changes in social interaction, sexual drive, attachment, and responses to stressors.³⁹ Animals show an increased response of adrenocorticotrophic hormone to stress in females in early adolescence, a process that is partly mediated by ovarian hormones.⁴⁰ In human beings there is also some evidence for pubertal changes in sex-specific responses to stressors, with men showing greater hypothalamic-pituitary-adrenal reactivity to achievement challenges and women to social rejection.⁴¹

A range of factors beyond gonadal hormones—genetic effects, nutrition, and sensory inputs—also seem to be involved in pubertal brain changes. Stress during puberty and early adolescence may affect brain development and vulnerability to psychopathologies of different kinds.³⁹ Conversely, enrichment of the social and learning environment in peripubertal rats can reverse many of the adverse effects of early maternal separation.⁴² This evidence of greater neural plasticity around puberty and persisting changes in neural function as a result of early adolescent experiences has major implications for health promotion.⁴³

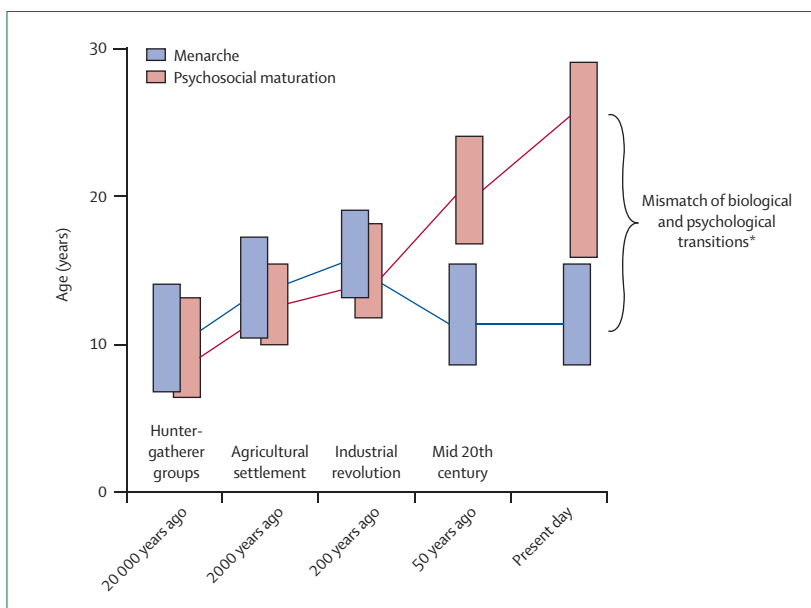


Figure 2: Changing relation between probable range of menarcheal age and psychosocial transitions into adulthood

Adapted from Gluckman and Hanson.¹⁰ *Psychosocial transitions range from first sexual activity through to marriage and parenthood

A possibility that behavioural problems arise because of a mismatch between the emotional reactions and cognitive capacities of young adolescents has long interested clinicians. Early studies of so-called off-time puberty commonly cited emotional immaturity, perhaps compounded by peer rejection, as the basis of the increased emotional and behavioural problems of early developers.^{44,45} The more recent understanding that neurodevelopment continues into early adulthood, especially in regions linked to regulation of behaviour and emotion, has again heightened interest in an idea that difficulties in emotional and impulse control in younger adolescents are the result of brain immaturity. A reduction in grey matter in the pre-frontal cortex and expansion of cortico-cortical communication continues into the third decade of life.^{46–48} These changes correlate with the development of self-control and mature judgement, yet continue for more than a decade after puberty brings profound emotional and behavioural shifts. The importance of this biological gap might now be accentuated by later marriage and parenthood, social transitions that have historically been linked to maturing out of problem behaviours. The clinical relevance is evident in the early adolescent rise in deliberate self-harm, which peaks at around age 15 years in girls. Pubertal changes in depressive symptoms, substance misuse, and sexual activity are linked to the early adolescent increase in self-harm, but advancing age, a possible marker of brain maturation, is associated with a reduced risk of this problem.⁴⁹

Chronic physical illness

General paediatric wisdom has maintained that many of the commonest childhood conditions, such as asthma and other atopic conditions, chronic constipation, and primary nocturnal enuresis, remit in early adolescence. Children were thought to outgrow these conditions due to maturation of the autonomic and central nervous systems under the effect of sex steroids during puberty.^{50,51} However, data to support these clinical assumptions are scant. Puberty does not predict remission of asthma, and nearly two-thirds of children with chronic asthma have persistent symptoms throughout puberty.⁵² Chronic constipation persists into young adulthood in at least a third of individuals.⁵³ The prevalence of enuresis declines from 10% at age 7 years to 1% at 15 years, but no published studies have formally assessed the association between enuresis and puberty.⁵⁴

However, evidence suggests that early puberty is an independent risk factor for the persistence of asthma into adolescence and severity of asthma in adulthood.⁵⁵ The mechanism is unclear, and might reflect hormonal effects on reactivity of airways or common environmental risk factors for both asthma and early puberty.⁵⁶ Such evidence is not available for enuresis or constipation; the only longitudinal study to examine puberty in relation to constipation suggests that remission or

successful treatment was related to neither pubertal timing nor status.⁵³

Sex differences in chronic physical illnesses alter during puberty. The peak age of onset of type 1 diabetes is in the early pubertal years in both sexes, possibly due to the metabolic demands of growth and to heightened insulin resistance during puberty. However, this peak is about 2 years earlier in girls than in boys.⁵⁷ In many other autoimmune conditions, such as systemic lupus erythematosus, autoimmune thyroid conditions, and juvenile rheumatoid arthritis, puberty coincides with a rise in prevalence and a marked shift in sex ratio towards female.⁵⁸ A similar shift to female predominance at puberty is seen in atopic conditions. These differences between the sexes might arise from the different effects of oestrogen and testosterone on the initiation or course of underlying autoimmune processes.^{59–61}

Attention deficit hyperactivity disorder, antisocial behaviour, and substance misuse

Until two decades ago, a dominant clinical view was that attention deficit hyperactivity disorder (ADHD) remitted during the transition to adolescence. Findings of recent studies of children with ADHD at puberty have challenged this view. Antisocial behaviour, substance misuse, and academic failure become more prominent during adolescence in individuals with ADHD, and psychostimulants remain useful in the treatment of adolescents with childhood-onset ADHD.^{62–64} A decrease in the proportion of individuals meeting diagnostic criteria for ADHD does occur in adolescence as the mean levels of hyperactive, impulsive, and inattentive behaviours drop, but whether this fall reflects a fundamental change in the underlying disorder is unclear.⁶⁵ No studies have examined the effect of puberty compared with age on symptoms of ADHD.

Evidence is more consistent that puberty is linked to antisocial behaviour and delinquency, with boys who mature early having increased rates of antisocial behaviour.^{66,67} More recent findings have emphasised the effects of pubertal status rather than age on risk for violent crimes, property damage, and precocious sexual behaviour.⁶⁸ This effect seems to be more prominent in boys with delinquent and antisocial friends, suggesting that advancing pubertal stage brings either a change in peer group or a greater susceptibility to peer influence.

Substance use and misuse rarely occur before puberty. With downwards secular trends in the age of initiation for many substances, the early teens now commonly herald the onset of substance use and misuse.^{69–71} Substance misuse is associated with risky sexual behaviour and injuries in teenagers, and strongly predicts substance misuse and dependence in adulthood.⁷² Puberty was first implicated by the finding that girls who matured early had increased use of tobacco and alcohol.^{31,70,73} Conversely, late maturation was associated with persisting abstinence, a difference that continues

into young adulthood.^{74,75} More recent findings indicate that pubertal stage holds an association with use of tobacco, alcohol, and cannabis that is independent of age.⁷⁶ Links with substance misuse seem to be even stronger, with late puberty associated with a three-fold increase in rate of such problems.⁷⁶ The most widely accepted explanations for the association of pubertal stage and substance use concern altered patterns of sensation-seeking or differential peer affiliation with substance users, or both, in individuals who reach puberty early.⁷⁵⁻⁷⁷ This pattern might be equivalent to the increases in novelty seeking, orientation to adult stimuli, and sensitivity to social status found in peri-adolescent animals.⁷⁸⁻⁸⁰ Since early puberty is not associated with increased substance use in adult life, it is possible that the association of early puberty with substance use does not persist beyond adolescence.⁸¹

Depression and anxiety

Differences between the sexes in internalising emotional disorders characterised by depression and anxiety appear in early adolescence.⁸² Such disorders commonly persist into adulthood, so that the early adolescent rise in female depression largely accounts for the persisting higher rates of depression in women than in men throughout the reproductive years.⁸³ Evidence of increases in overall prevalence in recent decades suggests that sociocultural influences have a role in development of these disorders in adolescence.⁸⁴

The study of depression in adolescence and any link with puberty was overlooked in early epidemiological research, partly because adolescent emotional disturbances were seen as transient and universal, and depression as a distinct disorder of adulthood. In fact, depressive symptoms in girls shift markedly in early adolescence so that by the mid-teens, rates of depressive disorder are over two-fold higher in girls than in boys.^{85,86} Panic attacks are also rare before puberty, but increase markedly in girls with pubertal development.⁸⁷ Early explanations emphasised the different consequences of puberty with more negative psychological reactions to bodily changes or more difficult transitions in social and sexual roles in girls than in boys.⁸⁸ Altered responses of post-pubertal girls to adversity, including a propensity to ruminate and adopt self-blaming coping styles were further possible factors.⁸⁹⁻⁹² Certainly conflict and an absence of closeness with parents, as well as difficulties in adjustment to secondary school and peer victimisation, seemed to be linked to depression in girls.^{93,94}

Earlier findings showed inconsistent associations between gonadal and adrenocortical hormones and internalising symptoms in girls, but study power was limited in many instances.^{23,95} With convincing evidence that advancing pubertal stage rather than chronological age accounts for the early adolescent rise in female depressive symptoms, the role of pubertal biological changes again came into focus.^{83,96,97} Changing concentrations of gonadal

hormones parallel the change in depression across pubertal stage independent of altered body morphology, timing of pubertal change, or levels of stress.^{97,98} However, an absence of association between depressive symptoms and menarche in African-American and Hispanic or Latino young people suggests that sociocultural context might be an important moderator of the association.⁹⁹

A recent finding that peak dehydroepiandrosterone concentrations predict later major depression in a group at high risk because of life events and temperament has raised a question about whether pubertal changes in the hypothalamic-pituitary-adrenal axis are also implicated in the altered risks for depression in early adolescence.¹⁰⁰ Pubertal changes in the regulation of oxytocin and vasopressin might also be relevant through promotion of heightened need for affiliation in girls compared with boys.¹⁰¹ These physiologically driven processes might then interact with genetic, social, and psychological vulnerabilities to give rise to depressive symptoms. Pubertal changes in affective arousal might interact with neurobiological development and the loss of social controls traditionally associated with earlier marriage and parenthood to explain the upsurge in early adolescent depression. This early adolescent gap in emotional regulation is likely to be particularly acute in social contexts characterised by family conflict, divorce, or peer violence and rejection.

Other mental disorders

Incidence of psychotic disorders markedly increases during the post-pubertal years, more evidently in boys than in girls. A possibility that puberty stimulates pathological brain development in individuals with antenatally acquired brain abnormalities underlies neurodevelopmental hypotheses of schizophrenia.¹⁰² The later age of onset for schizophrenia in girls might arise from the different effect of male and female gonadal hormones on brain development.¹⁰³ Consistent with this hypothesis is the observation that early menarche predicts later onset of schizophrenic symptoms in females.¹⁰⁴

Eating disorders are rarely seen before puberty and are marked by differences between the sexes in prevalence from early adolescence. Anorexia nervosa is uncommon in childhood but rises steeply in early adolescence in girls with a peak age of onset around 14 years. Pubertal stage seems to be more important than age as a predictor of subclinical bulimia nervosa, disordered eating, and abnormal eating attitudes.¹⁰⁵⁻¹⁰⁷ For this reason, early developing girls are more likely to have symptoms of eating disorders than are late developers. Speculation has centred on the pubertal increase in body fat contributing to body dissatisfaction and use of dieting, a major risk factor for eating disorders in post-menarcheal girls.^{108,109} No association has been reported between anorexia nervosa and menarche or other indices of pubertal stage, but the power of available studies to find such an association has been limited.¹¹⁰

Disorders of gender identity typically emerge around age 3–4 years, but undergo dramatic shifts across puberty. The majority of prepubertal gender identity cases do not persist into adolescence. Once past puberty, the likelihood of gender dysphoria persisting is high, although some further shifts may occur through to late adolescence.¹¹¹ Although the cause of gender identity disorder remains unclear, it has been suggested that gonadal hormone changes at puberty bring completion of a process of CNS reorganisation that began in prenatal life.¹¹² However, current understanding of the role of puberty in the development of gender identity and its disorders are limited.

Epilepsy

Frequency of seizures in women with intractable epilepsy changes across the menstrual cycle in response to changing concentrations of oestrogen, which lowers seizure thresholds, and progesterone, which has the reverse effect.¹¹³ These effects prompted investigation of changes in epilepsy around the time of menarche. Retrospective studies of patients with ongoing epilepsy suggest that seizures commonly worsened at around menarche in girls.¹¹⁴ Some retrospective studies have also shown that rates of seizure onset are higher within 2 years of menarche^{114,115} but this has not been so in all series.¹¹⁶ To date, no prospective study has been done of either the course of childhood onset epilepsy or incident seizures across pubertal stage.

Musculoskeletal disorders, pain and somatic symptoms

The pubertal growth spurt, which is unique to *H sapiens*, might contribute to musculoskeletal morbidities in adolescence. Bone mineral accretion accelerates during puberty under the influence of gonadal steroids, with peak bone mass achieved by the early 20s.¹¹⁷ Delayed puberty and low weight during puberty can impair bone mineral accretion, leading to osteoporosis and increased fracture risk. So-called growing pains are common in younger adolescents.¹¹⁸ Major musculoskeletal problems such as adolescent idiopathic scoliosis and slipped capital femoral epiphysis are linked to peak growth velocity during puberty.^{119,120} Other poorly studied conditions seem to have a peak onset around puberty, including Scheuermann's disease, Osgood-Schlatter's disease, and osteochondritis dissecans, which can increase risk of chronic musculoskeletal pain in adult life.¹²¹

Several common pain syndromes begin or worsen in early adolescence. Migraine and tension headaches are commoner in women than men during the reproductive years, a pattern that emerges from around age 11 years and is linked to puberty.^{122–124} The early adolescent increase in back, facial, and stomach pains is associated with pubertal status in both sexes.^{125–127} It therefore appears that pain, pain perception, or both, are affected

by puberty. Possible mechanisms include physical stresses associated with the pubertal growth spurt, a heightened attentiveness to somatic symptoms as a consequence of rapid physical growth, and heightened post-pubertal negative affect in girls leading to a greater awareness of somatic symptoms.^{125,128} Gonadal hormones may be directly involved in altering pain thresholds, consistent with the observation of fluctuations in pain perception throughout the menstrual cycle in adult women.¹²⁹

Obesity, polycystic ovarian syndrome, and cardiovascular risk

Childhood body fat affects the timing of puberty in a sexually dimorphic pattern, with an association between higher body-mass index (BMI) and earlier onset of menses in girls.¹³⁰ A suggestion that rising childhood obesity has driven a reduction in the age of puberty in the USA¹³¹ seems unlikely, since increasing childhood obesity has not brought change in the timing of puberty elsewhere.^{132,133} Whereas boys with higher BMI are more likely to have pubertal delay,¹³⁴ in girls obesity is associated with earlier adrenarche and puberty, and with early development of polycystic ovarian changes.¹³⁵ The features of polycystic ovarian syndrome commonly emerge around menarche and include hyperandrogenism, menstrual irregularities, an elevated ratio of luteinising hormone to follicle-stimulating hormone, and polycystic ovaries on sonography. This syndrome is the commonest cause of female infertility and is strongly linked with the metabolic syndrome and with premature and excessive mortality in the long term.¹³⁶ The emergence of polycystic ovarian syndrome during pubertal transition is thought to be related to maturation in the pattern of luteinising hormone secretion, and the typical pubertal increase in insulin resistance.¹¹

Pubertal timing seems to affect cardiovascular risk separately from BMI. Women who report early menarche have an increased BMI in adolescence and adulthood independent of childhood BMI.¹³⁷ Some evidence exists of a similar association in men.¹³⁸ Blood pressure and lipid profiles seem to be more strongly associated with pubertal stage than with age and body size during adolescence, so that in boys early puberty leads to an earlier transition to male lipid patterns.¹³⁹ Intriguingly, individuals with advanced puberty at age 15 years in the 1946 British birth cohort study¹⁴⁰ had a mean adult blood pressure 6·4 mm Hg higher than that of individuals with minimal or no signs of puberty at that age. It is unclear whether this association reflects different pre-existing biological risks or differences in health-risk behaviour in those with early puberty.

Cancer

Early puberty has been linked to cancer in later life through several mechanisms. Longer duration of exposure to gonadal steroids might increase the risk of steroid-

dependent cancers such as breast¹⁴¹ and ovarian cancer¹⁴² in women, and possibly prostate cancer in men.¹⁴³ Increased rates of obesity in early developers might heighten oxidative stresses (hyperglycaemia, hyperleptinaemia, increased lipid concentrations in tissue, inadequate antioxidant defenses, increased rates of free radical formation, enzymatic sources within the endothelium, and chronic inflammation) that raise risks for a range of cancers.¹⁴⁴ Hyperinsulinaemia might also promote cell growth to increase risks for colon cancer.¹⁴⁵ There is also a possibility that behaviours associated with cancer, including smoking and poor diet, might differ in those with early puberty, thus affecting future risks of the disease.

Conclusions and implications

Human puberty probably evolved its unique qualities to ensure that an individual possessed the necessary physical, emotional, and social qualities to ensure successful mating and parenting in primitive social groups. Those characteristics included rapid physical development and a readiness to develop attachments outside the immediate family group. The social context of modern industrialised society differs greatly from what prevailed during human evolutionary history. A delay in social role transitions into marriage and parenthood has occurred at a time when a more dominant youth culture, likened to a “super-peer”, has had a profound influence on the lifestyles of youth.¹⁴⁶ To the extent that industries from entertainment and fashion to food market through youth culture, so too they will have a major influence on youth lifestyles that in turn will affect health in later life.

Despite this growing recognition that puberty is a phase of high risk for many health problems, preventive work has often had a narrow focus around themes such as the initiation of substance use or risky sexual behaviours. Yet the potential of such work seems much greater, particularly around promotion of mental health. Puberty occurs at a time of neural plasticity, where the effects of earlier adversity may be ameliorated and where experience may shape brain development and later emotional functioning. Major gaps remain in our knowledge of important areas such as the relationship between puberty and CNS development. Pubertal hormones have a demonstrable effect on neuronal function, but whether puberty and cortical maturation merely co-occur temporally or are causally related remains unclear. This question might be relevant for the prevention of mental disorders in adolescence and clinical intervention for childhood emotional and behavioural problems that may or may not persist into adolescence.

The modern mismatch between biological and social maturity is of great significance for health and reproductive success. A prolonged adolescence, shaped by powerful socioeconomic forces, has seen new health problems emerge.²⁶ For young people without strong family and

educational connections, puberty is a high risk period which can mark the beginning of a fast-track to adulthood with early transitions into sexual activity and school leaving as well as the development of psychiatric and substance use disorders. The health consequences for groups such as young offenders may be devastating.¹⁴⁷ Maintaining strong links to family and school will remain a cornerstone of promoting adolescent health social development. Yet success in promoting adolescent health might ultimately rely on the extent to which we can integrate the gains of the 20th century for young people, in terms of education and economic prosperity, with opportunities to assume adult roles closer to the age at which they are biologically equipped to do so.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

George Patton receives salary support from the Victorian Health Promotion Foundation.

References

- 1 Spear LP. Adolescent brain development and animal models. *Ann N Y Acad Sci* 2004; **1021**: 23–26.
- 2 Delemarre-van de Waal HA. Regulation of puberty. *Best Pract Res Clin Obstet Gynaecol* 2002; **16**: 1–12.
- 3 Arlt W, Martens JW, Song M, Wang JT, Auchus RJ, Miller WL. Molecular evolution of adrenarche: structural and functional analysis of p450c17 from four primate species. *Endocrinology* 2002; **143**: 4665–72.
- 4 Goodyer IM, Herbert J, Tamplin A, Altham PME. First episode major depression in adolescents: affective, cognitive and endocrine characteristics of risk status and predictors of onset. *Br J Psychiatry* 2000; **176**: 142–49.
- 5 Dahl RE. Adolescent brain development: A period of vulnerabilities and opportunities. *Ann N Y Acad Sci* 2004; **1021**: 1–21.
- 6 Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970; **45**: 13–23.
- 7 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; **44**: 291–303.
- 8 Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bouguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev* 2003; **24**: 668–93.
- 9 van den Berg SM, Setiawan A, Bartels M, Polderman TJ, van der Vaart AW, Boomsma DI. Individual differences in puberty onset in girls: bayesian estimation of heritabilities and genetic correlations. *Behav Genet* 2006; **36**: 1–10.
- 10 Gluckman PD, Hanson MA. Evolution, development and timing of puberty. *Trends Endocrinol Metab* 2006; **17**: 7–12.
- 11 Stafford DEJ, Gordon CM. Adolescent androgen abnormalities. *Curr Opin Obstet Gynecol* 2002; **14**: 445–51.
- 12 Juul A, Teilmann G, Scheike T, et al. Pubertal development in Danish children: comparison of recent European and US data. *Int J Androl* 2006; **29**: 247–55.
- 13 Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics* 1997; **99**: 505–12.
- 14 Herman-Giddens ME, Wang L, Koch G. Secondary sexual characteristics in boys: estimates from the national health and nutrition examination survey III, 1988–1994. *Arch Pediatr Adolesc Med* 2001; **155**: 1022–28.
- 15 Viner RM. Splitting hairs: is puberty getting earlier in girls? *Arch Dis Child* 2002; **86**: 8–10.
- 16 Kaplowitz P. Pubertal development in girls: secular trends. *Curr Opin Obstet Gynecol* 2006; **18**: 487–91.
- 17 Mul D, Fredriks AM, van Buuren S, Oostdijk W, Verloove-Vanhorick SP, Wit JM. Pubertal development in The Netherlands 1965–1997. *Pediatr Res* 2001; **50**: 479–86.

- 18 Hall GS. Adolescence: Its psychology and its relations to physiology, anthropology, sociology, sex, crime, religion and education. London: Sidney Appleton; 1905.
- 19 Freud A. Adolescence as a developmental disturbance. In: Caplan G, Lebovici S, eds. Adolescence. New York: Basic Books; 1969.
- 20 Kestenberg J. Phases of adolescence with suggestions for a correlation of psychic and hormonal organization. Antecedents of adolescent organization in childhood. *J Am Acad Child Adolesc Psychiatry* 1967; **6**: 426–63.
- 21 Gottlieb G. The roles of experience in the development of behavior and the nervous system. In: Gottlieb G, ed. Neural and behavioral specificity: studies on the development of behavior and the nervous system. New York: Academic Press, 1976.
- 22 Lerner RM. Concepts and theories of human development. 2nd edn. New York: Random House, 1986.
- 23 Brooks-Gunn J, Warren MP. Biological and social contributions to negative affect in young adolescent girls. *Child Dev* 1989; **60**: 40–55.
- 24 Schlegel A, Barry H. Adolescence: an anthropological enquiry. New York: Free Press, 1991.
- 25 Furlong A, Cartmel F. Young people and social change: individualisation and risk in late modernity. Maidenhead: Open University Press, 1997.
- 26 Graham P. The end of adolescence. Oxford: Oxford University Press, 2004.
- 27 Rutter M, Graham P, Chadwick OFD, Yule W. Adolescent turmoil: fact or fiction. *J Child Psychol Psychiatr* 1976; **17**: 35–56.
- 28 Jones MC. Psychological correlates of somatic development. *Child Dev* 1965; **36**: 899–911.
- 29 Jones MC, Bayley N. Physical maturing among boys as related to behaviour. *J Educ Psychol* 1950; **41**: 129–48.
- 30 Schofield M. The sexual behaviour of young people. London: Longmans, 1965.
- 31 Stattin H, Magnusson D. Pubertal maturation in female development. Hillsdale: Erlbaum, 2003.
- 32 Primus RJ, Kellogg CK. Pubertal-related changes influence the development of environment-related social interaction in the male rat. *Devel Psychobiol* 1989; **22**: 633–43.
- 33 Adriani W, Chiarotti F, Laviola G. Elevated novelty seeking and peculiar d-amphetamine sensitization in periadolescent mice compared with adult mice. *Behav Neurosci* 1998; **112**: 1152–66.
- 34 Insel TR. A neurobiological basis of social attachment. *Am J Psychiatry* 1997; **154**: 726–35.
- 35 Rosenblum LA. A comparative perspective on adolescence. In: Bancroft J, Reinsch JM, eds. Adolescence and puberty. New York: Oxford University Press, 1990: 63–69.
- 36 Moore J. Dispersal, nepotism, and primate social behaviour. *Int J Primatology* 1992; **13**: 361–78.
- 37 McEwen BS, Alves SE. Estrogen actions in the central nervous system. *Endocrine Rev* 2003; **20**: 279–307.
- 38 Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neurosci* 1999; **2**: 861–63.
- 39 Cameron JL. Interrelationships between hormones, behavior, and affect during adolescence. *Ann N Y Acad Sci* 2004; **1021**: 110–23.
- 40 Young EA, Alemus M. Puberty, ovarian steroids, and stress. *Ann N Y Acad Sci* 2004; **1021**: 124–33.
- 41 Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: social rejection versus achievement stress. *Biol Psychiatry* 2002; **52**: 318–27.
- 42 Francis DD, Diorio J, Plotsky PM, Meaney MJ. Environmental enrichment reverses the effects of maternal separation on stress reactivity. *J Neurosci* 2002; **22**: 7840–43.
- 43 Giedd JN. Structural magnetic resonance imaging of the adolescent brain. *Ann N Y Acad Sci* 2004; **1021**: 77–85.
- 44 Mussen PH, Jones MC. The behavior inferred motivations of late and early maturing boys. *Child Dev* 1958; **29**: 61–67.
- 45 Alsaker FD. The impact of puberty. *J Child Psychol Psychiatr* 1996; **37**: 249–58.
- 46 Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neurosci* 1999; **2**: 859–61.
- 47 Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature* 2000; **404**: 190–93.
- 48 Lewis DA. Development of the prefrontal cortex during adolescence: Insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology* 1997; **16**: 385–98.
- 49 Patton GC, Hemphill S, Beyers JM, et al. Pubertal stage and deliberate self-harm in adolescents. *J Am Acad Child Adolesc Psychiatry* (in press).
- 50 Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004; **170**: 78–85.
- 51 Ernst P, Ghezzo H, Becklake MR. Risk factors for bronchial hyperresponsiveness in late childhood and early adolescence. *Eur Respir J* 2002; **20**: 635–39.
- 52 Nicolai T, Illi S, Tenborg J, Kiess W, Mutius E. Puberty and prognosis of asthma and bronchial hyper-reactivity. *Pediatr Allergy Immunol* 2001; **12**: 142–48.
- 53 van Ginkel R, Reitsma JB, Buller HA, van Wijk MR, Taminau JA, Benninga MA. Childhood constipation: longitudinal follow-up study beyond puberty. *Gastroenterology* 2003; **125**: 357–63.
- 54 Watson AR, Taylor CM, McGraw M. Disorders of the urinary system. In: McIntosh N, Helms PJ, Smyth RL, eds. Forfar and Arneil's textbook of pediatrics. 6th edn. Edinburgh: Churchill Livingstone, 2003: 599–650.
- 55 Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005; **171**: 334–39.
- 56 Teilmann G, Juul A, Skakkebaek NE, Toppari J. Putative effects of endocrine disrupters on pubertal development in the human. *Best Pract Res Clin Endocrinol Metab* 2002; **16**: 105–21.
- 57 Pundziute-Lycka A, Dahlquist G, Nystrom L, et al. The incidence of type 1 diabetes has not increased but shifted to a younger age at diagnosis in the 0–34 years group in Sweden 1983–1998. *Diabetologia* 2002; **45**: 783–91.
- 58 Beeson PB. Age and sex associations of 40 autoimmune diseases. *Am J Med* 1994; **96**: 457–62.
- 59 Gillespie KM, Nolsoe R, Betin VM, et al. Is puberty an accelerator of type 1 diabetes in IL6-174CC females? *Diabetes* 2005; **54**: 1245–48.
- 60 Verthelyi D. Sex hormones as immunomodulators in health and disease. *Int Immunopharmacol* 2001; **1**: 983–93.
- 61 Lamason R, Zhao P, Rawat R, et al. Sexual dimorphism in immune response genes as a function of puberty. *BMC Immunol* 2006; **7**: 2.
- 62 Brown RT, Borden KA. Hyperactivity at adolescence: Some misconceptions and new directions. *J Clin Child Psychol* 1986; **15**: 194–209.
- 63 Clampitt MK, Pickle JB. Stimulant medication and the hyperactive adolescent: myths and facts. *Adolescence* 1983; **18**: 811–21.
- 64 Thorley G. Review of follow-up and follow-back studies of childhood hyperactivity. *Psychol Bull* 1984; **96**: 116–32.
- 65 Willoughby MT. Developmental course of ADHD symptomatology during the transition from childhood to adolescence: a review with recommendations. *J Child Psychol Psychiatr* 2003; **44**: 88–106.
- 66 Duke-Duncan P, Ritter PL, Dornbusch SM, Gross RT, Carlsmith JM. The effect of pubertal timing on body image, school behavior, and deviance. *J Youth Adolesc* 1985; **14**: 227–35.
- 67 Flannery DJ, Rowe DC, Gulley BL. Impact of pubertal status, timing and age on adolescent sexual experience and delinquency. *J Adolesc Res* 1993; **8**: 21–40.
- 68 Felson RB, Haynie DL. Pubertal development, social factors and delinquency among adolescent boys. *Criminology* 2002; **40**: 967–88.
- 69 Martin CA, Kelly TH, Raynens MK, et al. Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *J Am Acad Child Adolesc Psychiatry* 2002; **41**: 1495–502.
- 70 Dick DM, Rose RJ, Viken RJ, Kaprio J. Pubertal timing and substance use: associations between and within families across late adolescence. *Dev Psychol* 2000; **36**: 180–89.
- 71 Wichstrom L. The impact of pubertal timing on adolescents: alcohol use. *J Res Adolesc* 2001; **11**: 131–50.
- 72 Anthony JC, Petronis KR. Early-onset drug use and the risk of later drug problems. *Drug Alcohol Depend* 1995; **40**: 9–15.
- 73 Lanza ST, Collins LM. Pubertal timing and the onset of substance use in females during early adolescence. *Prevention Sci* 2002; **3**: 69–82.

- 74 Aro H, Taipale V. The impact of timing of puberty on psychosomatic symptoms among fourteen to sixteen-year-old Finnish girls. *Child Dev* 1987; **58**: 261–68.
- 75 Stattin H, Magnusson D. Pubertal maturation in female development: paths through life. Hillsdale: Erlbaum, 1990.
- 76 Patton GC, Hemphill S, Toumbourou J, McMorris BJ, Catalano RF. Pubertal stage and the onset of substance abuse. *Pediatrics* 2004; **114**: 300–06.
- 77 Martin CA, Kelly TH, Rayens MK, et al. Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *J Am Acad Child Adolesc Psychiatry* 2002; **41**: 1495–502.
- 78 Shugrue PJ, Merchenthaler I. Estrogen is more than just a “sex hormone”: novel sites for estrogen action in the hippocampus. *Front Neuroendocrinol* 2000; **21**: 95–101.
- 79 Book A, Stazyk K, Quinsey V. The relationship between testosterone and aggression: a meta-analysis. *Aggression Violent Behav* 2001; **6**: 579–99.
- 80 Spear LP, Brake SC. Periadolescence: age-dependent behavior and psychopharmacological responsiveness in rates. *Devel Psychobiol* 1983; **16**: 83–109.
- 81 Viner RM, Cole TJ, Taylor B. What are the implications of early pubertal development? Findings in adulthood from a national birth cohort. *Arch Dis Child* 2006; **91** (suppl 1): A86.
- 82 Hayward C, Sanborn K. Puberty and the emergence of gender differences in psychopathology. *J Adolesc Health* 2002; **30** (suppl 4): 49–58.
- 83 Kessler RC. Epidemiology of women and depression. *J Affect Dis* 2003; **74**: 5–13.
- 84 Rutter M, Smith D. Psychosocial disorders in young people: time trends and their causes. Chichester: Wiley and Sons; 1995.
- 85 Wade TJ, Cairney J, Pevalin DJ. Emergence of gender differences in depression during adolescence: national panel results from three countries. *J Am Acad Child Adolesc Psychiatry* 2002; **41**: 190–98.
- 86 Garrison CZ, Waller JL, Cuffe SP, McKeown RE, Addy CL, Jackson KL. Incidence of major depressive disorder and dysthymia in young adolescents. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 458–65.
- 87 Hayward C, Killen JD, Hammer LD, et al. Pubertal stage and panic attack history in sixth- and seventh-grade girls. *Am J Psychiatry* 1992; **149**: 1239–43.
- 88 Wichstrom L. The emergence of gender difference in depressed mood during adolescence. *Dev Psychol* 1999; **35**: 232–45.
- 89 Nolen-Hoeksema S, Girgus JS. The emergence of gender differences in depression during adolescence. *Psychol Bull* 1994; **115**: 424–43.
- 90 Petersen AC, Sarigiani PA, Kennedy RE. Adolescent depression: why more girls? *J Youth Adolesc* 1991; **20**: 247–71.
- 91 Simmons RG, Blyth DA, VanCleave EF, Bush DM. Entry into early adolescence: the impact of school structure, puberty and early dating on self-esteem. *Am Sociol Rev* 1979; **44**: 948–67.
- 92 Piccinelli M, Wilkinson G. Gender differences in depression: critical review. *Br J Psychiatry* 2000; **177**: 486–92.
- 93 Resnick MD, Bearman PS, Blum RW, et al. Protecting adolescents from harm: findings from the National Longitudinal Study on Adolescent Health. *JAMA* 1997; **278**: 823–32.
- 94 Bond L, Carlin J, Thomas L, Patton GC. Does bullying cause emotional problems? A longitudinal study of young secondary school students. *BMJ* 2001; **323**: 480–84.
- 95 Paikoff RL, Brooks-Gunn J, Warren MP. Predictive effects of hormonal change on affective expression in adolescent females over the course of one year. *J Youth Adolesc* 1991; **20**: 191–214.
- 96 Patton GC, Hibbert ME, Carlin J, et al. Menarche and the onset of depression and anxiety in Victoria, Australia. *J Epidemiol Community Health* 1996; **50**: 661–66.
- 97 Angold A, Costello EJ, Erkanli A, Worthman CM. Pubertal changes in hormone levels and depression in girls. *Psychol Med* 1999; **29**: 1043–53.
- 98 Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status, and pubertal timing. *Psychol Med* 1998; **28**: 51–61.
- 99 Hayward C, Gotlib IH, Schraedley PK, Litt IF. Ethnic differences in the association between pubertal status and symptoms of depression in adolescent girls. *J Adol Health* 1999; **25**: 143–49.
- 100 Goodyer IM, Herbert J, Tamplin A, Altham PM. Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *Br J Psychiatry* 2000; **177**: 499–504.
- 101 Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression. *Arch Gen Psychiatry* 2000; **57**: 21–27.
- 102 Weinberger DR. Implication of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987; **44**: 660–69.
- 103 Haefner H, Maurer K, Loeffler W, Riecher-Roessler A. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry* 1993; **162**: 80–86.
- 104 Cohen RZ, Seeman MV, Gotowiec A, Kopala L. Earlier puberty as a predictor of later onset of schizophrenia in women. *Am J Psychiatry* 1999; **156**: 1059–64.
- 105 Killen JD, Hayward C, Litt IF, et al. Is puberty a risk factor for eating disorders? *Am J Dis Childhood* 1992; **146**: 323–25.
- 106 Cauffman E, Steinberg L. Interactive effects of menarcheal status and dating on dieting and disordered eating among adolescent girls. *Dev Psychol* 1996; **32**: 279–87.
- 107 Swarr A, Richards M. Longitudinal effects of adolescent girls' pubertal development, perceptions of pubertal timing and parental relationships on eating problems. *Dev Psychol* 1996; **32**: 636–42.
- 108 Abraham S, O'Dea JA. Body mass index, menarche, and perception of dieting among peripubertal adolescent females. *Int J Eat Disord* 2001; **29**: 23–28.
- 109 O'Dea JA, Abraham S. Onset of disordered eating attitudes and behaviors in early adolescence: interplay of pubertal status, gender, weight and age. *Adolescence* 1999; **34**: 671–79.
- 110 Stice E, Presnell K, Bearman SK. Relation of early menarche to depression, eating disorders, substance abuse, and comorbid psychopathology among adolescent girls. *Dev Psychol* 2001; **37**: 608–19.
- 111 Bradley SJ, Zucker KJ. Gender identity disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 872–80.
- 112 Rahman Q. The neurodevelopment of human sexual orientation. *Neurosci Biobehav Rev* 2005; **29**: 1057–66.
- 113 Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. *Epilepsia* 1993; **38**: 1082–88.
- 114 Klein P, van Passel-Clark L, Pezzullo JC. Onset of epilepsy at the time of menarche. *Neurology* 2003; **60**: 495–97.
- 115 Svalheim S, Tauboll E, Bjornenak T, et al. Onset of epilepsy and menarche—is there any relationship? *Seizure* 2006; **15**: 571–75.
- 116 Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993; **34**: 453–68.
- 117 Loud KJ, Gordon CM. Adolescent bone health. *Arch Pediatr Adolesc Med* 2006; **160**: 1026–32.
- 118 Friedland O, Hashkes PJ, Jaber L, et al. Decreased bone speed of sound in children with growing pains measured by quantitative ultrasound. *J Rheumatol* 2005; **32**: 1354–57.
- 119 Burwell RG. Aetiology of idiopathic scoliosis: current concepts. *Pediatr Rehabil* 2003; **6**: 137–70.
- 120 Puylaert D, Dimeglio A, Bentahar T. Staging puberty in slipped capital femoral epiphysis: importance of the triradiate cartilage. *J Pediatr Orthop* 2004; **24**: 144–47.
- 121 Harreby MS, Neergaard K, Hesselsoe G, Kjer J. Are low back pain and radiological changes during puberty risk factors for low back pain in adult age? A 25-year prospective cohort study of 640 school children. *Ugeskr Laeger* 1997; **159**: 171–74.
- 122 Bille B. Migraine in school children. *Acta Paediatrica* 1962; **51** (suppl 136): 16–18.
- 123 Facchinetti F, Sgarbi L, Piccinini F. Hypothalamic resetting at puberty and the sexual dimorphism of migraine. *Funct Neurol* 2000; **15**: 137–42.
- 124 Laurell K, Larsson B, Eeg-Olofsson O. Prevalence of headache in Swedish schoolchildren, with a focus on tension-type headache. *Cephalgia* 2004; **24**: 380–88.
- 125 Wedderkopp N, Andersen LB, Froberg K, Leboeuf-Yde C. Back pain reporting in young girls appears to be puberty-related. *BMC Musculoskelet Disord* 2005; **6**: 52.
- 126 LeResche L, Mancl LA, Drangsholt MT, Saunders K, Korff MV. Relationship of pain and symptoms to pubertal development in adolescents. *Pain* 2005; **118**: 201–09.

- 127 Rhee H. Relationships between physical symptoms and pubertal development. *J Pediatr Health Care* 2005; **19**: 95–103.
- 128 Mechanic D. Adolescent health and illness behavior: review of literature and a new hypothesis for the study of stress. *J Hum Stress* 1983; **9**: 4–13.
- 129 Riley JL, III, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. *Pain* 1999; **81**: 225–35.
- 130 Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. *Int J Androl* 2006; **29**: 272–77.
- 131 Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics* 2001; **108**: 347–53.
- 132 Mul D, Fredriks AM, van Buuren S, Oostdijk W, Verloove-Vanhorick SP, Wit JM. Pubertal development in The Netherlands 1965–1997. *Pediatr Res* 2001; **50**: 479–86.
- 133 Juul A, Teilmann G, Scheike T, et al. Pubertal development in Danish children: comparison of recent European and US data. *Int J Androl* 2006; **29**: 247–55.
- 134 Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. *Pediatrics* 2002; **110**: 903–10.
- 135 Dunger DB, Ahmed ML, Ong KK. Effects of obesity on growth and puberty. *Best Pract Res Clin Endocrinol Metab* 2005; **19**: 375–90.
- 136 Gleicher N, Barad D. An evolutionary concept of polycystic ovarian disease: does evolution favour reproductive success over survival? *Reprod Biomed Online* 2006; **12**: 587–89.
- 137 Laitinen J, Power C, Jarvelin MR. Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. *Am J Clin Nutr* 2001; **74**: 287–94.
- 138 Sandhu J, Ben Shlomo Y, Cole TJ, Holly J, Davey SG. The impact of childhood body mass index on timing of puberty, adult stature and obesity: a follow-up study based on adolescent anthropometry recorded at Christ's Hospital (1936–1964). *Int J Obes (Lond)* 2006; **30**: 14–22.
- 139 Shankar RR, Eckert GJ, Saha C, Tu W, Pratt JH. The change in blood pressure during pubertal growth. *J Clin Endocrinol Metab* 2005; **90**: 163–67.
- 140 Hardy R, Kuh D, Whincup PH, Wadsworth ME. Age at puberty and adult blood pressure and body size in a British birth cohort study. *J Hypertens* 2006; **24**: 59–66.
- 141 Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. *N Engl J Med* 2004; **351**: 1619–26.
- 142 Jordan SJ, Webb PM, Green AC. Height, age at menarche, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2045–48.
- 143 Giles GG, Severi G, English DR, et al. Early growth, adult body size and prostate cancer risk. *Int J Cancer* 2003; **103**: 241–45.
- 144 Vincent HK, Taylor AG. Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans. *Int J Obes (Lond)* 2006; **30**: 400–18.
- 145 Frezza EE, Wachtel MS, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. *Gut* 2006; **55**: 285–91.
- 146 Brown JD, Halpern CT, L'Engle KL. Mass media as a sexual super peer for early maturing girls. *J Adolesc Health* 2006; **36**: 420–27.
- 147 Coffey C, Veit F, Wolfe R, Cini E, Patton GC. Mortality in young offenders: retrospective cohort study. *BMJ* 2003; **326**: 1064–66.