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Puberty and Perimenopause: Reproductive Transitions and their Implications for Women's Health

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Abstract

This scoping review synthesizes existing research on two major transitions in females' lives: puberty and perimenopause. These two periods of vast physiological change demarcate the beginning and the end of the reproductive life cycle and are associated with major neuroendocrine reorganization across two key systems, the hypothalamic-pituitary-gonadal (HPG) axis the hypothalamus-pituitary-adrenal (HPA) axis. Despite growing evidence suggesting that the timing and experience of puberty and perimenopause are related to various physical and mental health outcomes (e.g., mood disorders, metabolism, cardiovascular health, autoimmune conditions and cancer), these two processes are rarely examined together. In this paper, we bridge these disparate literatures to highlight similarities, isolate inconsistencies, and identify important areas for future research in women's health.

Keywords

puberty; perimenopause; chronic disease; women's health; life course health; HPG axis; HPA axis

Puberty and perimenopause demarcate the beginning and the end of the female reproductive life cycle and are two major transitions in a woman's life. Despite underlying biological parallels, previous research suggests a weak or non-existent relationship between these reproductive life events (Forman, Mangini, Thelus-Jean, & Hayward, 2013). Growing evidence, however, suggests that the experience and timing of puberty and perimenopause are independently associated with the many of the *same* health outcomes. For example, prevalence of mental health conditions, autoimmune diseases, and cardiometabolic risk all

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appear to increase during both puberty (Patton & Viner, 2007) and perimenopause (Greendale, Lee, & Arriola, 1999). Similarly, the timing in which these reproductive events occur (i.e., early or late as compared to average) in women's lives is also associated with various disease outcomes and mortality (Forman et al., 2013).

A life course approach to women's health recognizes that biological and social factors act interactively and cumulatively throughout the entire lifespan to shape health outcomes in later life (Kuh & Hardy, 2002). However, distant developmental periods (such as adolescence and middle age) are rarely examined together in an integrative and cohesive way to understand the epidemiology of common disease processes. The aim of this paper was to map a wide range of literature on the association of chronic conditions with puberty and perimenopause in order to identify the similarities and differences across these two key reproductive transitions. We propose that exploring these chronologically distant, yet physiologically connected, reproductive events together will help us understand important issues in women's health.

First, we summarized the neuroendocrine processes that define these two periods of change and development. Next, we conducted a scoping review (Arksey & O'Malley, 2005; Armstrong, Hall, Doyle, & Waters, 2011; Levac, Colquhoun, & O'Brien, 2010) of these fields to examine the relationships between progression and timing of puberty and perimenopause with long-term health and disease risk. We concluded with the implications of these findings and identified important areas for future research.

Neuroendocrine changes during puberty and perimenopause

Puberty is initiated in late childhood through a cascade of neuroendocrine changes that results in extensive physical growth, sexual maturation, and reproductive capability. Pubertal maturation consists of two associated but independent processes: adrenarche, the reappearance of adrenal androgen production (around age 6–8); and gonadarche, the pubertal reactivation of the hypothalamic-pituitary-gonadal (HPG) axis a few years later (Grumbach, 2004). Menarche, the initiation of the menstrual cycle, occurs toward the end of puberty, around the ages of 12–13 in most developed countries (Patton & Viner, 2007).

Perimenopause is defined as the period immediately preceding menopause when endocrinological, biological, and clinical features of approaching menopause commence (Hale & Burger, 2009; J. Prior, 1998). Women typically begin the shift from a reproductive state to non-reproductive state during their mid-to late 40s, and they remain in this transitory state for approximately 4–5 years before reaching menopause (Burger, Woods, et al., 2007; J. Prior & Hitchcock, 2011). Perimenopause culminates with menopause, when menses have ceased for a period of at least 12 consecutive months (Burger, 2008).

The neuroendocrine system presides over the significant hormonal changes occurring in the HPG axis during puberty and perimenopause (see Table 1 for a summary). In particular, both of these periods are characterized by major changes in the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which together regulate ovarian follicle growth and ovulation, and estradiol, the most abundant form of endogenous estrogen (Albin, Niklasson, Westgren, & Norjavaara, 2012; Archibald, Graber, & Brooks-Gunn,

2003; Burger, 2008; Burger, Hale, Robertson, & Dennerstein, 2007; Burger, Woods, et al., 2007; Nelson, 2008; J. Prior & Hitchcock, 2011; J. C. Prior, 2006). Mean levels of estradiol increase across pubertal development until menarche, when estradiol levels stabilize and then cycle regularly through the menstrual cycle each month. During late perimenopause, concentration of estradiol falls markedly from its elevated levels present during early perimenopause and eventually begins to stabilize (see Figure 1).

In addition to the HPG axis changes related to puberty and perimenopause, another set of endocrine changes occur in the hypothalamus-pituitary-adrenal (HPA) axis. Levels of cortisol, the major hormonal output of the HPA system, vary throughout the day based on: (1) a strong circadian rhythm (i.e., basal pattern with high morning levels, low evening levels, and a strong negative slope), and (2) experiences of stress or challenge (i.e., cortisol reactivity) (McEwen et al., 1997). A growing body of research suggests that the overall basal activity of the HPA axis increases with sexual maturation in girls (i.e., higher average levels of cortisol across the day) (Adam, 2006; Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Legro, Lin, Demers, & Lloyd, 2003; Netherton, Goodyer, Tamplin, & Herbert, 2004; Schiefelbein & Susman, 2006; Shirtcliff, Granger, Booth, & Johnson, 2005; Stroud et al., 2009). Initial research also suggests that girls experience increased cortisol reactivity (i.e., hypercortisolism) to stressful tasks across puberty (Gunnar et al., 2009; Stroud et al., 2009; Stroud, Papandonatos, Williamson, & Dahl, 2004).

Although comparatively less is known about the HPA axis changes during perimenopause, some studies have found an increase in cortisol levels as women transition from an early to late menopausal transition stage (Woods, Carr, Tao, Taylor, & ES, 2006; Woods, Mitchell, & Smith-DiJulio, 2009). Other research suggests that estrogen regulates corticotropin-releasing hormone gene expression, resulting in elevated cortisol levels (Vamvakopoulos & Chrousos, 1993). Therefore, as women approach menopause, increasing levels of FSH stimulate ovarian follicles to produce excess estrogen, which may influence cortisol levels (Santoro, Brown, Adel, & Skurnick, 1996). There is also some evidence for greater HPA reactivity among postmenopausal women, with older women showing higher cortisol in response to challenge compared to both younger women and similarly-aged male (Seeman, Singer, Wilkinson, & McEwen, 2001). Importantly, HPA activity is involved in regulating many physiological processes relevant to health including cardiovascular activity, blood pressure, and immune and inflammatory functioning (Chrousos & Gold, 1998).

The years surrounding both the initiation and completion of the female reproductive cycle are associated with major neuroendocrine reorganization that is distinct from other periods of the life course. In particular, dramatic changes occur across two key systems: the HPG axis— including fluctuations of LH, FSH, and estradiol— and hyperactivation of the HPA axis. By exploring the shared biological processes and associated health outcomes related to both puberty and perimenopause, we sought to answer: (1) What chronic diseases show a discontinuous increase in prevalence across *both* transitions? (2) Independent of the experience of these transitions, what is the association of pubertal and perimenopausal timing on health and disease?

Methods

To examine the extent, range, and nature of these literatures, we conducted a comprehensive scoping review to summarize a breadth of evidence on chronic diseases and conditions related to puberty and perimenopause. Following methodological guidelines for this type of literature review (Arksey & O'Malley, 2005; Armstrong et al., 2011; Levac et al., 2010) we defined our research focus as links between reproductive transitions and health outcomes. We included all literature presenting theoretical or empirical approaches to this broad area and that directly pertained to a health condition and puberty or menopause or whose study participants were pubertal or menopausal females. We narrowed our focus to include evidence from industrialized countries only and selected papers published between 1990 and 2014. Exceptions included significant theoretical works published earlier or older papers related to particular diseases when more recent papers could not be identified.

All studies and reviews from peer-reviewed journals and books were identified using electronic databases (Pub Med, Google Scholar, Psych Info), key health journals relevant in the areas of puberty, menopause, and women's health, and topic-related expert networks and websites (e.g., Global Library of Women's Medicine, NIH Office of Research on Women's Health.) We also reviewed the reference lists of relevant articles to identify additional studies our search strategy may have missed.

Keywords for the literature search were selected from two broad areas: female reproductive transition (e.g., puberty, menarche, pubertal timing; perimenopause, menopause, menopause timing) and health outcome (e.g., cancer, cardiovascular disease, life expectancy, mortality, diabetes, mental health, depression, anxiety, obesity, insulin resistance, autoimmune disease). We also searched specific types of cancer (e.g., breast, endometrial, ovarian), and specific types of autoimmune diseases (e.g., lupus, rheumatoid arthritis). Data from the literature review were charted to identify specific disease outcomes relevant to both reproductive transitions. For instances when evidence for a health outcome was found for one transition, but not the other, another round of selection and review was conducted.

Five major health outcomes were identified: mental health, cardiometabolic health, autoimmune conditions, cancer, and mortality. Over 5,000 articles were assessed in the initial screening process, although only 300 representative studies, reviews, and chapters were ultimately included in the final stage of review and systematized using a bibliographic-managing software (EndNote®). These studies were charted according to key issues and themes, and discrepancies between literatures from the two reproductive periods were mapped. Finally, the reviewed literature was systematically reported, with results structured thematically along each dimension of health.

Results

1. Association of pubertal and perimenopausal transitions with health outcomes

Biological, behavioral, environmental, and social influences across the life span continuously interact to affect health of both individuals and populations (Ben-Shlomo & Kuh, 2002; Halfon, Larson, Lu, Tullis, & Russ, 2014). Central to the life course framework

is the idea that health trajectories may be altered more readily during certain windows of rapid development or biological reorganization, also termed “critical” or “sensitive periods.” Whereas exposures acting in critical periods affect health in such a way that cannot be modified in any dramatic way by later experience, sensitive periods are windows when an exposure has a stronger effect on development and subsequent disease risk than it would at other times (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). Although most of the literature on critical and sensitive periods has focused on prenatal development or the first few years of life, there is considerable evidence that discrete periods of hormonal activity during puberty and perimenopause also hold important implications for mental and physical health outcomes. Hormones mediate the interaction between an individual the environment (McEwen & Wingfield, 2003); therefore, hormonal changes occurring in the HPG and HPA systems during these transitional periods may cause females to become particularly sensitive to their environment.

Mental health—Puberty is marked by a substantial increase, and emerging sex difference, in many psychological and physiological disorders. In particular, a large body of work identifies a rise in clinical depression and depressive symptoms in girls around the middle of puberty (Angold, Costello, & Worthman, 1998; Joinson et al., 2012; Saluja et al., 2004), leading to a gender gap in depression prevalence between the ages of 11–15 that persists into adulthood (Cyranowski, Frank, Young, & Shear, 2000; Kessler, 2003). Many studies also indicate that the risk of depression is greater for perimenopausal women compared with pre-menopausal or post-menopausal women, even after adjusting for variables such as history of depression, premenstrual syndrome, hot flashes, health behaviors, BMI, stressful life events, age, race, and employment status (Freeman, Sammel, Lin, & Nelson, 2006; Freeman et al., 2004; Halbreich & Kahn, 2001; Schmidt, 2005; Schmidt, Haq, & Rubinow, 2004). Women may also be more susceptible to high anxiety during perimenopause: at least one study has found that odds of high anxiety peak during late perimenopause—although not among women with high anxiety upon entering the menopausal transition (Bromberger et al., 2013).

Higher prevalence of mood disorders and symptoms during puberty and perimenopause is usually tied to fluctuations in sex hormones (Angold, Costello, Erkanli, & Worthman, 1999; Freeman et al., 2006; Freeman et al., 2004; Goodyer, Park, Netherton, & Herbert, 2001; Goodyer, Tamplin, Herbert, & Altham, 2000; Halbreich & Kahn, 2001; Nolen-Hoeksema, 2001; Schmidt, 2005; Steiner, Dunn, & Born, 2003). Most theories propose one of two types of models to explain the developmental rise of mood disorders during reproductive transitions: an indirect model whereby hormones affect some general physiological system such as psychological arousal, neurotransmitters, or reactivity to stressors that increases risk for mood disorders; or an interaction model in which social context or environments, in addition to hormones, contribute to risk (Hyde, Mezulis, & Abramson, 2008). For instance, gonadal steroids estrogen and progesterone have been shown to affect brain regions known to be involved in the modulation of mood and behavior, including the prefrontal cortex, hippocampus, thalamus, and brain stem (Soares & Zitek, 2008). Gonadal steroids also modulate regulation of the HPA axis. Therefore, hormonal changes may trigger dysregulation of the biological stress response during puberty and perimenopause, making

these women more vulnerable to depression, particularly when they are confronted with stress (Nolen-Hoeksema, 2001).

Metabolism and cardiovascular health—Increases in ovarian steroids affect metabolism and promote fat deposition, contributing to the large sex difference in body composition initiated at puberty (Worthman, 2002). Rapid changes in body size and shape, combined with the formation of dietary and physical activity patterns during puberty, implicate this window as a sensitive period for the development of excessive weight gain and obesity (Alberga, Sigal, Goldfield, Prud'Homme, & Kenny, 2012; Daniels et al., 2005; Dietz, 1994; Lawlor & Chaturvedi, 2006). Studies similarly find increased risk for unhealthy weight gain and excessive adiposity during perimenopause. Research indicates that, independent of aging, abdominal adiposity increases during the menopausal transition, coinciding with a decrease in lean mass (Sternfeld, Aradhana, Wang, Sharp, & Quesenberry, 2005; Toth, Tchernof, Sites, & Poehlman, 2000).

Independent, but related, changes in insulin sensitivity also occur during puberty and perimenopause, with studies showing that females are more insulin resistant than males throughout both reproductive transitions (Goran & Gower, 2001; Moran et al., 1999; Schianca, Castello, Rapettie, LImoncini, & Bartoli, 2006; Wildman et al., 2008). While insulin resistance appears to play an integral role in healthy somatic growth at the beginning of puberty (likely driven by both growth hormones and sex steroids), continued insulin resistance later in puberty could lead to unhealthy weight gain and put youth at increased risk for type 2 diabetes during adolescence and for cardiovascular disease (CVD) later in life (Goran & Gower, 2001). Likewise, changes in body fat distribution and insulin resistance during perimenopause are associated with increased risk for CVD (Matthews et al., 1989; Schianca et al., 2006).

Other evidence, however, suggests that women’s increased vulnerability to developing CVD during the menopausal transition may be due to factors independent of weight gain or changes in insulin homeostasis (Schianca et al., 2006). For example, one study has shown that the thickness and diameter of the carotid artery changes during perimenopause, which increase women’s vulnerability to developing CVD (El Khoudary et al., 2013). Another study indicates that low-density lipoprotein (LDL) cholesterol (i.e., “bad” cholesterol) and total cholesterol rises during late perimenopause increase women’s risk of developing CVD (Matthews et al., 2009). Still other studies have found associations between vasomotor menopausal symptoms and risk of future coronary heart disease (Gast et al., 2011; Thurston, Sutton-Tyrell, Everson-Rose, Hess, & Matthews, 2008). Although the precise biological mechanisms are yet to be specified, it appears that risk for CVD increases during both reproductive transitions.

Autoimmune conditions—Other health outcomes associated with endocrine changes occurring during puberty and perimenopause include a number of autoimmune conditions, such as systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, and autoimmune thyroid conditions (Bove, 2013; Patton & Viner, 2007; Wilder, 1995). Changes in risk, onset, and progression of such conditions occur during puberty and perimenopause, and these conditions are significantly more prevalent among females. The sexual

dimorphism in autoimmune disorders may be tied to the different effects of estradiol and testosterone on the initiation or course of underlying autoimmune processes (Lamason et al., 2006; Verthelyi, 2001).

Cancer—The pubertal transition is a sensitive period specifically for the developing mammary gland with respect to future cancer risk. Pubertal girls who are exposed to carcinogens in the presence of a changing hormonal profile may be at higher risk for cancer as a result of susceptibility of the mammary epithelial cells to early insults and mutations that make them vulnerable to carcinogenesis (Golub et al., 2008; Hiatt, Haslam, & Osuch, 2009), although the underlying mechanisms are still unknown (Diamanti-Kandarakis et al., 2009). Even less is known about the possibility of perimenopause as a sensitive period for hormonal carcinogenesis. Although some research in the 1980s hypothesized an increased risk of breast cancer for perimenopausal women (Alexander & Roberts, 1987; Korenman, 1980), there is no conclusive evidence at this time. Associations between various cancers and puberty and perimenopause are more related to the timing of these events rather than their experience.

2. The effect of pubertal and perimenopausal timing on health and disease

The sensitive period hypothesis described in the previous section focused on the discrete set of years during which females transition into and out of the reproductive lifecycle. However, much of the research relating either puberty or perimenopause with long-term health outcomes centers on the relative *timing* of these transitions (i.e., pubertal or perimenopausal onset). Overall, there is no consistent evidence for an association between pubertal onset and age at menopause (Forman et al., 2013). However, the timing of puberty and natural age at menopause are each independently associated with a number of chronic diseases as well as all-cause mortality. In most cases, the proposed mechanism is related to hormonal exposure over the life course. However, we also highlight a number of behavioral, social, and psychological mechanisms and modifiers that may help explain inconsistencies in a direct-hormonal hypothesis.

Mental health—A large body of work has found that early pubertal timing is associated with heightened prevalence and intensity of depressive symptoms, adjustment problems, anxiety, and psychopathology among adolescent females (Ge, Elder Jr, Regnerus, & Cox, 2001; Graber, Lewinsohn, Seeley, & Brooks-Gunn, 1997; Harlow, Cohen, Otto, Spiegelman, & Cramer, 1999; Mendle, Turkheimer, & Emery, 2007; Natsuaki, Biehl, & Ge, 2009). Biological explanations for these associations stem from evidence that early maturing girls secrete higher levels of estradiol from adolescence across the transition to adulthood, which may cause heightened sensitivity to negative life events (Apter, Reinilä, & Vihko, 1989). Individual differences in the age of pubertal onset also create variation in the point at which the brain is exposed to sex hormones, influencing the developmental trajectory of neural maturation and risk for sex-biased psychopathologies (Sisk & Foster, 2004; Sisk & Zehr, 2005). Some scholars have found opposing evidence, however, arguing that estrogen has stimulating effects on the serotonergic system in the brain. Girls who experience early puberty, therefore, may have better mental health outcomes in the long run than later maturing girls (Herva et al., 2004).

Other theories suggest that the psychological and behavioral implications associated with either early or late pubertal timing may be implicated in the increasing incidence of and gender disparity in mental health problems starting in adolescence (Caspi & Moffitt, 1991). The most common psychosocial theory, the early timing hypothesis, holds that early pubertal girls must confront new norms and expectations before they are psychologically and cognitively prepared for such challenges, and may experience distress related to poor body image or harassment from peers tied to exhibiting the physical manifestations of puberty (e.g., secondary sex characteristics) before their peers (Ge, Conger, & Elder, 1996; Mendle et al., 2007). However, others argue that both early or late pubertal timing (off-time hypothesis) may be associated with heightened stress related to social comparisons (Weichold, Silbereisen, & Schmitt-Rodermund, 2003). An interaction hypothesis, which alternatively suggests that only pubertal timing combined with stressful life events increases the risk for depression (Ge, Conger, & Elder Jr, 2001; Hyde et al., 2008), could help to explain inconsistencies in the literature.

Evidence is less conclusive about the impact of menopausal timing on mental health outcomes. One study found that psychological distress was unrelated to timing of menopausal transition (Busch, Zonderman, & Costa Jr, 1994), while other studies have found an inverse relationship between menopausal age and late-life depression among women (Harlow, Wise, Otto, Soares, & Cohen, 2003; Ryan, Carrière, Scali, Ritchie, & Ancelin, 2008). Women with relatively lower levels of education appear to be at particular risk of depression from a lower age at menopause (Ryan et al., 2008). Like the early puberty hypothesis, it is plausible that menopause timing occurring significantly earlier than the average age in the population may be a source of psychological distress for some women (Lennon, 1982). The relationship between depression and earlier age of menopause may also stem from prolonged exposure to a hypoestrogenic state (Ryan et al., 2008).

Cardiovascular disease—Emerging evidence from epidemiological studies indicates that early pubertal timing is associated with increased risk of CVD and CVD-precursors and comorbid conditions, such as hypertension and diabetes (He et al., 2010; Jacobsen, Oda, Knutsen, & Fraser, 2009; Lakshman et al., 2009; Remsberg et al., 2005). In a recent meta-analysis, early menarche was associated with a 15% increase in CVD risk (Prentice & Viner, 2012). The association between pubertal timing and poor cardiovascular health may also reflect pre-existing biological risk, related to childhood or adult body size (Bleil et al., 2013; Bleil et al., 2012; Kivimäki et al., 2008; Patton & Viner, 2007), or differences in health-risk behavior associated with early timing, such as substance use and low physical activity (Baker, Birch, Trost, & Davison, 2007; Davison, Werder, Trost, Baker, & Birch, 2007; Kaltiala-Heino, Marttunen, Rantanen, & Rimpela, 2003).

One major criticism of previous studies examining the relationship between pubertal timing and adult cardiovascular health outcomes is the lack of measurement of child or adolescent body weight. Many scholars contend that early menarche is only a risk marker, and not an independent predictor of cardiovascular disease. In other words, elevated childhood BMI contributes to an earlier age of menarche, which in turn leads to a higher adult BMI and associated cardiovascular risk (Kivimäki et al., 2008). Critics question, therefore, whether menarcheal age is an independent predictor of cardiovascular risk factors in adulthood.

Research has generally found a similar association between an early age at menopause (i.e., before age 40) and an increased risk for coronary heart disease (Atsma, Bartelink, Grobbee, & van der Schouw, 2006; Mondul, Rodriguez, Jacobs, & Calle, 2005; Shuster, Rhodes, Gostout, Grossardt, & Rocca, 2010), although a number of studies have produced inconsistent results (Atsma et al., 2006). The main challenges associated with determining the relationship between timing of menopause and cardiovascular disease include distinguishing the effect of menopause from age-related effects (Lawlor, Ebrahim, & Smith, 2002) and health-related behaviors (van der Schouw, van der Graaf, Steyerberg, Eijkemans, & Banga, 1996). Although several studies have reported adverse relationships between menopause and lipid profiles, blood pressure, and weight gain, these factors also vary with age (Lawlor et al., 2002). Smoking is also a well-known risk factor for CVD and is associated with decreased age of menopause. A meta-analysis of early menopause and risk factors for cardiovascular disease found, however, that the effects of smoking are unclear. Although the relationship between postmenopausal status and CVD disappears upon controlling for smoking, the effect of early menopause on CVD was also more pronounced after controlling for smoking (Atsma et al., 2006).

Biological mechanisms proposed to explain the association between age at menopause and CVD include the role of estrogen in the maintenance of immune function (Mondul et al., 2005) and a cardioprotective effect of estrogen (Ossewaarde, Bots, Verbeek, & Peeters, 2005; Roeters van Lennep, Westerveld, Erkelens, & van der Wall, 2002). Decreasing estrogen levels during the menopausal transition have been linked to adverse vascular changes. In particular, low-density lipoprotein cholesterol (LDL-C) levels increase, while high-density lipoprotein cholesterol (HDL-C) levels remain stable or slightly increase. These changes have consistently been found associated with increased risk of CVD (Woodard et al., 2011).

Autoimmune conditions—Almost all autoimmune diseases are more prevalent in women than men, and it has been hypothesized that hormonal or reproductive factors, such as estrogen exposure, may play an important role in disease pathogenesis (Simard & Costenbader, 2007). While a few studies suggest that early menarche is associated with systemic lupus erythematosus (SLE) (Costenbader, Feskanich, Stampfer, & Karlson, 2007) and rheumatic arthritis (Avila et al., 1990; Karlson, Mandl, Hankinson, & Grodstein, 2004), findings are not consistent across studies. In other research, no clear association was found between age of menarche and SLE (Cooper, Dooley, Treadwell, St Clair, & Gilkeson, 2002), and still others have found that earlier age of menarche was inversely related to rheumatic arthritis (Pedersen et al., 2006; Pikwer, Bergstrom, Nilsson, Jacobsson, & Turesson, 2012).

More consistent observations have been found between an earlier age at menopause (i.e., prior to age 45) and autoimmune diseases, including disorders involving the thyroid and adrenal glands, pernicious anemia, alopecia, Chron's disease, SLE, and rheumatoid arthritis (Bove, 2013; Costenbader et al., 2007; Leidy, 1994; Pikwer et al., 2012; Sammaritano, 2012). The pathophysiological mechanisms explaining these relationships are likely complex, although hypothesized explanations for this relationship include an insufficient

HPA axis or immune changes regulated by estrogen, androgens, progesterone, or estrogen/androgen ratios.

Cancer—Numerous studies have shown that earlier pubertal timing is a key risk factor for breast cancer (Ahlgren, Melbye, Wohlfahrt, & Sorensen, 2004; D. Apter & Vihko, 1983; Hsieh, Trichopoulos, Katsouyanni, & Yuasa, 1990; Kelsey & Bernstein, 1996), endometrial cancer (Kaaks, Lukanova, & Kurzer, 2002; Purdie & Green, 2001) and ovarian cancer (Jordan, Webb, & Green, 2005). A later age at menopause, on the other hand, is also associated with an increased risk of breast and endometrial cancer (DeLellis Henderson, Bernstein, Henderson, Kolonel, & Pike, 2008; Ossewaarde et al., 2005; Purdie & Green, 2001). Additionally, some studies find an association between later age of menopause and colon cancer, although this link is less well established relative to the associations found with reproductive tract cancers (Franceschi et al., 2000).

For both early puberty and late menopause, the hypothesized biological pathway to the occurrence of various cancers is increased lifetime exposure to estrogen and progesterone (DeLellis Henderson et al., 2008; Key et al., 2011). Although early menarche and late menopause increase cancer risk, the effects are not necessary equivalent. For example, excess risk for breast cancer is greater if women's reproductive years are extended by one year at puberty compared with excess risk associated with lengthening one year at menopause (Collaborative Group on Hormonal Factors in Breast Cancer, 2012).

The relation between reproductive timing and cancer risk is potentially confounded or modified by BMI and cigarette smoking. Not only is higher BMI associated with both earlier puberty and later menopause, but obesity may also heighten oxidative stresses, an independent risk factor for a wide range of cancers (Dai et al., 2009; Vincent & Taylor, 2006). BMI also affects the concentration of circulating sex hormones (Akahoshi et al., 2002; Gold et al., 2013) and research indicates that a higher BMI modifies the risk of breast, endometrial, and colon cancer depending upon menopausal status (Reeves et al., 2007). Cigarette smoking is one of the strongest and most consistently associated factors for an earlier age of menopause (Hardy, Kuh, & Wadsworth, 2000; Harlow & Signorello, 2000). The association found between late menopause and endometrial cancer, for example, may be due to the anti-estrogenic effects of cigarette smoking (Terry & Rohan, 2002; Zhou et al., 2008).

Mortality—Some evidence from epidemiologic research suggests that early pubertal timing is associated with a shorter lifespan. For example, one study found a 4% reduced risk of all-cause mortality per year delay in onset of menarche in a population-based cohort study in the United Kingdom (Lakshman et al., 2009). This finding is consistent with previous research in Norway (Jacobsen, Heuch, & Kvale, 2007) and California (Jacobsen et al., 2009) that found a 2.4 and 4.5% (respectively) reduced risk of overall mortality associated with a one-year delay in onset of menarche. Many studies have also linked all-cause mortality to an early age at menopause (some studies indicate earlier than age 40, while others suggest the relationship occurs prior to age 45) (Gold, 2011; Jacobsen, Heuch, & Kvale, 2003; Li et al., 2013; Mondul et al., 2005; Ossewaarde et al., 2005; Shuster et al., 2010). Studies also have found that women who experienced menopause prior to age 40 experience mortality ranging

from 35–95% higher compared with women who reported menopause occurring at age 50 years or older (Gold et al., 2001).

Many complex mechanisms may underlie the relationship between timing of reproductive events and mortality, including genetic, behavioral, environmental, and hormonal factors (Gold et al., 2001; Mishra, Cooper, Tom, & Kuh, 2009). While there is growing evidence that reproductive timing is associated with a number of specific diseases (as discussed in the sections above), some argue that early reproductive timing is a biological marker of cumulative stress (Barkow, 1984; Belsky, Steinberg, & Draper, 1991; Chisholm, Quinlivan, Petersen, & Coall, 2005) or accelerated somatic aging (Li et al., 2013; Svejme, Ahlborg, Nilsson, & Karlsson, 2012).

Discussion

The aim of this article was to review the dramatic physiological changes occurring during the beginning and end of women's reproductive lives and how they are linked to later life health outcomes and mortality. We presented evidence using the sensitive periods model to suggest that events occurring during puberty and perimenopause—as well as their timing—are correlated with or influence risk for some of the leading causes of morbidity and mortality in women. We do not deny that other life course models (e.g., accumulation/chains of risk) may also influence women's health; rather, we chose to highlight the importance of exposure-time interactions with respect to puberty and perimenopause.

Hormonal fluctuations that are common across both reproductive life events may help explain why puberty and perimenopause are sensitive periods for the development of depression and anxiety, metabolic and cardiovascular risks, and autoimmune conditions. Overall, it is hypothesized that hormones increase vulnerability that, in interaction with stressful life events, chronic stress, risky behaviors, or poor environments cause initiation or progression of disease. Although less studied, some research suggests that these hormonal shifts provoke high arousal, excitability, or excessive emotionality more generally, which may make individuals more sensitive to *all* environmental conditions (Steiner et al., 2003). We urge future researchers to look beyond risks, and examine these reproductive transitions as periods of opportunity to improve positive health and psychological well-being.

Despite dramatic changes across both gonadal and adrenal systems during the pubertal and perimenopausal transitions, most of the literature is focused on sex steroids, namely estradiol, with relatively little research on the integrative functioning of the HPG and HPA axes (Nolen-Hoeksema, 2001; Woods, Mitchell, & Smith-DiJulio, 2009). There is evidence showing that the adrenal axis regulates gonadal function through inhibitory effects of stress on reproductive behavior and the release of sex steroids (Viau, 2002), but the relation is not unidirectional. The HPA axis is also subject to gonadal influences, as evidenced by gender differences in basal cortisol levels, stress reactivity of the HPA system, and prevalence rates of stress-related diseases (Dallman et al., 2002; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). However, *how* sex steroids operate within the central nervous system to regulate the HPA axis remains unresolved. Future studies should examine the interactive and

bidirectional effects of stress steroids and glucocorticoids during these important reproductive transitions to help identify underlying causes of health and disease.

While this review has highlighted many similarities between the beginning and end of the female reproductive lifespan that may underlay common disease pathways, we have also found inconsistencies between puberty and perimenopause timing and their associated health outcomes. In particular, earlier ages of both puberty and menopause have been associated with higher risk of CVD and decreased life expectancy. There is considerable evidence for the protective effect of estrogen against atherosclerosis in older women, however estrogen exposure earlier in life may be harmful. It is possible that the timing of estrogen exposures may play at least as important a role in affecting health as lifetime exposure. For example, there are robust estrogen benefits for cardiovascular health during the perimenopausal and early postmenopausal years, with no or possibly deleterious estrogen effects during the late postmenopausal years (Clarkson, 2007). Such inconsistencies underlie the complexity of the relationship between hormonal exposure and disease and highlight the importance of developmental timing, genetic, environment, and behavioral influences.

There is also still much to learn about the initiation of puberty and perimenopause, which together determine the length of a female's reproductive lifespan. Although some research suggests that reproductive characteristics in puberty and perimenopause may simply represent markers of the same underlying process (Kuh & Hardy, 2002), there is conflicting evidence concerning the direct relationship between timing of puberty (usually measured by menarche) and the timing of menopause. A recent review of the literature identified 36 studies that examine the association between these two sentinel events and found that ten reported a significant direct association (i.e., early menarche was associated with early menopause), two an inverse association (i.e., early menarche was associated with later menopause), and the majority had null findings (Forman et al., 2013).

The association between age at menarche and menopause and health conditions is complicated by the many social and environmental exposures that interact with a woman's physiology across her lifespan. Beyond a strong genetic component that influences timing of puberty and perimenopause, variation in timing is linked to socio-demographic characteristics, body size, and exposure to endocrine-disrupting chemicals (Gold, 2011; Patton & Viner, 2007). In particular, results from several large-scale studies suggest that non-Hispanic Black girls, and girls who are overweight or obese, experience puberty earlier than their peers (Chumlea et al., 2003; Kaplowitz, Slora, Wasserman, Pedlow, & Herman-Giddens, 2001). There is also a substantial body of work suggesting that stress-inducing family processes (e.g., harsh parenting, marital conflict) may accelerate onset of puberty (Belsky et al., 2007), and some evidence linking low socioeconomic status (SES) to early pubertal development, although results are not consistent across all measures (Braithwaite et al., 2009; Parent et al., 2003). Similarly, timing of menopause also varies by race/ethnicity (i.e. many studies report that African American and Latina women experience menopause earlier than White and Asian women). Lower SES, smoking, and exposure to endocrine disruptors have all been associated with earlier menopausal age, while higher parity and BMI have been associated with later menopausal age (Gold, 2011). Although all of the

empirical studies in this scoping review included some set of basic controls, covariate selection varied widely based on data availability and disciplinary priorities. In order to understand the constellation of factors related to pubertal onset and age at menopause, it is important to examine these dynamic and interrelated variables, which have important implications for reproductive timing and health trajectories.

Additionally, some life course researchers examine pregnancy as another sensitive period for health (Rich-Edwards, 2002). Although we have focused this review on the beginning and end of the reproductive life cycle for women, pregnancy represents another window of vast hormonal and physiological changes and may be similarly linked with long-term health outcomes. Research indicates that pregnancy produces significant changes in estrogen levels as well as suppression of the HPA axis during this time (Mastorakos & Ilias, 2000; Steiner et al., 2003), and changes in neuroendocrine activity may imply increased vulnerability or sensitivity to psychosocial, environmental, and physiological factors (Steiner et al., 2003).

The unique contribution this review provides to existing literature is the linkage of the physiological similarities between puberty and perimenopause and their relation to various health outcomes. Although the more narrow foci of the studies we reviewed presents critical information about pubertal and perimenopausal females' health, this review offers a broad perspective of how the changes occurring at the beginning and culmination of women's reproductive lives influence long-term health trajectories. This review has illustrated the complexity of the relationship between reproductive transitions, their timing, and health outcomes, revealing that exposure to various hormone changes during puberty and perimenopause do not always produce parallel responses. Such information may be useful in the study of how health capacities develop across different phases or periods of development (Halfon et al., 2014), as well as to policymakers or clinicians in deciding the most efficient way to organize health programs or services. Greater understanding of women's health across the life course and how different periods relate to each other may also inform disease risk and provide insight on how to modify health trajectories.

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Highlights

- Puberty and perimenopause involve reorganization across HPG and HPA systems.
- Many chronic health risks increase during both puberty and perimenopause.
- Environmental influences on health may intensify when hormone levels are changing.
- This review reveals inconsistent health consequences of lifetime estrogen exposure.

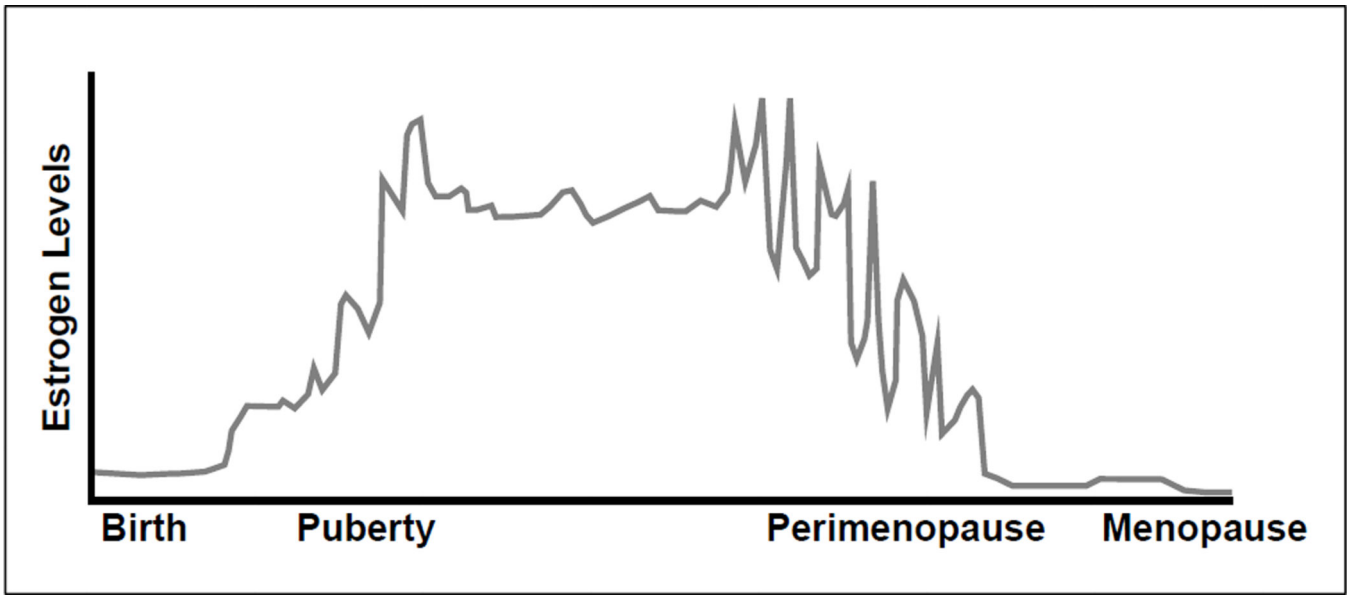

Figure 1.
Life cycle of estrogen.
Note. This depiction of the estrogen changes across women's life cycles provides a representation of the chaotic and higher estrogen levels in pubertal and perimenopausal women. (Fluctuations do not correlate to precise changes in estrogen levels). Adapted from Prior (2006) and reprinted with permission.

Table 1

Summary of changes in the hypothalamic pituitary gonadal (HPG) axis during puberty and perimenopause

	Puberty	Perimenopause
Gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and controls the synthesis and secretion of LH and FSH. In the brain, steroids influence GnRH secretion via neuroendocrine feedback loops to determine reproductive status during development.	The onset of puberty is characterized by a gradual increase in the frequency and amplitude of intermittent episodes of GnRH secretion.	GnRH pulse frequency decreases, in particular, during early perimenopause.
Luteinizing hormone (LH), produced by the pituitary gland, stimulates the ovaries to form androgenic precursors of estradiol. During the reproductive lifespan, a mid-cycle surge of LH triggers ovulation.	There are sleep-related increases in the pulsatile release of LH at the beginning of puberty, which eventually persist into the daytime and begin to cycle regularly by menarche.	Few observable changes in LH transpire until late perimenopause, when intermittent elevations in LH concentration and pulse amplitude occur.
Follicle-stimulating hormone (FSH), produced by the pituitary gland, stimulates gonadal growth and the production of gonadal hormones, such as estradiol and progesterone.	Starting at the beginning of puberty, FSH is secreted in parallel with LH, but increases relatively less. LH-to-FSH ratios are typically less than 1 during childhood and greater than 1 during puberty.	Intermittent elevations in FSH concentration occur at the beginning of perimenopause. The rise in FSH accelerates during late perimenopause.
Estradiol is the primary form of estrogen produced in women during her reproductive years. It is mostly released from the ovaries and adrenal glands, which subsequently downregulates secretion of LH and FSH.	Estradiol increases many-fold across pubertal development, and then levels off and begins to cycle regularly approximately one year after menarche.	Estradiol is erratic and elevated throughout early perimenopause. Estradiol decreases and is less erratic towards the end of perimenopause, accompanied by large increases in FSH and LH.
Progesterone is a hormone produced mainly by the ovaries and plays an important role in regulating the menstrual cycle. Production ceases if the egg is not fertilized, upon which menstruation occurs.	Production begins with menarche. Youth tend to have low or variable progesterone levels during the first few years after menarche.	Progesterone decreases gradually but continuously during perimenopause.