Ind. J. Phys. Anthrop. & Hum. Genet. Vol. 36. No. 1, (2017) : 11-37

A COMPREHENSIVE ANTHROPO-GENOMIC RECOUNT OF AGE AT MENARCHE AND AGE AT NATURAL MENOPAUSE IN LIGHT OF GWA STUDIES

Mahima Gulabani, Vipin Gupta and Mohinder Pal Sachdeva

ABSTRACT

Age at Menarche (AAM) and Age at Natural Menopause (ANM) are the major hallmark events of a woman's reproductive health and pubertal transition. The timing of these events varies between individuals, across different countries and ethnicity. Until recently many researches have reported the secular trend of AAM and ANM to be decreasing worldwide with a median age of 12 years and 44.5 years for AAM and ANM respectively. Both these traits have been found to have a complex etiology involving multiple genetic, environmental and lifestyle factors (smoking, nutrition, reproductive characteristics, socio-demographic factors etc.). Also, both these traits (AAM and ANM) have showed significant association with several health risks (such as CVD, Cancer, Diabetes, Osteoporosis etc.).

Biological anthropological studies have focussed on the assessment of variations in timings across women of different ethnicities in different ecological backgrounds. Besides this, anthropological studies have also extended to growth and developmental patterns, correlation with environmental and lifestyle covariates such as nutrition, socio-economic study, demographic and health profiles. However, cultural anthropological studies have primarily focussed on the cultural values underlying these two traits such as understanding of taboos and rituals associated with them, quality of life of females and socio-cultural models emphasising on social status and familial roles of women.

At a genomic level, our review shows that GWASs have played a significant role in contrast to candidate-gene association studies or genome-wide linkage analysis as age at menarche and age at natural menopause are not only influenced by genetic factors but also by the environmental factors. Although GWASs have proved to be revolutionary in offering narrow insight into the causative genetic variation mechanisms underlying age at menarche and age at natural menopause but might have represented only the tip of an iceberg of the ongoing research. However, an alliance of anthropology and genomics of menarche and menopause will not only add on to our understanding of the inter- and intra-population variation but will also advocates the consideration of the variation that vary between

Mahima Gulabani, Department of Anthropology, University of Delhi, Delhi-110007; **Vipin Gupta,** Assistant Professor, Department of Anthropology, University of Delhi, Delhi-110007; **Mohinder Pal Sachdeva**, Professor, Department of Anthropology, University of Delhi, Delhi-110007.

population as a reflection of unrevealed bio-cultural interactions. Thus future studies must focus on anthropo-genomic integrational research.

Keywords: *Menarche, Menopause, GWAS, Reproductive Health, Genomics*

INTRODUCTION

Anthropology, the science of man has contributed to both biological knowledge and cultural aspects of human growth and development. Epidemiological studies often use Age at Menarche (AAM), the onset of the first menstrual period in girls, to indicate the timing of puberty and Age at Natural Menopause (ANM) marking the end of the reproductive period. Menarche and menopause are the two anthropological variables whose socio-cultural significance has been studied by many anthropologists in various societies. Also many physical anthropologists have also studied age at menarche and age at natural menopause with respect to growth and development patterns and other covariates such as environmental and lifestyle factors.The word Menopause (menespausie) was used for the first time in 1816 by French Physician de Gardanne (Pathak *et al*., 2010) and Menarche by Kisch (1910) (Priya *et al*., 2009). Menarche (first menstruation) and menopause (the end of menstruation) are two significant qualitative developmental events in the lives of females (te Velde and Pearson, 2002), given its relevance to general as well reproductive health. These are a series of complex neuroendocrine events (Papaoiconomou *et al*., 2011) associated with physical, psychological (emotional) and social development (Susman *et al*., 1985).

Menarche is defined as the start of menstruation and occurs at a mean age of approximately13 years with a normal range of 9 to 17 years, normally about 2 years after the onset of puberty (Marshall *et al*., 1969; Perry *et al*., 2010). It represents the completion of female sexual maturation and attainment of reproductive capacity. As suggested by Asgharnia (2009), these two are events of major significance, denoting the achievement of a functional state, which involves, if not the ability to regularly conceive, at least the hypothalamic control of the ovarian cycle via the pituitary gland. Natural menopause is as defined by the World Health Organisation as at least twelve consecutive months of amenorrhea, not because of surgery or other obvious causes (i.e. bilateral oophrectomy, radiation treatment or chemotherapeutic agents) (World Health Organisation Scientific Group, 1996). It is highly variable among women of various ethnicities and can range between 40-60 years of age and seem to be influenced by the integration of multiple internal and external cues acting upon and genetically determined processes (Ebling, 2005). Thus, both ages at menarche (AAM) and age at menopause (ANM) are, amongst other things, important as retrospective markers for ovarian senescence (te Velde *et al*., 1998; Marozzi *et al*., 2000a).

Since these two traits (AAM and ANM) have great clinical, socio-cultural, socio-demographic and epidemiological implications on women's reproductive health, increased interest has been shown in the mechanisms responsible for the timing of

menarche and menopause to understand the reasons for variation in their timing. These two traits have been found to be associated with several diseases such as breast cancer (Kok *et al*., 2005; Velie *et al*., 2006), ovarian cancer (Hartge *et al*., 2009) and endometrial cancer (Cramer *et al*., 2012), obesity (Ong *et al*., 2007), type 2 diabetes (He *et al*., 2010), hypertension (Hartge, 2009), shorter adult stature (Ong *et al*., 2007), cardiovascular diseases (Atsma *et al*., 2006), osteoporosis (Grainage *et al*., 2001; Naves *et al*., 2005), mortality (Giles *et al*., 2010), mental health problems (Golub *et al*., 2008), reduced fertility span (te Velde and Pearsons, 2002), Alzheimer's diseases (Rees *et al*., 1995) and stroke (Cui *et al*., 2006). Also associated with increased risk for a number of psychosocial outcomes in adolescents including substance use, sexual risk taking, teenage pregnancy (Golub *et al*., 2008), depression (Kaltiala-Heino *et al*., 2003) and eating disorders (Kaltiala-Heino *et al*., 2001). Recent data also suggests that age at menarche is significantly associated with body composition, insulin sensitivity and blood lipid levels (Feng *et al*., 2008).

The timing of menarche and menopause varies substantially between individual as well as women across different geographical regions and different ethnic groups (He and Murabito. 2014) indicating them to be not simply a function of chronological age. In Indian context, the present mean age at menarche and natural menopause has been reported to be 12.88 ± 1.23 years (Talwar *et al*., 2012) and 46 years (range: 48.0 to 51.0 years) (Singh, 2012) respectively. AAM and ANM are complex traits that are influenced by several intricate array of environmental, lifestyle, epigenetic and genetic factors. On a large scale, AAM is mainly determined by extrinsic factors such as living conditions while ANM seems to be mainly influenced by intrinsic factors such as reproductive history of individuals (Thomas *et al*., 2011). These include improved nutritional status (ESHRE_Capri_Workshop_Group, 2006, Khadilkar *et al*., 2006), mother's age at menarche and menopause (Rizk *et al*., 1998; Ong *et al*., 2007), climatic influences (Khadilkar *et al*., 2006), smoking (Kok *et al*., 2005), socio-demographic factors, urbanization, sedentary lifestyle (Morris *et al*., 2010), hormonal regulation (IGF-1, ghrelin, leptin and insulin) (Parent *et al*., 2003; DiVall and Radovick, 2008), improved socio-economic (Khatoon *et al*., 2011) and sanitary conditions (Gama, 2008), decreased physical activity (Cho *et al*., 2010), body mass index(BMI) and childhood obesity (Khatoon *et al*., 2011) etc.

However, it has also been estimated that environmental and lifestyle factors explain only a small proportion (about 3%) of observed variation in AAM (Chie *et al*., 1997) and ANM (van Noord *et al*., 1997; Voorhuis *et al*., 2010; Carty *et al*., 2013). Although the exact physiological processes underlying the timing of AAM and ANM are far from being elucidated at present, genetic factors have proved to play a important role in determining the variation, as demonstrated in several mother-daughter (Treloar and Martin *et al*., 1990; Torgerson *et al*., 1997), twin and sib-pair studies (Voorhuis *et al*., 2010). The heritability estimated from family and twin studies ranges from 53% to 74% for AAM (Meyer *et al*., 1991; Kaprio *et al*., 1995;Chie *et al*., 1997; Sharma, 2002; van der Berg *et al*., 2007) and from 44% to 65% for ANM (Sneider *et*

al., 1998;de Bruin *et al*., 2001; van Asselt *et al*., 2004b;Murabito *et al*., 2005a; and Voorhuis *et al*., 2010).

Therefore, this review at first briefly discusses anthropological (both biological and socio-cultural) studies conducted so far globally on age at menarche and age at natural menopause followed by genetic and genomic studies with special emphasis on genome-wide association studies (GWAS) related to age at menarche and age at natural menopause. And ultimately this review provides the significant insight in to how genomic and anthropological knowledge can jointly contribute and enhance our understanding of the two hallmarks (menarche and menopause) of women's reproductive health.

Anthropological studies conducted on age at menarche and age at natural menopause

Several longitudinal and cross-sectional anthropological (biological) studies conducted on menarche and menopause are just not limited to the analysis of variations in their timings but also extends to growth and development patterns (maturational tempo differences), genetic determinants, environmental and lifestyle covariates associated with them (such as education level, nutrition, socio-demographic status etc.), prevalence of clinical and non-clinical menopausal symptoms, comparative studies on the basis of rural and urban residence, association with metabolic parameters (such as obesity measures, metabolic profile, blood pressure etc.) and ethnic/racial differences. However, cultural studies have majorly focussed on understanding the taboos, rites and rituals associated with these traits, KAP (knowledge, attitudes/perceptions and practices) studies of menarche and menopause, bringing out gender indifference in terms of segregation and untouchability attitudes, effect of these traits on the quality of lives of females, socio-cultural models emphasising on social status and familial roles of women etc. Few of these biological as well as socio-cultural studies deserve a mention here and are discussed as follows.

Bio-cultural anthropological studies on menarche and menopause: The research on menarche and menopause has remained polarized since a long time. The clinical model of menopause has mainly focused on identifying symptoms of the climacteric syndrome, whereas endocrinologists have defined menopause as a deficiency disease directly linked to the lack of estrogen. However, social scientists have focussed on the social and cultural construct of menarche and menopause, emphasising on whether and how climacteric symptoms are experienced. But anthropologists are the only one who have studied these traits in both biological and socio-cultural aspects. Cross-cultural and anthropological studies have challenged the concept of menarche and menopause as universal phenomena which are highly variable among women of different ethnic origins living in different geographical regions. A general assessment of age at menarche (Priya *et al*., 2009; Pathak *et al*., 2010; Prakash *et al*., 2010) and menopause (Priya *et al*., 2009) has been done by many anthropologists both in India and worldwide. Also, as discussed

earlier menarche and menopause are affected by several genetic and environmental factors therefore knowledge of these factors is likely to improve our understanding of female reproductive health. Thus several anthropological studies have been conducted in relation to understanding and determination of factors influencing menarche and menopause such as ethnicity (Kaplowitz *et al*., 2001; Chumlea *et al*., 2003), social class differences, number of siblings, birth order, geographical location (Gustavo & Gonzales, 1994), body mass index (Kaplowitz *et al*., 2001), body size and physique(Sharma *et al*., 1998; Berkey *et al*., 2000; Talwar and Bajwa, 2005; Kaur *et al*., 2009; Talwar *et al*., 2012), body fat (Frisch, 2003; Lassek *et al*., 2007; Kaur *et al*., 2011), education (Nag and Singhal, 2013), occupation, residence (Priya *et al*., 2009; Khatoon *et al*., 2011), skeletal maturity, physiological variables (Talwar and Bajwa, 2005; Talwar *et al*., 2010), physical activity and secular trends (Bagga and Kulkarni, 2000; Jarvelaid *et al*., 2001; Okasha *et al*., 2001; Kaplowitz *et al*., 2006), diet (vegetarian and non-vegetarian with age at menarche (Bagga and Kulkarni, 2006), secular trends and stature with age at menarche (Khanna and Kapoor, 2004). Several other studies have focussed on determining the declining secular trend of these traits in developed countries (Anderson *et al*., 2003; Anderson & Must, 2005; Biro *et al*., 2006) and as well as in developing countries (Singh & Malhotra, 1988; Bagga & Kulkarni, 2000; Hwang *et al*., 2003; Hosny *et al*., 2005; Goon *et al*., 2010).A review discussed the findings by anthropologists that revealed the complex and dynamic adaptations of human reproductive functioning in high altitude environments including age at menarche and age at menopause (Vitzthum *et al*., 2013).

An anthropological study also focussed on quantitative assessment of rural-urban differences in both menopausal age and reporting of menopausal problems (e.g., vasomotor, psychosomatic, psychological, and urinary problems) and presented a maiden attempt to explore the health problems of menopausal women and the predictor variables in the eastern part of India (Dasgupta and Ray *et al*., 2009).An anthropological approach on menopause used by Fedigan *et al*. (1994) threw light on the various covariates incorporating primatological, historical, cross-cultural and evolutionary data. Many other studies have also attempted to understand the evolution of menopause (Austad, 1994; Peccei *et al*., 1995; Herrigton *et al*., ; Shanley *et al*., 2001; Perls *et al*., 2001). Peccei (2001) emphasised on the most important question of menopause whether it is an adaptation or an epiphenomenon and critically reviewed the evidence for the adaptation, physiological trade-off and by-product of increased longevity explanations for the origin of menopause. Age at menarche has also been studied as a fitness trait (Reed, 1991). Another study tried to quantitatively assess the quality of life and the impact of hormonal changes in perimenopausal and postmenopausal women and correlated the prevalence of the symptoms with their duration since menopause (Poomalar *et al*., 2012; Shafeie *et al*., 2013).

With respect to cultural studies conducted by anthropologists, review of literature reveals that the studies have majorly focussed on menopause and not on menarche. Cross-cultural research on menopause has its foundations in an anthropological

study of menopausal women in Northern India (Melby *et al*., 2005). Noteworthy anthropological studies focussing specifically on menopause such as by Flint (1975) among the Rajputs of Northern India have been extremely rare until recently. A study has also made an attempt to use personal-construct approach for exploration of meanings behind a woman who is anticipating or experiencing menopause (Foster *et al*., 2003). Another study by Melby *et al*. (2005) tried to review the research conducted on the relationship of culture and menopausal symptoms. They suggested that both biological variation and cultural differences contribute to the menopausal transition, and therefore proposed a bio-cultural framework that in future can make use of both biological and cultural parameters to elucidate the interaction between biology and culture in female ageing.In another review menopause was discussed in bio-cultural perspectives and laid an emphasis on need of bio-cultural and developmental anthropological approach (Melby *et al*., 2011).

Overall, anthropological researches suggest that variation in ANM and AAM are a result of perpetual feedback network of biology and culture.

Genetics and genomics of age at menarche and age at natural menopause

Irrespective of the general belief that the timing of menarche and natural menopause is a polygenic trait, not many genes have been identified to be associated with age at menarche and natural menopause. Till date various genetic approaches have been employed in identifying gene associated with AAM and ANM viz. candidate - gene association studies, genome – wide linkage studies and genome – wide association studies (GWAS). Linkage and candidate gene studies have not confirmed any loci that influence normal variation in age at menarche. Whereas a revolutionising approach viz. Genome-wide association studies (GWAS) has proven successful in identifying common susceptibility genes with small effect sizes for many complex diseases and traits and might be suitable to identify genetic factors involved in determining age at menarche and menopause (Stolk *et al*., 2009). Up till today, GWASs have identified around 42 novel susceptibility loci for AAM and 17 loci for ANM. However, candidate genes identified through recent GWAS published conducted for age at menarche and menopause demands their validation on different populations across the world.

Former **candidate gene association studies** have revealed genes involved in several biochemical pathways such as of steroid-hormone metabolism and biosynthesis pathway: estrogen receptor genes (ESR1 and ESR2) (Dvornyk *et al*. 2006; He *et al*. 2007), sex hormone binding globulin gene (SHBG) (Xita *et al*. 2005), estrogen biosynthesis genes (CYP17, CYP19, and HSD17) (Fiegelson *et al*., 1997; Lai *et al*., 2001;Guo *et al*., 2006b; Mitchell *et al*., 2008) and ANM (Gorai *et al*., 2003; Hefler *et al*., 2005; Kok *et al*., 2005; Long *et al*., 2006; Mitchell *et al*., 2008)., hydroxylation (CYP1A1, CYP1B1, and CYP3A4) (Long *et al*., 2006; Guo *et al*., 2006b; He *et al*., 2007; Mitchell *et al*., 2008; Mitchell *et al*., 2008; Xita *et al*., 2010) etc. Other Candidate-gene association studies identified several miscellaneous genes including IGF1 (Zhao *et*

al. 2007), AMHR2 (Kevenaar *et al*. 2007), APOE (Koochmeshgi *et al*. 2004), NOS3 (Hefler *et al*. 2002; Worda *et al*. 2004) etc.

Another significant study was recently conducted by He *et al*. (2010), whereby they consolidated biologically relevant information for testing whether the common genetic polymorphisms in candidate genes of nine groups of biologically plausible pathways and related phenotypes were associated with age at menarche and age at natural menopause. They found that common variants in the steroid-hormone metabolism and biosynthesis pathways were significantly associated with age at menarche; and the groups of genes involved extremes of the phenotypes, i.e. precocious or delayed puberty and premature ovarian failure, were significantly associated with age at menarche and age at natural menopause, respectively. Overall we can see that candidate gene association studies have not yielded findings that have been consistently validated.

Recently, **genome-wide linkage analyses** using microsatellite markers have revealed chromosomal regions that may contain genes for menarche (Guo *et al*. 2006; Rothenbuhler *et al*. 2006;Pan *et al*. 2008; Anderson *et al*., 2008) and natural menopause (van Asselt *et al*. 2004; Murabito *et al*. 2005b). But with the advent of GWAS, significant genomic associations with AAM and ANM have been found as discussed below.

GWAS of Age at Menarche: Since 2009 many studies have been carried out on European ancestry to study the genomic association of age at menarche (AAM) (Table 1 A). A significant study was carried out by He *et al*. (2009), whereby they carried out a joint analysis of two Genome-wide association studies (GWAS) for AAM in a total sample of 17,438 women from two prospective cohort studies, the Nurses' Health Study (NHS) and the Women's Genome Health Study (WGHS). This study identified ten associated SNPs ($P < 10^{-7}$ to 10^{-13}) clustered at two newly identified genetic loci viz. 6q21 (in or near the gene LIN28B) and 9q31.2 (in an intergenic region). Meanwhile, in the same year 2009, four more GWA studies were being conducted. Ong *et al*. (2009), tried to identify common variants associated with the timing of puberty, and conducted a GWAS for AAM in 4,714 women from two general population studies and one obese case study. This study identified only one SNP, rs314276 in intron2 of LIN28B (chromosome 6), which reached genome-wide statistical significance. Here, overall major C-allele was found to be associated with a mean 0.22 years earlier menarche. Another study by Sulem *et al* (2009) confirmed the findings of He *et al* (2009). This study also reported significant associations on 6q21 between rs314280 (T-allele), near LIN28B gene and 1.2 months later AAM per T-allele among the GWA study conducted on 15,297 Icelandic women.

A meta-analysis of genome-wide association study conducted by Perry *et al* (2009) was found to be consistent with He *et al* (2009) study, showing the strongest signal at 9q31.2 (intergenic region) (nearest gene: TMEM38B, FKTN, FSD1L, TAL2 and ZNF462) followed by the next best signal near LIN28B gene (rs7759938). Another

GWAS conducted on 38,000 SNPs in 477 Caucasian women by Liu *et al* (2009) followed by a replication study identified a novel gene, SPOCK (Sparc/Osteonectin, CWCV, and Kazal-like domains proteoglycan), which had seven SNPs (rs2348186, rs7701979, rs13357391, rs1859345, rs10054991, rs12653349, rs19779700) associated with AAM. However, no further replication of this gene has been done in large cohort size GWAS.

More recently, Elks *et al* (2010) identified loci for AAM in a meta-analysis of 32 genome-wide association studies in 87,802 European females. In addition to known loci at LIN28B and 9q31.2 (He *et al*., 2009), this study identified 30 new loci associated with Age at Menarche. Overall, these 42 loci accounted for 3.6-6.1% of the total observed variation in age at menarche. In the year 2013, few more studies joined the list of GWASs conducted on AAM n ANM. Hong *et al*. (2013) conducted a replicated study of genome wide association study on age at menarche in the Korean females. They examined the association of the SNPs reported in ReproGen Genome wide association study (Elks *et al*., 2010) with individuals from Korean Genome and Epidemiology study (KoGES) cohort. They found replication of the ReproGen study in 2 SNPs; one SNP (rs466639) in the retinoic acid receptor gamma gene (RXRG), showing a significant association with early menarche and the second SNP (rs10899489) in GRB2 (growth factor receptor bound protein 2) associated binding protein 2 (GAB2), associated with late menarche, suggesting that genetic factors related to age at menarche in Korean population would be different from European population and indicated the role of modulating or interacting factors (environmental factors such as nutrition) in determining age at menarche.

In another study by Delahanty *et al*. (2013), they tried to comprehensively evaluate the transferability of age at menarche-associated genetic variants (37 of the already identified 42 loci by Elks *et al*., 2010) from European to Asian ancestry (Chinese) women. They reported the same direction of allelic association for 32 of 37 evaluated variants between women of European and Chinese ancestry, 9 of which were statistically significant suggesting that the associated SNPs and the causal alleles are in LD with each other for both the ancestry. But this study needs replication and validation. Carty *et al*. (2013) conducted a multi-ethnic Population Architecture using Genomic Epidemiology (PAGE) study and replicated three SNPs (two loci), previously associated with age at menarche (rs314277, rs314280, rs7861820; He *et al*., 2009; Sulem *et al*., 2009) in American-Indians, African-Americans, Asians, European-American, Hispanics and Native Hawaiians. They replicated finding for age at menarche SNPs in the LIN28B locus and an intergenic region on 9q31.2 in European-Americans. Also, LIN28B SNPs (rs314277 and rs314280) were significantly associated with age at menarche in Asians but not in other race/ethnicity groups. However, fine mapping of these regions may show strong and consistent effect across all populations.

Demerath *et al*. (2013) conducted an extensive and the largest genome wide association study till date of age at menarche in African-American women from 15 cohort studies followed by meta-analysis and conditional analysis and investigation

of 42 loci in European-American women. Although no single SNP reached wide significance but identified a number of suggestive associations near FLRT2 and PIK31 and conditional analysis identified two independent SNPs (rs339978 and rs980000) in or near RORA that might help define novel biological pathways involved in age at menarche. They also confirmed that many menarche loci [about 60% (25)] identified in European-American women generalise to African-American women, providing the first evidence of cross-ethnic generalization of menarche loci.

Lastly a study was conducted in 2013 by Tanikawa *et al*. who performed a large-scale meta-analysis of genome wide association study related to age at menarche among Japanese females. They evaluated 33 SNPs of already identified SNPs in the European ancestry and among them found two SNPs: rs4452860 and rs7028916 in TMEM38B, to be associated with age at menarche in the same direction as reported in earlier studies. In addition six loci in or near CCDC85A, LoC100421670, CA10, ZNF483, ARNT2 and RORA exhibited suggestive association with age at menarche. As no SNPs reached genome-wide significance, a large- sized study is needed to identify other genetic factors with modest effects.

Besides genomic associations, above studies on AAM also found associations with secondary characters viz., earlier breast development, earlier voice breaking, a faster tempo of height in boys and girls and shorter adult height in women and men (Ong et., 2009), Body Mass Index (BMI) (Sulem *et al*., 2009 and Elks *et al*., 2009). Also, LIN28B was identified as the first genetic marker associated with the timing of pubertal growth and development (Ong *et al*., 2009). A consistent finding for association with adult height was also shown and provided the first evidence for common genetic variants influencing female sexual maturation (Perry *et al*., 2009). Also found was the association for energy homeostasis, hormonal regulation. Further, ingenuity and gene-set enrichment pathway analysis identified coenzyme A and fatty acid biosynthesis as biological processes related to menarcheal timing (Elks *et al*., 2010). Also there have been suggestive evidences for association of age at menarche with a number of variant loci involved in growth and insulin signalling (Demerath *et al*., 2013). A positive relationship between age at menarche and adult WHR (waist-hip ratio) which may emphasize the relationship of AAM – over – nutrition – obesity was found among Koreans (Hong *et al*., 2013)

GWAS of Age at Natural Menopause: Like age at menarche, since 2007 several genetic loci have been identified to be associated with age at natural menopause (ANM) (Table 1 B). Women with natural cessation of menses were only considered in the studies excluding the cases of surgical menopause and other artificial factors for menopause. Lunetta *et al* (2007) conducted the first study in terms of ANM genomic association. 1,345 Framingham study participants from 330 families were tested and SNP association for ANM included rs6910534 near FOX03a and rs3751591 in CYP19A1. However, no further independent replication studies have been conducted or if conducted have failed for this gene (Hirschhorn *et al*., 2002). This gene has also been found to be implicated in oocyte death, depletion of functioning

ovarian follicles and infertility, representing a plausible candidate gene for menopause (Brenkman *et al*., 2003; Castrillion *et al*., 2003).

He *et al* (2009) also identified new loci for age at menopause in a joint analysis of two GWAS in total 17,438 women from two cohort studies, the Nurses' Health Study (NHS) and Women's Genome Health Study (WGHS). For ANM, 13 associated SNPs clustered at 20p 12.3 (in the gene MCM8), 19q13.42 (in or near gene BRSK1), 5q35.2 (in or near genes UIMC1 and HK3) and 6p24.2 (in gene SYCP2L) were identified. In consistency with the above finding Stolk *et al*. (2009) also identified six SNPs in three loci to be associated with ANM among 2,979 European females viz. chromosome 19q13.4 (rs1172822), chromosome 20p12.3 (rs236114), chromosome 13q34 (rs7333181). These two studies however explained < 1.5% of the phenotypic variation of ANM, suggesting that additional loci of small effect will probably be discovered in larger samples (Stolk *et al*., 2012).

Very recently, Stolk *et al* (2012) have identified several loci for age at natural menopause by conducting a meta-analysis of 22 genome-wide association studies in 39,968 women of European ancestry, followed by their replication. In addition to four known loci, they identified 13 new loci associated with ANM (at $P < 5x10^{-8}$). However, common genetic variants associated with age at natural menopause were also found to regulate timing of ovarian aging, an important risk factor for breast cancer, osteoporosis and cardiovascular diseases.More recently, three studies (with significant findings) were conducted in 2013 for identifying common genetic variants influencing age at natural menopause (Perry *et al*., 2013; Carty *et al*., 2013). Perry *et al*. (2013) conducted a meta-analysis of genome wide association study of early menopause and combined effect of identified variants. Thus, their study suggested that EM and POI represent the tail of menopause distribution and thus have overlapping genetic etiology of variation in normal age at natural menopause and is at least partly explained by additive effects of the same polygenic variants, in consistency with study by Murray *et al*. (2011).

The second study in 2013 was conducted by Carty *et al*. (2013), who conducted a multi-ethnic Population Architecture using Genomics and Epidemiology (PAGE) study and replicated five SNPs previously associated with age at natural menopause (rs365132, rs2153157, rs7333181, rs1172822 and rs16991615) in American-Indian, African-American, Asians, European-Americans, Hispanics and Native Hawaiians. Three SNPs were found to be significantly associated with age at natural menopause in other race/ethnicity populations: rs2153157 (6p24.2/ SYCPL2), rs365132 (5q35/ U1MC1) and rs16991615 (20p12.3/MCM8). While rs1172822 (19q13/BRSK1) was not found to be significantly in the populations of non-European descent, effect size also showed similar trends. The third study was conducted by Spencer *et al*., 2013. They tried to replicate previously associated loci for AAM and ANM and to identify novel menarche and menopause variants using the Metabochip in African-American women from Population Architecture using Genomics and Epidemiology (PAGE) study. They successfully replicated or generalised one previously identified variant for age at menarche (rs1361108/CENPW) and two variants for age at natural

menopause (rs897798/BRSK1 and rs769450/APOE) to African-American cohort. Overall, generalization of the majority of previously-identified variants for AAM and ANM, including LIN28B and MCM8, was not observed in this African American sample. They identified three novel loci associated with ANM that reached significance after multiple testing correction (LDLR rs189596789, $p=5x10^{-08}$; KCNQ1 rs79972789, $p=1.9x10^{-07}$; COL4A3BP rs181686584, $p= 2.9x10^{-07}$).

Besides genomic associations, candidate genes located at the newly associated loci with age at natural menopause include genes implicated in DNA region (EXO1, HELQ, U1MC1, FAM175A, FANC1, and TLK1, POLG and PRIM1) and immune functions (IL11, NLRP11 and PRRC2A (aka BAT2). Gene-set enrichment pathway analyses also identified exoDNase, NF-êB signalling and mitochondrial dysfunction as biological processes related to timing of menopause. More interestingly, none of the genome-wide significant SNPs for age at menarche was found to be associated with age at natural menopause and vice versa (He *et al*., 2009; Otero *et al*., 2010). Moreover, here we saw that all the earlier studies were majorly conducted on European descent with later studies on Chinese, Japanese, Korean and multiethnic populations including Asians but South Asians in particular were not studied. In light of the findings of the above studies we can see that genome wide association studies have played a significant role in contrast to candidate gene association studies or genome wide linkage analysis as age at menarche and age at natural menopause are not only influenced solely by genetic factors but also by environmental factors.

How integration of anthropology and genomics can contribute to the understanding of age at menarche and age at natural menopause

Menarche and menopause are known to be complex bio-cultural processes and their origin, biology and evolution have raised many questions among biologists, geneticists and anthropologists. Anthropologists have documented population differences in reproductive endocrinology and developmental trajectories, and ethnic differences in hormones and symptoms at menarche and menopause demonstrating that these stages of life history are not exempt from the influence of cultural and biological factors (Melby and Lampl, 2011). Human beings are encapsulated in socio- cultural, socio-political, global and ecological contexts (Trevathan, 2007). Therefore, as described earlier, culture in terms of nutrition, reproductive behaviour and practices, public-health practices, use of contraceptives and other medications and smoking, etc. can alter the basic biology of menarche and menopause. Also, genetic and genomic studies on age at menarche and age at natural menopause have revealed their association with various estrogen-signalling pathways, vascular-function related pathways and other genetic polymorphisms. Biological anthropology and reproductive ecology have made significant offering to our understanding of woman reproductive biology by emphasising on the impact of ecological and cultural factors on fertility and chronic disease (Melby *et al*., 2005).

These anthropological (both biological and cultural) and genomic studies brings us the need for their joint venture in understanding the underlying basis of age at menarche and age at natural menopause. It becomes necessary to understand how culture affects the biological systems throughout the lifespan and not just during the reproductive or menstruating phase of women's life. These complex interactions between genetics, culture and environment itself warrants AAM and ANM to be one of the most important anthropo-genomic variables. This need for integration is supported by the argument presented by Melby *et al*. (2005) in their paper "Culture and Symptoms reporting at Menopause" where they highlighted that "using a lifespan approach, Leidy has argued that although variation in age at the menstruation is confined to a narrow spectrum, it is nevertheless significant and is influenced by family history. She notes: 'genetically, parents pass to their daughters the parameters for number of oocytes and/or rate of atresia. Behaviourally, a mother's activity while pregnant affects the ovarian store her daughter possesses at birth. From birth until menopause the environment and behaviour of the individual affects her own ovarian stores' (Leidy, 1994)".

Thus, throughan emerging field of anthropology i.e. anthropological genetics, which seeks to understand how human genetics, biological variations and cultural processes play an important role in origin and distribution of diseases/traits susceptibility genes among certain populations, one can undertake in to consideration how genetics and socio-cultural factors contribute to certain phenotypes.Moreover, understanding the anthropo-genomics of menarche and menopause is important because very little anthropo-genomic research has been done on these events in Indian context. This raises a stringent need to recognise these significant events as important issues in women's health care. These events demand a priority in rapidly changing Indian scenario, attributable to rapid globalisation, urbanization, awareness and increased life expectancy and growing populations of menopausal women (Sharma, 2007).

Throughout the world, human populations are found to be diverse in nature. Small homogeneous populations can be further divided into subpopulations based on socio-cultural factors which tend to be genetically differentiated. Therefore, anthropo-genomic perspective on AAM and ANM will not only add on to our understanding of the inter- and intra-population variation but will also advocate the consideration of the variation that vary between population as a reflection of unrevealed bio-cultural interactions.

Anthropologists have always tried to evaluate and delineate the concept of "normal" in health indicators, emphasising on developmental processes in addition to proximate and ultimate forces affecting health and enhancement of understanding of contemporary health disparities and geneticists have always looked for underlying pathways and genetic polymorphisms.Thus, integration of genetic and genomic information with data on prevailing ecological conditions will result in the development of powerful community specific studies focussing on genes-environment interaction modelling. This will also have direct application in

improving population growth of various populations living under challenging conditions (like infectious disease, malnutrition, etc.) by effectively controlling diseases affecting women's reproductive period. By involving anthropologists at the clinical level the impact of cultural factors can be reduced on disease susceptibility (Campbell, 2010). This can help the anthropologists or more precisely medical anthropologists to contribute significantly to the formulation of women's health policy.

In future, Anthropologists can help in the development of theory and hypothesis testing by studying health changes in populations undergoing urbanization and globalisation to revaluate the changes contemplated by evolutionary studies for the transition from hunting-gathering to sedentary lifestyle in human evolutionary context (Trevathan, 2007). Anthropologists can build socio-cultural models emphasising on social status and familial roles of women (Flint, 1975) along with the explanation of the complexity of the relationship between culture and menarche and menopause. So for building these models and conducting cross-cultural studies we need specially designed longitudinal studies using standardised questionnaires and a universally agreed definition on menarche and menopause (Melby *et al*., 2011).

As research across endocrinology, epidemiology, genomics and anthropology becomes more integrated, the confluence of perspectives will yield an enhanced understanding of the influences on the tempo of a woman's reproductive life cycle as well as accelerates the progress toward more sophisticated preventive strategies for chronic disease (Forman *et al*., 2013). Therefore, with combination of genomics and anthropology a more interdisciplinary, systematic and rigorous research needs to be carried out on establishing how endocrine or other biological factors differ across cultures and how cross-cultural variations in genetics, fertility patterns, diet and environment shape the subjective timing of menarche and menopause.

SUMMARY

Age at Menarche (AAM) and Age at Natural Menopause (ANM) are the major hallmark events of a woman's reproductive health and pubertal transition. The timing of these events varies between individuals, across different countries and ethnicity. Until recently many researches have reported the secular trend of AAM and ANM to be decreasing worldwide with a median age of 12 years and 44.5 years for AAM and ANM respectively. Both these traits have been found to have a complex etiology involving multiple genetic, environmental and lifestyle factors (smoking, nutrition, reproductive characteristics, socio-demographic factors etc.). Also, both these traits (AAM and ANM) have showed significant association with several health risks (such as CVD, Cancer, Diabetes, Osteoporosis etc.).

Biological anthropological studies have focussed on the assessment of variations in timings across women of different ethnicities in different ecological backgrounds. Besides this, anthropological studies have also extended to growth and

developmental patterns, correlation with environmental and lifestyle covariates such as nutrition, socio-economic study, demographic and health profiles. However, cultural anthropological studies have primarily focussed on the cultural values underlying these two traits such as understanding of taboos and rituals associated with them, quality of life of females and socio-cultural models emphasising on social status and familial roles of women.

At a genomic level, our review showed that GWASs have played a significant role in contrast to candidate-gene association studies or genome-wide linkage analysis as age at menarche and age at natural menopause are not only influenced by genetic factors but also by the environmental factors. Although GWASs have proved to be revolutionary in offering narrow insight into the causative genetic variation mechanisms underlying age at menarche and age at natural menopause but might have represented only the tip of an iceberg of the ongoing research.

However, an alliance of anthropology and genomics of menarche and menopause will not only add on to our understanding of the inter- and intra-population variation but will also advocates the consideration of the variation that vary between population as a reflection of unrevealed bio-cultural interactions. Thus future studies must focus on anthropo-genomic integrational research.

Table 1: Novel genetic loci identified through Genome-Wide Association Study (GWAS)

Study Reference	*Study Design*	*Sample size and Ethnicity*	*GWAS Findings*				
			Locus	*SNP*	*Nearest Gene(s)*	*Function*	*Reported p-value*
		(A) AGE AT MENARCHE					
He *et al.*, **2009a**	Meta-analysis of two cohorts	17,406 women of European ancestry	6q16.3	rs314277	LIN28B	intronic	2.70E-13
			9q31.2	rs7861820	TMEM38B	~400 kb	3.40E-09
Liu *et al.*, **2009**	Two stage design	477 women of European ancestry in initial scan, and 1616 women of European ancestry and 1387 Chinese women in replication stage	5q31.2	rs2348186	SPOCK1	Intronic	4.90E-07
Ong *et al.*, **2009**	Two stage design	4717 women of European ancestry in initial scan, and 16,373 women of European ancestry in replication stage	6q16.3	rs314276	LIN28B	intronic	3.60E-16
Perry *et al.*, **2009**	Meta-analysis of eight cohorts	17,510 women of European ancestry	6q21	rs7759938	LIN28B	~26 kb	7.10E-09
			9q31.2	rs2090409	TMEM38B	~400 kb	1.70E-09
Sulem *et al.*, **2009**	Two stage design	15,297 women of European ancestry in initial scan, and 10,040 women of European ancestry in replication stage	6q16.3	rs314280	LIN28B	intronic	1.80E-14
Elks *et al.*, **2010**	Meta-analysis of 32 GWAS including He, Perry, Ong, Sulem *et al.*; and two stage design	87,802 Caucasian women in meta-analysis, and 14,731 Caucasian women in replication stage	6q16.3	rs7759938	LIN28B	~26 kb	5.40E-60
			9q31.2	rs2090409	TMEM38B	~400 kb	2.20E-33
			7p14.1	rs1079866	INHBA	~250 kb	5.50E-14
			1q23.3	rs466639	RXRG	intronic	1.30E-13
			3q13.32	rs6438424	Intergenic	Intergenic	1.40E-13
			18q21.1	rs1398217	FUSSEL18	intronic	2.30E-13
			2q33.1	rs12617311	PLCL1	~195 kb	6.00E-13
			17q21.33	rs9635759	CA10	~94 kb	7.30E-13
			11q24.1	rs6589964	BSX	~18 kb	1.90E-12
			9q31.3	rs10980926	ZNF483	intronic	4.20E-11
			2p16.1	rs17268785	CCDC85A	intronic	9.70E-11

contd. table 1

Study Reference	*Study Design*	*Sample size and Ethnicity*	*GWAS Findings*				
			Locus	*SNP*	*Nearest Gene(s)*	*Function*	*Reported p-value*
			5q31.1	rs13187289	PHF15	~12 kb	1.90E-10
			3p12.1	rs7642134	VGLL3	~70 kb	3.50E-10
			2q24.1	rs17188434	NR4A2	~84 kb	1.10E-09
			3q27.2	rs2002675	TRA2B, ETV5	~4 kb, ~135 kb	1.20E-09
			8q21.11	rs7821178	PXMP3	~181 kb	3.00E-09
			16p13.12	rs1659127	MKL2	~28 kb	4.00E-09
			19p13.11	rs10423674	CRTC1	intronic	5.90E-09
			11q14.1	rs10899489	GAB2	intronic	8.10E-09
			14q32.2	rs6575793	BEGAIN	intronic	1.20E-08
			11p15.4	rs4929923	TRIM66	3'-UTR	1.20E-08
			3q22.1	rs6439371	TMEM108, NPHP3	~146 kb, ~170 kb	1.30E-08
			11p15.2	rs900145	ARNTL	~5 kb	1.60E-08
			3p21.31	rs6762477	RBM6	intronic	1.60E-08
			2p25.3	rs2947411	TMEM18	~53 kb	1.70E-08
			6q22.32	rs1361108	C6orf173, TRMT11	~98 kb, ~407 kb	1.70E-08
			16q22.1	rs1364063	NFAT5	~10 kb	1.80E-08
			1q25.2	rs633715	SEC16B	~44 kb	2.10E-08
			6q16.2	rs4840086	PRDM13, MCHR2	~145 kb, ~160 kb	2.40E-08
			3p21.31	rs7617480	KLHDC8B	intronic	2.80E-08
			16q12.2	rs9939609	FTO	intronic	3.10E-08
			20p12.1	rs852069	PCSK2	~84 kb	3.30E-08
Delahanty *et al.*, 2013	Meta-analysis of 3 ongoing GWAS	6929 women of Chinese ancestry	6q21	rs7759938	LIN28B	~26 kb	3.80E-06
			9q31.2	rs2090409	TMEM38B	~400 kb	6.00E-03
			2q33.1	rs12617311	PLCL1	~195 kb	4.00E-03
			3q13.32	rs6438424	Intergenic	Intergenic	8.00E-03
			1q23.3	rs466639	RXRG	intronic	2.30E-02
			9q31.3	rs10980926	ZNF483	intronic	4.70E-02
			3q27.2	rs2002675	TRA2B, ETV5	~4 kb, ~135 kb	2.60E-02

contd. table 1

Study Reference	Study Design	Sample size and Ethnicity	GWAS Findings				
			Locus	SNP	Nearest Gene(s)	Function	Reported p-value
			16p13.12	rs1659127	MKL2	~28 kb	4.90E-02
			5q31	rs757647	KDM3B	intronic	3.00E-03
Hong *et al.*, **2013**	Two staged design from 2 cohorts	3149 women of Korean ancestry	1q23.3	rs466639	RXRG	intronic	1.00E-02
			11q14.1	rs10899489	GAB2	intronic	5.30E-02
Carty *et al.*, **2013**	Two staged design from 4 sites including 10 cohorts	42251 women from multi-ethnic populations (American Indians, African-American, Asians, European-American, Hispanics and Native Hawaiians	6q16.3	rs314277	LIN28B	intronic	1.00E-04
			6q16.3	rs314280	LIN28B	intronic	2.0E-08 (Eu-Am), 1.2E-03 (Asians)
			9q31.2	rs7861820	TMEM38B	~400 kb	1.50E-06
Demerath *et al.*, **2013**	Two staged design from 15 cohorts	18089 women from African-American ancestry	14q24	rs8014131	FLRT2	intronic	3.44E-07
			5q13.1	rs10940138	PIK3R1	intronic	4.90E-07
Tanikawa *et al.*, **2013**	Meta-analysis of 4 cohorts	15495 women from Japanese ancestry	6q21	rs364663	LIN28B	intronic	5.49E-07
(B) AGE AT NATURAL MENOPAUSE							
Lunetta *et al.*, **2007**	One-stage design	438 women of European ancestry	6q21	rs6910534	FOXO3a	~54 kb	3.00E-05
			15q21.2	rs3751591	CYP19A1	intronic	6.00E-05
He *et al.*, **2009**	Meta-analysis of two cohorts	9112 women of European ancestry	20p12.3	rs16991615	MCM8	Missense Glu→Lys	1.20E-21
			19q13.42	rs1172822	BRSK1	intronic	1.80E-19
			5q35.2	rs365132	UIMC1	Coding-Synonymous	8.40E-14
			6p24.2	rs2153157	SYCP2L	intronic	5.10E-08
Stolk *et al.*, **2009**	Meta-analysis of two cohorts	2979 women of European ancestry	19q13.42	rs1172822	BRSK1	intronic	6.30E-11
			20p12.3	rs236114	MCM8	intronic	9.70E-11
			13q34	rs7333181	ARHGEF7	~265 kb	2.50E-08

contd. table 1

Study Reference	*Study Design*	*Sample size and Ethnicity*	*GWAS Findings*				
			Locus	*SNP*	*Nearest Gene(s)*	*Function*	*Reported p-value*
Stolk *et al.*, **2012**	Meta-analysis of 22 GWAS including He, Stolk *et al.*, 2009; and two stage design	39,968 women of European ancestry in meta-analysis, and 14,435 women of European ancestry in replication stage	20p12.3	rs16991615	MCM8	Missense Glu→Lys	1.40E-73
			19q13.42	rs11668344	TMEM150B	intronic	1.50E-59
			5q35.2	rs365132	UIMC1	Coding-Synonymous	9.10E-32
			4q21.23	rs4693089	HEL308	intronic	2.40E-19
			12q13.3	rs2277339	PRIM1	Missense Asp→Ala	2.50E-19
			1p34.3	rs4246511	RHBDL2	intronic	9.10E-17
			6p21.33	rs1046089	BAT2	Missense Arg→His	1.60E-16
			2q31.1	rs10183486	TLK1	intronic	7.70E-15
			8p11.23	rs2517388	ASH2L	intronic	9.30E-15
			15q26.1	rs2307449	POLG	intronic	3.60E-13
			2p23.3	rs2303369	FNDC4	intronic	2.30E-12
			6p24.2	rs2153157	SYCP2L	intronic	7.80E-12
			16p13.13	rs10852344	GSPT1, TNFRSF17	~7 kb, ~42 kb	1.00E-11
			11p14.1	rs12294104	C11orf46, PPED2	~24 kb, ~49 kb	1.50E-11
			13q21.2	rs4886238	TDRD3	intronic	9.50E-11
			1q43	rs1635501	EXO1	intronic	8.50E-10
			19q13.42	rs12461110	NLRP11 Pro→Leu	Missense	8.70E-10
Carty *et al.*, **2013**	Two staged design from 4 sites including 10 cohorts	42251 women from multi-ethnic populations (American Indians, African-	5q35.2	rs365132	UIMC1	Coding-Synonymous	6.9E-09 (MEC), 8.3E-05 (WHI), 1.1E-03 (Af-Am)

contd. table 1

Study Reference	*Study Design*	*Sample size and Ethnicity*	*GWAS Findings*				
			Locus	*SNP*	*Nearest Gene(s)*	*Function*	*Reported p-value*
		American, Asians, European-American, Hispanics and Native Hawaiians	6p24.2	rs2153157	SYCP2L	intronic	7.0E-04 (Eu-Am), 7.2e-03 (Am-Ind)
			19q13.42	rs1172822	BRSK1	intronic	2.3E-11 (Eu-Am)
			20p12.3	rs16991615	MCM8	Missense Glu→Lys	7.6E-15 (Eu-Am), 4.0E-04 (Hispanics), 1.0E-03 (Am-Ind)
Spencer *et al*., 2013	Two staged design from 2 cohorts	4159 women of African-American ancestry from WHI and 186 from ARIC study as a part of PAGE study.	19p13.2	rs189596789	LDLR	upstream	5.00E-08
			11p15.5	rs79972789	KCNQ1	intronic	1.90E-07
			5q13.3	rs181686584	COL4A3BP	intronic	2.90E-07

REFERENCES

Anderson, C.A., Zhu, G., Falchi, M., van den Berg, S.M., Treloar, S.A., Spector, T.D., Martin, N.G., Boomsma, D.I., Visscher, P.M. and G.W. Montgomery, 2008. A genome-wide linkage scan for age at menarche in three populations of European descent. *J. Clin. Endocrinol. Metab.* 93 (10), 3965–3970.

Anderson, S.E., Dallal, G.E. and A. Must, 2003. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. *Pediatrics* 111 (4 Pt 1), 844–850.

Anderson, S.E. and A. Must, 2005. Interpreting the continued decline in the average age at menarche: results from two national reproductive surveys of US girls studied 10 years apart. *Journal of Pediatrics* 147(75): 60.

Asgharnia M., Faraji, R., Sharami, H., Yadak, M. and M., Oudi, 2009. A study of menarcheal age in northern Iran (Rasht). *Oman Medical Journal*. 24(2), 95-98; doi:10.5001/omj.2009.22

Atsma F, Bartelink ML, Grobbee DE and YT. van der Schouw, 2006. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause*, 13: 265–279.

Bagga, A. and S. Kulkarni, 2000. Age at menarche and secular trend in Maharashtrian (Indian) girls. *Acta Biologica Szegediensis* 44(1-4): 53-57, 2000.

Berkey, C.S., Jane, D., Gardner, A, Frazier, L.A. and G.A. Colditz, 2000. Relation of childhood diet and body size to menarche and adolescent growth in girls. *American Journal of Epidemiology*.152: 446-452.

Biro FM, Huang B, Crawford PB, Lucky AW, Striegel-Moore R, Barton BA and S. Daniels,2006. Pubertal correlates in black and white girls. *Journal of Pediatrics*. 148: 234-240.

Brenkman, A.B. and B.M. Burgering, 2003. FoxO3a eggs on fertility and aging. *Trends Mol. Med.* 9 (11), 464–467.

Carty, C.L. Spencer, K.L. Setiawan, V.W. Fernandez-Rhodes, L., *et al*., 2013. Replication of genetic loci for ages at menarche and menopause in the multi-ethnic Population Architecture using Genomics and Epidemiology (PAGE) study. *Human Reproduction*, 1-12.

Castrillon, D.H., Miao, L., Kollipara, R., Horner, J.W. and R.A. De Pinho, 2003. Suppression of ovarian follicle activation in mice by the transcription factor Foxo3a. *Science* 301 (5630), 215–218.

Chie, W.C., Liu, Y.H., Chi, J., Wu, V. and A. Chen, 1997. Predictive factors for early menarche in Taiwan. *J. Formos. Med. Assoc*. 96 (6), 446–450.

Cho, G., Park, H.T., Shin, J.H., *et al*., 2010. Age at menarche in a Korean population: secular trends and influencing factors. *European Journal of Pediatrics*. 169(1): 89-94.

Chumlea, W.C., Schubert, C.M., Roche, A.F., Kulin, H.E., Lee, P.A., Himes, J.H. and S.S., Sun, 2003. Age at menarche and racial comparisons in US girls. *Pediatrics* 111 (1): 110–113.

Cramer, D.W., 2012. The epidemiology of endometrial and ovarian cancer. *Hematol Oncol Clin North Am.* 26: 1-12.

Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Inaba Y and A. Tamakoshi; JACC Study Group.2006. Relationships of age at menarche

and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J. Epidemiol*. 16: 177–184.

Dasgupta, D. and S. Ray, 2009. Menopausal Problems Among Rural and Urban Women From Eastern India, *Journal of Social, Behavioral & Health Sciences, 3*: 1–24.

de Bruin, J.P. Bovenhuis, H. van Noord, P.A.H. Pearson, P.L. van Arendonk, J.A.M. te Velde, E.R. Kuurman, W.W. and M. Dorland, 2001. The role of genetic factors in age at natural menopause. *Hum. Reprod*. 16 (9): 2014–2018.

Delahanty, R.J. Beeghly-Fadiel, A. Long, J.R. Gao, Y.T. Lu, W. Xiang, Y.B. Zheng, Y. Ji, B.T. Wen, W.Q. Cai, Q.Y. Zheng, W. and X.O. Shu, 2013. Evaluation of GWAS-identified genetic variants for age at menarche among Chinese women. *Human Reproduction,* 28(4): 1135-43.

Demerath, E.W., Liu, C.T., Franceschini, N., Chen, G.P., Julie R. P. *et al*., 2013. Genome-wide association study of age at menarche in African-American women. *Human Molecular Genetics*. 22(16): 3329-3346, doi: 10.1093/hmg/ddt181

DiVall, S.A. and S. Radovick, 2008. Pubertal development and Menarche. *Ann. N.Y. Acad.Sci.,* 1135:19-28. Doi: 10.1196/annals.1429.026

Dvornyk, V. and Ul-Haq, W., 2012. Genetics of age at menarche: a systematic review. *Hum Reprod Update* 18 (2): 198-210.

Dvornyk, V., Long, J.R., Liu, P.Y., Shen, H., Recker, R.R. and H.W. Deng, 2006a. Polymorphisms of the vitamin D receptor gene predict the onset of surgical menopause in Caucasian females. *Gynecol. Endocrinol*. 22 (10): 552–556.

Dvornyk, V., Long, J.R., Liu, P.Y., Zhao, L.J., Shen, H., Recker, R.R. and H.W. Deng, 2006b. Predictive factors for age at menopause in Caucasian females. *Maturitas* 54 (1): 19–26.

Elks, C.E. and K., Ong, 2011. Whole genome associated studies for age at menarche. *Briefings in functional genomics*. 10(2): 91-97.

Elks, C.E., Perry, J.R., Sulem, P., Chasman, D.I., Franceschini, N., He, C., Lunetta, K.L., Visser, J.A., Byrne, E.M., Cousminer, D.L., *et al*., 2010. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* 42 (12): 1077–1085.

ESHRE Capri Workshop Group, 2006. Nutrition and reproduction in women. *Hum Reprod Update*, 12: 193-207.

Feigelson, H.S., Coetzee, G.A., Kolonel, L.N., Ross, R.K. and B.E. Henderson, 1997. A polymorphism in the CYP17 gene increases the risk of breast cancer. *Cancer Res,* 57: 1063–1065.

Feng, Y., hong, X., Wilker, E., Li, Z., Zhagul., J.D., Liu, X., Zang, T., Xu, X. and X. Xu, 2008. Effects of age at menarche, reproductive years and menopause in metabolic risk factors for CVD. *Atherosclerosis* 196: 590-597.

Flint M., 1975. The menopause: reward or punishment? *Psychosomatics.* 16(4): 161-163.

Forman, M. R., Mangini, L. D., Thelus-jean, R., and M. D. Hayward, 2013. Life-course origins of the ages at menarche and menopause, *Adolescent Health, Medicine and Therapeutics,* 4: 1–21.

Giles, L.C., Glonek, G.F., Moore, V.M., Davies, M.J. and M.A. Luszcz, 2010. Lower age at menarche affects survival in older Australian women: results from the Australian longitudinal study of ageing. *BMC Public Health,* 10: 341.

Golub, M.S., Collman, G.W., Foster, P.M. *et al*., 2008. Public health implications of altered puberty timing. *Pediatrics,* 121(Suppl. 3): S218-230.

Goon, D. T., Toriola, A. L., Uever, J., Wuam, S. and O. M. Toriola, 2010. Growth status and menarcheal age among adolescent school girls in Wannune, Benue State, Nigeria. *BMC Pediatrics*, 10: 60.

Grainage, M.J., Coupland, C.A., Cliffe, S.J., Chilvers, C.E. and D.J. Hosking, 2001. Reproductive, menstrual and menopausal factors: which are associated with bone mineral density in early postmenopausal women? *Osteoporos. Int.* 12 (9): 777–787.

Guo, Y., Shen, H., Xiao, P., Xiong, D.H., Yang, T.L., Guo, Y.F., Long, J.R., Recker, R.R. and H.W. Deng, 2006a. Genomewide linkage scan for quantitative trait loci underlying variation in age at menarche. *J. Clin. Endocrinol. Metab.* 91 (3): 1009–1014.

Guo, Y., Xiong, D.H., Yang, T.L., Guo, Y.F., Recker, R.R. and H.W. Deng, 2006b. Polymorphisms of estrogen-biosynthesis genes CYP17 and CYP19 may influence age at menarche: a genetic association study in Caucasian females. *Hum. Mol. Genet.* 15 (16): 2401–2408.

Hartge, P., 2009. Genetics of reproductive lifespan. *Nat. Genet*. 41: 637-638 doi:10.1038/ng0609-637

He, C., Kraft, P., Chasman, D.I., Buring, J.E., Chen, C., Hankinson, S.E., Pare, G., Chanock, S., Ridker, P.M. and D.J. Hunter, 2010. A large-scale candidate gene association study of age at menarche and age at natural menopause. *Hum. Genet.* 128 (5): 515–527.

He, C., Kraft, P., Chen, C., Buring, J.E., Pare, G., Hankinson, S.E., Chanock, S.J., Ridker, P.M., Hunter, D.J. and D.I. Chasman, 2009a. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. *Nat. Genet.* 41 (6): 724–728.

He, C. and J.M., Murabito, 2014. Genome wide association studies of age at menarche and age at natural menopause. *Molecular and Cellular Endocrinology*, 382(1): 767–79.

He, C., Zhang, C., Hunter, D.J., Hankinson, S.E., Louis, G.M., Hediger, M.L., Hu, F.B., 2010. Age at menarche and risk of Type 2 Diabetes: results from 2 large Prospective cohorts. *Am. J. Epidemiol*. 171, 334-344.

He, L.N., Recker, R.R., Deng, H.W. and V. Dvornyk, 2009. A polymorphism of apolipoprotein E (APOE) gene is associated with age at natural menopause in Caucasian females. *Maturitas*, 62 (1), 37–41.

He, L.N., Xiong, D.H., Liu, Y.J., Zhang, F., Recker, R.R. and H.W. Deng, 2007. Association study of the oestrogen signalling pathway genes in relation to age at natural menopause. *J. Genet.* 86 (3): 269–276.

Hefler, L.A., Worda, C., Huber, J.C., Tempfer, C.B., 2002. A polymorphism of the Nos3 gene and age at natural menopause. *Fertil. Steril.* 78 (6), 1184–1186.

Hirschhorn, J.N., Lohmueller, K., Byrne. E and K. Hirschhorn, 2002. A comprehensive review of genetic association studies. *Genet Med*; 4: 45–46.

Hong, K.W., Kim, C.S., Min, H., Park, S.J., Park, J.K., Ahn, Y., Kim, S.S., and Y. Kim, 2013. Replication of genomewide association studies on age at menarche in the Korean population. *Genes & Genomics*. 35: 69-75.

Hosny, L.A., El-Ruby, M.O., Zaki, M.E., Agian, M.S., Zaki, M.S., El, Gammal, M.A. and I.M. Mazen, 2005. Assessment of pubertal development in Egyptian girls. *Journal of Paediatrics and Endocrinology Metabolism,* 18: 577-584.

Hwang, J.Y., Shin, C., Frongillo, E.A., Shin, K.R. and I. Jo, 2003. Secular trend in age at menarche for South Korean women born between 1920 and 1986: The Ansan Study. *Ann Hum Biol*., 30: 434-442.

Kaltiala-Heino, R., Kosunen, E. and M. Rimpela, 2003. Pubertal timing, sexual behaviour and self-reported depression in middle adolescence. *J Adolesc*., 26: 531–545.

Kaltiala-Heino, R., Rimpella, M., Rissanen, A. and P., Rantanen, 2001. Early puberty and early sexual activity are associated with bulimic-type eating pathology in middle adolescence. *J. Adolesc Health,* 28: 346-352.

Kaplowitz P.B., 2008. Link between body fat and the timing of puberty. *Pediatrics,* 121(Suppl 3): S208–217.

Kaprio, J., Rimpela, A., Winter, T., Viken, R.J., Rimpela, M. and R.J. Rose, 1995. Common genetic influences on BMI and age at menarche. *Hum. Biol.* 67 (5) : 739–753.

Kevenaar, M.E., Themmen, A.P., Rivadeneira, F., Uitterlinden, A.G., Laven, J.S., van Schoor, N.M., Lips, P., Pols, H.A. and J.A. Visser, 2007. A polymorphism in the AMH type II receptor gene is associated with age at menopause in interaction with parity. *Hum. Reprod*. 22 (9): 2382–2388.

Khadilkar, V.V., Stanhope, R.G. and V. Khadilkar, 2006. Secular Trends in Puberty. *Indian Pediatrics*. 43: 475-478

Khanna, G. and S. Kapoor, 2004. Secular Trend in Stature and Age at Menarche Among Punjabi Aroras Residing in New Delhi, India. *Collegium Anthropologicum*. 28(2), 571 575.

Khatoon, T., Verma, A.K., Kumari, R., Rupam, R., Singh, M., and A. Rizvi, 2011. Age at menarche and affecting bio-social factors among the girls of Lucknow, UP. J. *Indian Acad Forensic Med*. 33(3): 221-223.

Kok, H.S., Onland-Moret, N.C., van Asselt, K.M., van Gils, C.H., van der Schouw, Y.T., Grobbee, D.E., P.H. and Peeters, 2005. No association of estrogen receptor alpha and cytochrome P450c17alpha polymorphisms with age at menopause in a Dutch cohort. *Hum. Reprod.* 20 (2): 536–542.

Koochmeshgi, J., Hosseini-Mazinani, S.M., Morteza Seifati, S., Hosein-Pur-Nobari, N. and L. Teimoori-Toolabi, 2004. Apolipoprotein E genotype and age at menopause. *Ann. N.Y Acad. Sci.* 1019: 564–567.

Liu, Y.Z., Guo, Y.F., Wang, L., Tan, L.J., Liu, X.G., Pei, Y.F., Yan, H., Xiong, D.H., Deng, F.Y., Yu, N., Zhang, Y.P., Zhang, L., Lei, S.F., Chen, X.D., Liu, H.B., Zhu, X.Z., Levy, S., Papasian, C.J., Drees, B.M., Hamilton, J.J., Recker, R.R. and H.W. Deng, 2009. Genome-wide association analyses identify SPOCK as a key novel gene underlying age at menarche. *PLoS Genet*. 5 (3): e1000420

Lunetta, K.L., D'Agostino Sr., R.B., Karasik, D., Benjamin, E.J., Guo, C.Y., Govindaraju, R., Kiel, D.P., Kelly-Hayes, M., Massaro, J.M., Pencina, M.J., Seshadri, S. and J.M. Murabito,

2007. Genetic correlates of longevity and selected age-related phenotypes: a genome-wide association study in the Framingham study. *BMC Med. Genet.* 8 (Suppl 1): S13.

Marozzi, A., Manfredini, E., Tibiletti, M.G., Furlan, D., Villa, N., Vegetti, W., Crosignani, P.G., Ginelli, E., Meneveri, R. and L. Dalpra, 2000a, Molecular definition of Xq common-deleted region in patients affected by premature ovarian failure. *Hum Genet* 107, 304–311.

Marshall, W.A. and J. M. Tanner, 1969. Variations in pubertal changes in girls. *Arch Dis Child.,* 44(235): 291-303.

Melby, M. K., and M. Lampl, 2011. Menopause, A Biocultural Perspective. *Annual Review of Anthropology,* 40(1): 53–70.

Melby, M. K., Lock, M. and P. Kaufert, 2005. Culture and symptom reporting at menopause. *Human reproduction update*, 11(5): 495–512.

Meyer, J.M., Eaves, L.J., Heath, A.C. and N.G., Martin, 1991. Estimating genetic influences on the age-at-menarche: a survival analysis approach. *Am. J. Med. Genet.* 39(2): 148–154.

Morris, D.H., Jones, M.E., Schoemaker, M.J., Ashworth, A. and A.J. Swerdlow, 2010. Determinants of age at menarche in the UK: analyses from the Breakthrough Generations Study. *Br. J. Cancer,* 103 (11): 1760–1764.

Murabito, J.M., Yang, Q., Fox, C., Wilson, P.W. and L.A. Cupples, 2005a. Heritability of age at natural menopause in the Framingham Heart Study. *J. Clin. Endocrinol. Metab*. 90: 3427–3430.

Naves, M., Diaz-Lopez, L.B., Gomez, C., Rotriguez-Rebollar, A. and J.B. Cannata-Andia, 2005. Determination of incidence of osteoporotic fractures in the female Spanish population older than 50. *Osteoporosis Int,* 16: 2013-2017.

Ong, K.K., Northstone, K., Wells, J.C., Rubin, C., Ness, A.R., Golding, J. and D.B. Dunger, 2007. Earlier mother's age at menarche predicts rapid infancy growth and childhood obesity. *PloS Med.,* 4: e132.

Otero, U. B., Chor, D., Carvalho, M.S., Faerstein, E., Lopes Cde, S. and G.L.Werneck, 2010. Lack of association between age at menarche and age at menopause: Pró-Saúde Study, Rio de Janeiro, Brazil. *Maturitas* 67(3): 245-250.

Pan, F., Xiao, P., Guo, Y., Liu, Y.J., Deng, H.Y., Recker, R.R. and H.W. Deng, 2008. Chromosomal regions 22q13 and 3p25 may harbor quantitative trait loci influencing both age at menarche and bone mineral density. *Hum. Genet.* 123 (4): 419–427.

Parent, A.S., Teilmann, G., Juul, A., Skakkebaek, N.E., Toppari, J. and J.P. Bourguignon, 2003. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr. Rev.* 24 (5): 668–693.

Pathak, P. K., Tripathi, N. and S. V. Subramanian, 2014. Secular Trends in Menarcheal Age in India-Evidence from the Indian Human Development Survey, *PLoS ONE,* 9(11). doi:10.1371/journal.pone.0111027

Peccei, J.S., 2000. Genetic correlation between the ages of menarche and menopause. *Hum Nat*, 11:43–63.

Perry, J.R., Corre, T., Esko, Tonu., Chasman, D.I., Fischer, K., Franceschini, N., He, C., *et al*., (2013). A genome-wide association study of early menopause and the combined impact

of identified variants. *Human Molecular Genetics.* 22(7), 1465-1472, doi:10.1093/hmg/dds551

Perry, J.R., Stolk, L., Franceschini, N., Lunetta, K.L., Zhai, G., McArdle, P.F., Smith, A.V., Aspelund, T., Bandinelli, S., Boerwinkle, E., Cherkas, L., Eiriksdottir, G., Estrada, K., Ferrucci, L., Folsom, A.R., Garcia, M., Gudnason, V., Hofman, A., Karasik, D., Kiel, D.P., Launer, L.J., van Meurs, J., Nalls, M.A., Rivadeneira, F., Shuldiner, A.R., Singleton, A., Soranzo, N., Tanaka, T., Visser, J.A., Weedon, M.N., Wilson, S.G., Zhuang, V., Streeten, E.A., Harris, T.B., Murray, A., Spector, T.D., Demerath, E.W., Uitterlinden, A.G. and J.M. Murabito, 2009. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. *Nat. Genet.* 41 (6): 648–650.

Poomalar, G.K. and B. Arounassalame, 2013. The quality of life during and after menopause among rural women. *J Clin Diagn Res.* 7(1): 135-139.

Prakash, C., Srvastava, B., Gaur, S., Bala, R. and A. Rai and Roham, 2010. Age of menarche in girls of Uttrakhand. *J. Indian Acad. Forensic Med.,* 32(1), 49-51.

Priya, B.D., Veeraju, P. and T.V. Rao, 2009. Menarcheal and Menopausal age distribution among the Kshatriya women of north coastal Andhra Pradesh. *Anthropologist*, 11(3):233-236.

Rees, M., 1995. The age of menarche. *Orgyn*. 4: 2–4.

Rizk, D.E., Bener, A., Ezimokhai, M., Hassan, M.Y. and R. Micallef, 1998. The age and symptomatology of natural menopause among United Arab Emirates women. *Maturitas*, 29:197–202.

Rothenbuhler, A., Lotton, C. and D. Fradin, 2009. Three common variants of LEP, NPY1R and GPR54 show no association with age at menarche. *Horm Res*., 71: 331–335.

Rothenbuhler, A., Fradin, D., Heath, S., Lefevre, H., Bouvattier, C., Lathrop, M. and P. Bougneres, 2006. Weight-adjusted genome scan analysis for mapping quantitative trait Loci for menarcheal age. *J. Clin. Endocrinol. Metab.* 91 (9): 3534–3537.

Shafeie, H. N., Kaveh, A. A., and M. Shafeie, 2013. Study of Nutrition and Mobility Effect on the Quality of Life in Menopause Women in Tabriz-Iran. *Advances in Bioresearch,* 4(4): 51–53.

Sharma, K., 2002. Genetic basis of human female pelvic morphology: a twin study. *Am. J. Phys. Anthropol*. 117(4): 327–333.

Sharma, S., Tandon, V.R. and A. Mahajan, 2007. Menopausal symptoms in urban women. JK Sci., 9(1): 13-17.

Singh, S.P. and P. Malhotra, 1988. Secular shifts in menarcheal age of Patiala (India) school girls between 1974 and 1986. *Ann. Hum. Biol*. 15(1): 77-80.

Singh, M., 2012. Early Age of natural menopause in India, a biological marker for early preventive health programs. *Climateric*. 15(6): 581-586.

Snieder, H., MacGregor, A. J. and T. D. Spector, 1998. Genes Control the Cessation of a Woman's Reproductive Life/ : A Twin Study of Hysterectomy and Age at Menopause. *Journal of Clinical Endocrinology and Metabolism*, 83(6): 1875-1880.

Stolk, L., Perry, J.R., Chasman, D.I., He, C., Mangino, M., Sulem, P., Barbalic, M., Broer, L., Byrne, E.M., Ernst, F., *et al*., 2012. Meta-analyses identify 13 loci associated with age at

menopause and highlight DNA repair and immune pathways. *Nat. Genet*. 44 (3): 260–268.

Stolk, L., Zhai, G., van Meurs, J.B., Verbiest, M.M., Visser, J.A., Estrada, K., Rivadeneira, F., Williams, F.M., Cherkas, L., Deloukas, P., Soranzo, N., de Keyzer, J.J., Pop, V.J., Lips, P., Lebrun, C.E., van der Schouw, Y.T., Grobbee, D.E., Witteman, J., Hofman, A., Pols, H.A., Laven, J.S., Spector, T.D. and A.G. Uitterlinden, 2009. Loci at chromosomes 13, 19 and 20 influence age at natural menopause. *Nat. Genet.* 41 (6): 645–647.

Sulem, P., Gudbjartsson, D.F., Rafnar, T., Holm, H., Olafsdottir, E.J., Olafsdottir, G.H., Jonsson, T., Alexandersen, P., Feenstra, B., Boyd, H.A., Aben, K.K., Verbeek, A.L., Roeleveld, N., Jonasdottir, A., Styrkarsdottir, U., Steinthorsdottir, V., Karason, A., Stacey, S.N., Gudmundsson, J., Jakobsdottir, M., Thorleifsson, G., Hardarson, G., Gulcher, J., Kong, A., Kiemeney, L.A., Melbye, M., Christiansen, C., Tryggvadottir, L., Thorsteinsdottir, U. and K. Stefansson, 2009. Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. *Nat. Genet.* 41 (6): 734–738.

Susman, E.O., Nottelmann, E.P., Dnoff-Germain, G.E., Dorn, L.D., Cutler, G.B. Jr, *et al*., 1985. The relation of relative hormonal levels and physical development and social-emotional behaviour in young adolescents. *Journal of Youth and Adolescence* 14: 245-254.

Talwar, I. and P. Bajwa, 2005. Age at Menarche in relation to body size and physiological variables among Rajput girls. *Pb.Univ.Res. J. (Sci).* 55: 1-5.

Talwar I, Sharma K and S. Kapur, 2010. Growth trends in body, fat, circumferential and physiological traits during adolescence among Rajput females of Theog, Shimla District (Himachal Pradesh), India. *Ann Hum Biol,* 37(4): 536–553.

Talwar, I., Kansal, A. and P. Jindal, 2012. Growth Pattern and Menarcheal Status in Relation to Body Size and Physique among Adolescent Rural Girls of Pinjore-Nalagarh dun Valley. *Human Biology Review* 1 (1): 68-83.

Tanikawa, C., Okada, Y., Takahashi, A., Oda, K., Kamatani, N., Kubo, M., Nakamura, Y. and K. Matsuda, 2013. Genome Wide Association Study of Age at Menarche in the JapanesePopulation. *PloS ONE,* 8(5): e63821. Doi:10.1371/journal.pone.0063821

teVelde, E.R., Dorland, M. and F.J. Broekmans, 1998a. Age at menopause as a marker of reproductive ageing. *Maturitas,* 30: 119–125.

teVelde, E.R. and P.L., Pearson, 2002. The variability of female reproductive ageing. *Hum. Reprod. Update* 8 (2): 141–154.

Torgerson, D.J., Thomas, R.E. and D.M. Reid, 1997. Mothers and daughters menopausal ages: is there a link? *Eur. J. Obstet. Gynecol. Reprod. Biol*. 74 (1): 63–66.

Treloar, S.A. and N.G. Martin, 1990. Age at menarche as a fitness trait: nonadditive genetic variance detected in a large twin sample. *Am. J. Hum. Genet.* 47 (1): 137–148.

Trevathan, W. R., 2007. Evolutionary Medicine. *Annual Review of Anthropology*, 36(1): 139–154. doi:10.1146/annurev.anthro.36.081406.094321

van Asselt, K.M., Kok, H.S., Putter, H., Wijmenga, C., Peeters, P.H., van der Schouw, Y.T., Grobbee, D.E., te Velde, E.R., Mosselman, S. and P.L. Pearson, 2004b. Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative trait loci influencing variation in human menopausal age. *Am. J. Hum. Genet*. 74 (3): 444–453.

van Noord, P.A., Dubas, J.S., Dorland, M., Boersma, H. and E., teVelde, 1997. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. *Fertil. Steril*. 68 (1): 95–102.

Velie, E.M., Nechuta, S. and J.R. Osuch, 2006. Lifetime Reproductive and Anthropometric Risk Factors for Breast Cancer in Postmenopausal Women. *Breast Disease*. 24(1): 17-35.

Vitzthum VJ., 2003. A number no greater than the sum of its parts: the use and abuse of heritability. *Hum Biol.*, 75:539–558.

Voorhuis, M., Onland-Moret, N.C., van der Schouw, Y.T., Fauser, B.C. and F. J. Broekmans, 2010. Human studies on genetics of the age at natural menopause: a systematic review. *Human Reproduction Update*, 16 (4): 364–377. doi: 10.1093/humupd/dmp055.

Worda, C., Walch, K., Sator, M., Eppel, W., Tempfer, C.B., Schneeberger, C., Huber, J.C. and L.A., Hefler, 2004. The influence of Nos3 polymorphisms on age at menarche and natural menopause. *Maturitas*, 49 (2): 157–162.

World Health Organisation Scientific Group. Research on the menopause in the 1990s. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser 1996; 866:1–107.

Xita, N., Chatzikyriakidou, A., Stavrou, I., Zois, C., Georgiou, I. and A. Tsatsoulis, 2010. The (TTTA)n polymorphism of aromatase (CYP19) gene is associated with age at menarche. *Hum Reprod*, 25:3129–3133.

Zhao, J., Xiong, D.H., Guo, Y., Yang, T.L., Recker, R.R. and H.W. Deng, 2007. Polymorphism in the insulin-like growth factor 1 gene is associated with age at menarche in caucasian females. *Hum. Reprod.*, 22 (6): 1789–1794.