Ind. J. Phys. Anthrop. & Hum. Genet. Vol. 35. No. 1, (2016) : 49-76

UNDERSTANDING THE GENETICS OF AGE AT MENARCHE AND AGE AT NATURAL MENOPAUSE THROUGH THREE GENETIC APPROACHES: A REVIEW

Mahima Gulabani, Vipin Gupta and Mohinder Pal Sachdeva

ABSTRACT

Genetic studies on menarche and menopausal timings are sparse but represent just the beginning. This review presents the findings reported in light of candidate-gene association studies, genome-wide linkage analyses and genome-wide association studies with an emphasis on the possible future prospects for uncovering the hidden basis of age at menarche and menopause.

English-language articles until January 2017 were retrieved from Pub Med and Google Scholar databases (search string "candidate-gene, linkage, genome-wide, association study in combination with menarche and menopause") and reference lists of relevant articles. Few articles were excluded following HuGE review guidelines.

Menarche and menopause are complex traits and their timings vary with ethnicity and geographies. They are influenced by both genetic and environmental factors and have been found to be associated with several complex disorders. The genetic variation studies have been tried to understand, through candidate-gene association studies, genome-wide linkage analyses, and genome-wide association studies (GWAS), out of which only GWASs have proved to be highly successful in identifying significant associations in contrast to other two approaches.

The studies reveal that all the identified loci affecting menarche and menopausal timings needs replication and validation on diverse ethnic groups through the implementation of a systems approach which may lead to identification of causal variants, expanding our knowledge of the underlying physiology and biological regulation of these traits.

Key words: Menarche, Menopause, Genetic studies, MTHFR, TNFRSF11A

INTRODUCTION

A woman's health mainly revolves around pre- and post-reproductive phases. These two phases of a woman's life are significantly marked by the two hallmark events,

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

also epidemiologically denoted by age at menarche (AAM) and age at natural menopause (ANM). Menarche (first menstruation) and menopause (end of menstruation) are significant qualitative developmental events in the lives of females (te Velde and Pearson, 2002), given its relevance to general as well as reproductive health. Menarche is defined as the start of menstruation and occurs at a mean age of approximately 13 years with a normal range of 9 to 17 years, normally about 2 years after the onset of puberty. 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). Owing to women health implications, both the events have been found to be highly associated with several chronic health risks, followed by morbidity and mortality.

Early menarche is found to be associated with the risk for gynaecological cancers, viz. breast cancer (Kvale 1992; Peeters *et al.*, 1995; Velie *et al.*, 2006), ovarian cancer (Salehi *et al.*, 2008; Hartge *et al.*, 2009) and endometrial cancer (Kaaks *et al.*, 2002; Xu *et al.*, 2004; Dossus *et al.*, 2010; He *et al.*, 2010; Stockl *et al.*, 2011; Cramer *et al.*, 2012), obesity (Adair and Gordon-Larsen, 2001; Freedman, 2003; Ong *et al.*, 2007), type 2 diabetes (Lakshman *et al.*, 2008; He *et al.*, 2010), hypertension (Hartge, 2009) and shorter adult stature (Ong *et al.*, 2007). Earlier menopause has been linked with increased risk for cardiovascular diseases (Barett-Conor and Goodman Gruen, 1995; van der Schouw *et al.*, 1996; Wise *et al.*, 1996; Hu *et al.*, 1999; Mondul *et al.*, 2005; Atsma *et al.*, 2006; Lisabeth *et al.*, 2009), osteoporosis (Kritz Silverstein and Barett-Conor, 1993; Ito *et al.*, 1995; Osei-Hyiaman, 1998; Grainage *et al.*, 2001) and mortality (Hu *et al.*, 1999; Mondul *et al.*, 2005; Osserwade *et al.*, 2005; Jacobsen *et al.*, 2003, 2007; Lakshman *et al.*, 2009; Giles *et al.*, 2010).

A late menopause has been linked with increased risk for breast cancer (La Vecchia *et al.*, 1992; Kok *et al.*, 2005) and mental health problems (Golub *et al.*, 2008; Lakshman *et al.*, 2008). Conversely, late menarche and early menopause has been found to be associated with increased risk of osteoporosis (Silman, 2003; Paganini-Hill *et al.*, 2005; Naves *et al.*, 2006), decreased incidence of coronary heart disease (Kannel *et al.*, 1976; Rees *et al.*, 1995; van der Graaf *et al.*, 1997; Cooper *et al.*, 1999; Cui *et al.*, 2006), reduced fertility span (te Velde and Pearsons, 2002), Alzheimer's diseases (Paganini-Hill and Henderson, 1994, 1996; Rees *et al.*, 1995) and stroke (Cui *et al.*, 2006). Also associated with increased risk for a number of psychosocial outcomes in adolescents includes substance use, sexual risk taking, teenage pregnancy (Stice *et al.*, 2001; Harlow *et al.*, 2004; Golub *et al.*, 2008), depression (Kaltiala-Heino *et al.*, 2003) and eating disorders (Kaltiala-Heino *et al.*, 2001). Recent data also suggests that AAM is significantly associated with body composition, insulin sensitivity and blood lipid levels (Feng *et al.*, 2008; Dvornyk and Ul-Haq, 2012).

There is a secular trend in the AAM and ANM with a steady decline in past several decades (Hwang *et al.*, 2003; Herman-Giddens 2007; Dvornyk and Ul-Haq., 2012)

both in developed countries (Anderson *et al.*, 2003; Anderson and Must, 2005; Biro *et al.*, 2006) and developing countries (Singh and Malhotra, 1988; Bagga and Kulkarni, 2000; Hwang *et al.*, 2003; Hosny *et al.*, 2005; Goon *et al.*, 2010). AAM and ANM are complex traits that are influenced by several intricate array of environmental, lifestyle, epigenetic and genetic factors. Environmental and lifestyle factors include improved nutritional status (ESHRE_Capri_Workshop_Group, 2006; Khadilkar *et al.*, 2006), climatic influences (Albright *et al.*, 1990, Khadilkar *et al.*, 2005), smoking (van Asselt *et al.*, 2004c; Kok *et al.*, 2005), socio-demographic factors, urbanization, sedentary lifestyle (Treloar and Martin, 1990; Meyer *et al.*, 1991; Kaprio *et al.*, 1995; Chie *et al.*, 1997; Gold *et al.*, 2001; Morris *et al.*, 2010), hormonal regulation (IGF-1, ghrelin, leptin and insulin) (Parent *et al.*, 2003; DiVall and Radovick, 2008), improved socio-economic (Gold *et al.*, 2001; Khatoon *et al.*, 2011) and sanitary conditions (Gama, 2008), decreased physical activity (Kaplowitz, 2008; Cho *et al.*, 2009), body mass index(BMI) and childhood obesity (Khatoon *et al.*, 2011) etc. Heritability estimates from family and twin studies ranges from 53% to 74% for AAM (Chie *et al.*, 1997; Kaprio *et al.*, 1995; van der Berg *et al.*, 2007; Meyer *et al.*, 1991; Sharma, 2002) and from 44% to 65% for ANM (de Bruin *et al.*, 2001; Murabito *et al.*, 2005a; Sneider *et al.*, 1998; van Asselt *et al.*, 2004b and Voorhuis *et al.*, 2010). Also, it has 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), which suggest the possible involvement of genetic influences.

Therefore, in this review we have made an attempt to provide an overview of recent studies conducted on age at menarche and age at natural menopause via three genetic approaches namely candidate-gene association studies, genome-wide linkage analyses and genome-wide association studies. After discussing the major findings we sought to suggest the possible future prospects in relation to menarche and menopausal timings.

METHODS

All papers published in English language were searched until January 2014 from electronic databases such as MEDLINE (Pub Med) and Google Scholar using the keywords menarche, age at menarche, menopause and age at menopause in combination with 'polymorphism', 'genetics', 'candidate gene', 'linkage', 'genome wide' and 'association study'. In addition reference lists of relevant articles were also screened. All the retrieved papers were then screened for relevance to the topic of this manuscript following the HuGE guidelines (Bray *et al.*, 2006; Ioannidis *et al.*, 2008). Following these guidelines few papers were excluded and thus final selected set of articles included all papers on candidate gene association studies, genome-wide linkage analyses and genome-wide association studies on age at menarche and age at menopause (Figure 1).

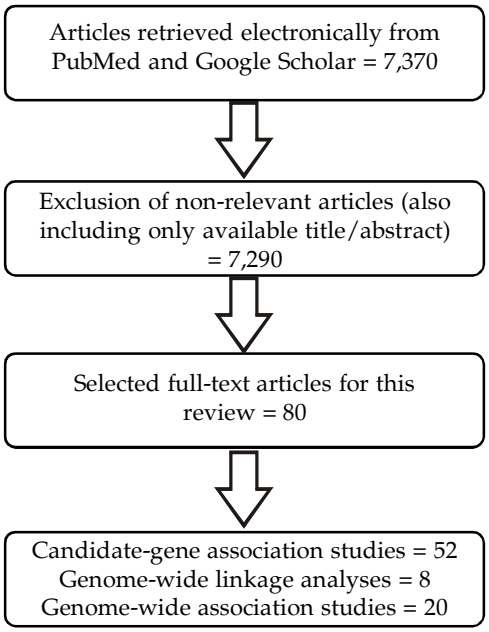

Figure 1: Flowchart depicting the process of selection of genetic studies for age at menarche and age at menopause

RESULTS

In total 7,370 articles on the genetics of age at menarche and menopause emerged. These include 52 articles on candidate-gene association studies, 8 on genome-wide linkage analysis and 20 on genome-wide association studies for menarche and menopause which are discussed as follows.

CANDIDATE GENE ASSOCIATION STUDIES

Till date many candidate gene association studies have been conducted in association with age at menarche (Table 1A) and age at natural menopause (Table 1B) on various ethnic groups including Europeans, Chinese, Japanese, Blacks, Indian-Pakistani and African-Americans. Of this majority of the genes can be divided into two major biological pathways: genes involved in Steroid-hormone or estrogen-metabolism and biosynthesis pathways and Vascular-function related genes and few other miscellaneous genes.

Candidate-genes related to estrogen-metabolism and biosynthesis pathways

As explained earlier, menarche and menopause are associated with significant changes in hormone levels, in particular organ-specific effects of estrogen on growth, differentiation, and function of reproductive tissues (Sizonenko, 1989; Voorhuis *et al.*, 2010; Dvornyk and Ul-Haq, 2012). However, many studies conducted have

yielded very few consistent associations. The first report published in 1997 in relation to association of estrogen-metabolizing genes with age at menarche found that A17A1 genotype of the common Msp1 polymorphism of the CYP17 genes was found to be associated with a later age at menarche (Fiegelson *et al.*, 1997). Subsequently, many other studies on CYP family genes were conducted in relation to both AAM (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). However, some studies did not reveal any effect of CYP polymorphisms on age at menarche, i.e. $p > 0.05$ (Kulik-Rechberger *et al.*, 2007) and age at natural menopause (Guo *et al.*, 2006b; He *et al.*, 2007). However, a CYP polymorphism was found to commonly associate with an earlier age at menarche (Mitchell *et al.*, 2008) and a later age at natural menopause (Long *et al.*, 2006), i.e. CYP1B1. Another member CYP19A1 gene was found to be associated with both AAM (Guo *et al.*, 2006b; Mitchell *et al.*, 2008; Xita *et al.*, 2010) and ANM (He *et al.*, 2007; Mitchell *et al.*, 2008). However, two of the studies related to AAM (Mitchell *et al.*, 2008; Xita *et al.*, 2010) must be treated cautiously as these employed very small sample sizes (130 and 152 respectively).

Estrogen receptor α (ESR1) is a pleiotropic gene commonly studied for its association with various phenotypes. Two frequently analysed polymorphisms of this gene are Xba I (rs9340799) and PvuII (rs2234693) (Dvornyk and Ul-Haq., 2012). The first candidate gene association study on age at natural menopause was conducted in 1999 by Weel *et al.* and found a significant association between the PvuII SNP in the estrogen-receptor gene (ESR1), which could not be replicated in subsequent studies (Gorai *et al.*, 2003; Kok *et al.*, 2005; Dvornyk *et al.*, 2006b). Another polymorphism of this ESR2 with ANM was found by He *et al.*, 2007 and later confirmed in 2010 by He *et al.* Both these polymorphisms were also found to be associated with age at menarche in some studies (Stavrou *et al.*, 2002; Long *et al.*, 2005; Stavrou *et al.*, 2006) but not in others (Stavrou *et al.*, 2002; Gorai *et al.*, 2003; Boot *et al.*, 2004; Mitchell *et al.*, 2008; Silva *et al.*, 2010; Manuck *et al.*, 2011). Another association of ANM in the estrogen-synthesizing gene hydroxysteroid dehydrogenase (HSD17B1) was found to be associated with late menopause (Mitchell *et al.*, 2008), but not studied in subsequent studies. One more study found a significant association of functional polymorphism (rs1042838, Val660Leu) of the progesterone receptor gene (PGR) with AAM (Taylor *et al.*, 2010).

Vascular-function related candidate genes

It has been hypothesised that disease associated with vascular ageing and traits (AAM and ANM) associated with reproductive importance are linked to each other such as, cardiovascular disease is associated with AAM and ANM (van der Schouw *et al.*, 1996; Hu *et al.*, 1999; Mondul *et al.*, 2005 and Lisabeth *et al.*, 2009) showing individual variation in these two traits (Kurjak and Kupesic, 1995; Hayward *et al.*, 2000). Conversely, cardiovascular risk factors are associated with AAM and ANM (Kok *et al.*, 2006).

Three genes involved in vascular function pathway such as Factor V (FV), apolipoprotein E gene (APOE) and nitric oxide synthase (Nos3) have been found to be significantly associated with AAM (Worda *et al.*, 2004; Tempfer *et al.*, 2005; Liu *et al.*, 2010) and age ANM (Hefler *et al.*, 2002; van Asselt *et al.*, 2003; Koochmeshgi *et al.*, 2004; Worda *et al.*, 2004; Tempfer *et al.*, 2005; He *et al.*, 2009b), but needs to be replicated due to conflicting results.

Miscellaneous Genes

Besides estrogen metabolizing genes and vascular function related genes, several other genes related to both age at menarche and natural menopause involved in other metabolic processes were also studied. Chemokine (C-C motif) receptor (CCR3) is involved in metabolic pathway related to endometrial function (Zhang *et al.*, 2000), was found to be significantly associated with AAM (Yan *et al.*, 2007), and later confirmed by Liu *et al.*(2009). Similarly, another study identified a novel candidate gene i.e. Sparc/Osteonectin CWCV and Kazal-like domains proteoglycan (SPOCK) related to AAM (Liu *et al.*, 2009). As mentioned earlier serum leptin levels have been found to be inversely correlated with AAM (Ebling *et al.*, 2005; DiVall and Radovick, 2008). However two leptin genes tested for association gave negative results (Corrings *et al.*, 2001; Rothenbuhler *et al.*, 2009). In contrast, a replacement polymorphism (Q223R) of the leptin receptor gene (LEPR) was found to be significantly associated with AAM (Riestra *et al.*, 2011).

Two another most important genes TNFRSF11A and TNFSF11 (aka RANK and RANK L respectively) were found to be associated with AAM (Lu *et al.*, 2010). These are involved in cell division regulation (proliferation, immunity, morphogenesis of the lymphoid tissues) (Anderson *et al.*, 1997; So *et al.*, 2006). Other candidate gene association studies related to AAM include IGF1 (Zhao *et al.*, 2007), VDR (Grimm *et al.*, 2005), but their results are inconclusive and therefore need replication and validation in future studies.

Likewise, for ANM, Histidine decarboxylase gene (HDC), a crucial enzyme for synthesis of histamine in humans, that in turn stimulates the secretion GnRH important for female reproduction, was found to be significantly associated (Zhang *et al.*, 2006), but need validation through other studies. Other candidate gene association studies related to ANM include AMHR2 (Kevenaar *et al.*, 2007a), IL-1RA (Riener *et al.*, 2004), VDR (Dvornyk *et al.*, 2006a), DAZL (Zerbetto *et al.*, 2008). Furthermore some SNPs may not be associated with AAM and ANM directly but may influence these through SNP/SNP or/and SNP/environment interactions. For instance, methylenetetrahydrofolate reductase (MTHFR) important for homocysteine metabolism was found to be associated through three SNP/SNP interactions (Liu *et al.*, 2010). In a recent study for ANM, pair wise interaction between two SNPs in AMH (rs10407022) and AMHR2 (rs11170547) was found to be significantly associated with it (Braem *et al.*, 2013). Anti-mullerian hormone (AMH), produced solely in the ovaries is a validated biomarker for ovarian ageing, as serum levels of this hormone are strongly correlated with the number of growing

follicles (Freeman *et al.*, 2012;Visser *et al.*, 2012; van Dorp *et al.*, 2013). Therefore, AMH levels are strong predictors of ANM (Freeman *et al.*, 2012; van Dorp *et al.*, 2013).

Beside all above, the most significant study was recently conducted by He *et al.* (2010) using whole gene approach, whereby the consolidated biologically relevant information for identifying and testing whether the common polymorphism in candidate genes (including regulatory and coding regions), adjusted for multiple testing, were statistically significant at gene level. Of these, nine genes from the group of genes of biological plausible pathways and related phenotypes were associated with AAM and sixteen genes with ANM. They also found that common variants in the steroid-hormone metabolism and biosynthesis pathways were significantly associated with AAM; and the group of genes involved in extremes of phenotypes i.e. precocious or delayed puberty and premature ovarian failure, were significantly associated with AAM and ANM respectively.

Interestingly, one SNP in the FSHB genes was found to be associated with an older AAM as well as older ANM. Overall we can see that candidate gene association studies have not yielded findings that have been consistently validated and thus needs further extensive candidate gene association studies.

GENOME-WIDE LINKAGE ANALYSIS

A genome wide linkage study is usually analysed using the logarithm of the odds (LOD) score. A LOD score ≥ 3 indicates a significant evidence of linkage, while a LOD score ranges between 2 and 3 is considered as a suggestive evidence of linkage. Very few studies have been conducted in relation to age at menarche and age at natural menopause and that to all only in European descent consisting of sister-pairs which are discussed as follows:

Age at Menarche (AAM)

Till date, in total four genome wide linkage analyses related to AAM have been published (Table 2A). A univariate genome wide linkage scan by Guo *et al.* (2006a) found a strong linkage signal at genomic region of 22q13 (LOD = 3.70) and other two suggestive linkage signals on 22q11 (LOD = 2.68) and 11q23 (LOD = 1.98) respectively. They also detected significant epistatic interactions between genomic regions 22q13 and 3q13. Pan *et al.* (2008) conducted a bivariate genome wide linkage scan and reported a significant signal at chromosomal region (LOD = 3.33) along with an additional suggestive genomic region 3p25 (LOD = 2.36) that may harbour genes for both AAM and bone mineral density.

Another study conducted by Rothenbuhler *et al.* (2006) reported two linkage regions at 16p21 (LOD = 3.33), 16p12 (LOD = 3.12) and one suggestive region at 8p12 (LOD = 2.18), who incorporated adjustments for menarcheal weight in their analysis. These loci might be involved in weight-independent variability of AAM (He and Murabito, 2014). However, the sample size of this study was much smaller, only 98

sister-pairs. The last and the most recent study till date was done by Anderson *et al.*(2008). Despite the large genome scan and large number of independent sister-pairs, no significant linkage signals were identified, but reported a suggestive locus at 12q (LOD = 2.0).

However, certain regions span about 1Mb and harbour nearly 50 genes, some of which may be candidate genes for AAM (Rothenbuhler *et al.*, 2006). Furthermore, all these linkage studies need replication for better understanding.

Age at natural menopause (ANM)

Only two genome wide linkage analyses related to ANM have been conducted till date (Table 2B). van Asselt *et al.* (2004) conducted the first genome wide linkage analysis related to ANM using selective sampling restricting the sib-sister pairs with menopausal ages in the extremes of menopausal age distribution (≤ 45years and/or ≥ 54years) (van Asselt *et al.*, 2004b). This study found a significant locus at Xp21.3 (LOD = 3.1) and a suggestive locus at 9p21.3 (LOD = 2.6). The observed region on X chromosome has been previously reported to be linked with a region involved in premature ovarian failure (POF) and a subgroup analysis later showed that this region not only influences POF but might also affect early menopause and/or menopausal age as a whole. Another region at chromosome 9 includes multiple genes of which BCL2 gene is involved in apoptosis and the rate of apoptosis in the ovarian follicle pool could well play a role in determining ANM (Billig *et al.*, 1996) and therefore, BCL2 could be a possible contributing gene for ANM.

The second and the last genome wide linkage analysis till date, related to ANM, was done by Murabito *et al.*, 2005. No significant loci were identified but three suggestive linkage of novel loci were reported on chromosome 8 at 26cM (8p22; LOD = 2.6), chromosome 16 at 11cM (16p13.3; LOD = 2.4) and analysis adjusted for generation, smoking and BMI revealed suggestive linkage at chromosome 11 at 113cM (11q23.3; LOD = 2.1). However, these linkage studies need replication for identification of underlying genes related to age at natural menopause.

GENOME-WIDE ASSOCIATION STUDIES

To overcome the limitations and difficulties of candidate gene association studies and genome wide linkage analysis in discovery of novel susceptibility loci for age at menarche and age at natural menopause, advent of genome wide association studies brought about a significant genomic association related to age at menarche and age at natural menopause.

GWAS of age at menarche (AAM)

Since 2009 till today many studies have been carried out to study the genomic association of age at menarche (AAM) and have identified many new novel genetic loci (Table 3A). All the studies up till 2010 included women of European ancestry. In addition, most recently in 2013 five more genome wide association studies related

to AAM have been conducted. Unlike earlier studies (till 2010), here women recruited were from Chinese, Korean, African-American, Japanese ethnicity and one of the studies included multiethnic females (American-Indians, African-Americans, Asians, European-Americans, Hispanics and Native Americans). The AAM was ascertained retrospectively by self-recall (accuracy tested by Must *et al.*, 2002) to the nearest whole year in all the studies. Women reporting an AAM less than 8 years or more than 18 years were excluded from the analysis.

A significant confounding 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 Nurse's 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 simultaneously 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 genes: TMEM38B, FKTN, FSD1L, TAL2 and ZNF462) followed by the next best signal near LIN28B gene (rs7759938). Another GWAS but much smaller one was 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. Thus, it likely represents a false positive finding.

For substantially increasing the power of the study and for identification of additional loci for the phenotype of interest, a much larger genome wide association study was needed. Therefore, all the above four study groups along with several other studies merged to form the International ReproGen Consortium, which includes more than 30 studies from the US, Europe and Australia to study the genetics of reproductive traits mainly among the women of European ancestry (Elks *et al.*, 2010; Stolk *et al.*, 2012; He and Murabito., 2014) and therefore, this ReproGen Consortium identified loci for AAM in an expanded meta-analysis of 32

genome-wide association studies in 87,802 European females with replication in up to 14,731 women. In addition to known loci at LIN28B (6q16.3) and 9q31.2 (He *et al.*, 2009), this study identified 30 novel loci and evidence for a further 10 possible new menarche loci. Overall, these 42 loci account for 3.6-6.1% of the total observed variation in AAM (Elks *et al.*, 2010).

Hong *et al.* (2013) conducted a replicated study of genome wide association study on AAM 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. Thus suggesting that genetic factors related to AAM in Korean population would be different from European population, indicating role of modulating or interacting factors (environmental factors such as nutrition) in determining AAM.

In another study by Delahanty *et al.* (2013), they tried to comprehensively evaluate the transferability of AAM-associated genetic variants (37 of the already identified 42 loci by Elks *et al.*, 2010) from European to Asian ancestry (Chinese) women. Three genome wide association study cohorts of Chinese ancestry: (i) the Shanghai Breast Cancer genetic study (SBCGS). (ii) The Shanghai Endometrial Cancer genetics study (SCCGS) and (iii) the Shanghai Diabetes genetics study (SDGS) were studied to unravel whether the loci influencing AAM in Europeans also do so in Asian populations. 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 AAM (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 AAM 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 AAM 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 AAM in African-American women from 15 cohort studies [including Women's Health Initiative (WHI); four cohorts within Candidate Gene Association Resource (CARe): ARIC, CARDIA, LFS, JHS, BHS, HANDLS; eight Breast Cancer case-control studies in African-American Breast Cancer

Consortium (AABC): CBCS, CARE, MEC, NBHS,NC-BCFR/SFBCS, PLCO,WFBC, WCHS and also Black Women's Health Study (BWHS)] 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 AAM. 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, and for some of these loci, examination of African-American samples allowed resolution of multiple signals, better localization of their respective signal and stronger association with menarche than the originally reported SNPs. However, certain limitations of this study (such as sample size, inability to identify rare variants, environmental heterogeneity, and insufficient statistical power) form an interesting avenue for future investigations.

Last but not the least study of 2013 was conducted by Tanikawa *et al*., who conducted a large-scale meta-analysis of genome wide association study related to AAM 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 AAM 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 AAM. For LIN28B, although the direction of association was consistent, indicating it to be a common AAM locus, but its effects were relatively small among the Japanese population. 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 showed pleiotropic 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 al.*, 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). It has been recently demonstrated that variants of LIN28B exhibit distinctive and sex-specific height-growth-regulating effects and influence the entire period of postnatal growth from birth to adulthood (Widen *et al.*, 2010; He and Murabito, 2014). Also, LIN28B has been found to be playing an important role in modulating the relationship between childhood obesity and AAM (Grandone *et al.*, 2013) 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 AAM

with a number of variant loci involved in growth and insulin signalling (Demerath *et al.*, 2013). A positive relationship between AAM 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 (ANM)

Like AAM, since 2007 till today several genetic loci have been identified to be associated with age at natural menopause (ANM) (Table 3B). ANM was ascertained by self-recall (accuracy tested by Must *et al.*, 2002) and women with natural cessation of menses for at least 12 months were only considered in the studies excluding the cases of surgical menopause and other artificial factors for menopause including oophrectomy, hysterectomy or menopause due to chemotherapy or irradiation, or after discrimination of oral contraceptives in women using hormone replacement therapy. Lunetta *et al.* (2007) conducted the first genome-wide association study (but small in size and limited genomic coverage) 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, it yielded only modest associations that didn't reach genome-wide significance and no further independent replication studies have been conducted or have failed for this gene (Hirschhorn *et al.*, 2002). The findings of this study is interesting as it 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 ANM 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 findings, 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; near ARHGEF7). These two studies however explained only 2.69% of the phenotypic variation of ANM, suggesting that additional loci of small effect will probably be discovered in larger samples (Stolk *et al.*, 2012). In women from the Breakthrough Generation Study (BGS), variants on chromosome 5, 6, 19, 20 were found to increase the odds of early menopause (age ≤ 45 years) suggesting that common genetic variants influencing natural menopause are risk factors for early onset of menopause (Murray *et al.*, 2011; He and Murabito, 2014).

Very recently, Stolk *et al.* (2012) have identified several loci for ANM 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 $P < 5x10^{-8}$) involving pathways associated with somatic as well as reproductive ageing. Together these explained 2.5-4.1% of

the population variation in menopausal age in independent replication samples. However, common genetic variants associated with ANM 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 ANM (Perry *et al.*, 2013; Carty *et al.*, 2013). Perry *et al.* (2013) conducted a genome wide association study of early menopause and combined effect of identified variants. They undertook a meta-analysis of ten independent GWASs including 3493 early menopause cases and 13598 controls. They did not find any novel genetic variants but 17 variants previously associated with normal ANM as a quantitative trait were also found to be associated with early menopause (EM) and premature ovarian insufficiency (POI). However no evidence was found that genes from a particular biological pathway were important in EM or POI. Thus, their study suggested that EM and POI represent the tail of menopause distribution and thus have overlapping genetic etiology of variation in normal ANM and is at least partly explained by additive effects of the same polygenic variants, in consistency with study by Murray *et al.* (2011). With individuals carrying more ANM-lowering variants, have increased risk of EM and POI. They also determined the combined effect of the identified SNPs to account for approximately 30% of the variance in early menopause suggesting that the significant proportion of the genetic component to the trait is likely to be due to rarer or complex variants not captured by SNP arrays.

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 ANM (rs365132, rs2153157, rs7333181, rs1172822 and rs16991615) in American-Indian, African-American, Asians, European-Americans, Hispanics and Native Hawaiians. They replicated all SNP of ANM reported by He *et al.* (2009) and Stolk *et al.* (2009) in European-Americans except one intergenic SNP region at 13q34, in consistency with recent GWAS by Stolk *et al.* (2012). Three SNPs were found to be significantly associated with ANM 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 (n=161098 SNPs) in 4159 and 1860 African-American women from WHI and ARIC cohorts, as a part of Population Architecture using Genomics and Epidemiology (PAGE) study. They successfully replicated or generalised one previously identified variant for AAM (rs1361108/CENPW) and two variants for ANM (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, $p=2.9x10^{-07}$). Their most significant AAM association was upstream of RSF1, a gene implicated in ovarian and breast cancers (rs11604207, $p=1.6x10^{-06}$). While most associations were identified in either AAM or ANM, they did identify genes suggestively associated with both AAM and ANM: PHACTR1 and ARHGAP42.

Besides genomic associations, candidate genes located at the newly associated loci with ANM 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. This has been further studied by bivariate analysis (Hsu *et al.*, 2011) and needs more exploration. However, all these identified loci with AAM and ANM needs fine mapping or sequencing that may lead to identification of causal variants, expanding our knowledge of the underlying physiology and biological regulation of these traits.

More interestingly, none of the genome-wide significant SNPs for AAM was found to be associated with ANM 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 AAM and ANM are not only influenced solely by genetic factors but also by environmental factors.

DISCUSSION

Ovarian function appears to be associated with age at menarche and age at natural menopause so can we expect a common genetic basis underlying both traits? Our review suggested that earlier candidate-gene and linkage studies have attempted to reveal this association but have yielded inconclusive results. But few later from candidate gene association studies suggests that at least some genes likely underlies both the traits such as Methylenetetrahydrofolate reductase (MTHFR) (Liu *et al.*, 2010; Dvornyk and Ul-Haq, 2012) and TNFRSF11A and TNFSF11 (Lu *et al.*, 2010; Dvornyk and Ul-Haq, 2012). Moreover few recent GWASs revealed few genetic variants associated with both traits such as 11q14.1 near GAB2 and 11p14.1 near FSHB gene (He *et al.*, 2010; He and Murabito, 2014). He *et al.* (2010) also indicated a possibility that different genetic variants of the same gene might be associated with different traits. This could be assisted using bivariate analysis of these two traits (He and Murabito, 2014). However, no recent publications on menarche and menopause post-2010 have revealed any shared genetic variants underlying both the traits.

Nonetheless our review showed the evidence of little overlapping in the more recent studies than the initial published studies on menarche and menopause. The lack of overlap in earlier studies could have been due to the differences in study designs. The loci identified by GWAS have smaller effect sizes which cannot be detected by linkage analysis. However in a study by Elks *et al.* (2010) two of 32 loci for AAM overlapped with the linkage signals at 16q12 and 3q13 as reported by Rothenbuhler *et al.* (2006) and Pan *et al.* (2008). 16q12 (FTO gene) is believed to be associated with childhood BMI (Frayling, 2007; Willer *et al.*, 2009; Thorleifsson *et al.*, 2009), which is believed to be associated with menarche (Ong *et al.*, 2009; Hong *et al.*, 2013). Although 13 loci identified for age at natural menopause showed no overlapping with the linkage analysis. Another reason for lack of overlap between candidate-gene and GWAS could be because of very strict significance threshold used in genome wide association studies to control the rate of false positives as by controlling the ratio of false positives, the rate of false negatives increases (Voorhuis *et al.*, 2010). Therefore, the significant associations found in candidate gene association studies appear to be false negatives and could be overlooked in GWAS. However, by liberating the significance thresholds in candidate gene association studies, genes (DMC1, EIF2B4, FSHB, POLG and RFPL4) were found to be significantly associated with age at natural menopause (Stolk *et al.*, 2012). More reasons attributing to unobserved overlaps could be genomic coverage (Pearson and Manolio, 2008; Li *et al.*, 2010; He and Murabito, 2014), population stratification and lack of power (Cooper *et al.*, 2008; Voorhuis *et al.*, 2010), small size and also the selection of wrong pathways, genes/polymorphisms (Hattersley and Mc Carthy, 2005). Therefore one needs to focus more on conducting large-scale meta-analyses and replication studies.

Although many genetic studies identified several candidate genes and genomic regions, lack of overlapping and inconsistent results still exists. This problem needs to be leveraged by more powerful future studies, focussing on modification of the existing methodologies such as by conducting meta-analyses one can increase study's sample size and statistical power. Other factors such as population stratification, ethnic and environmental heterogeneity must be controlled efficiently. Presently there is a lack of extensive data on epistatic and dominant interactions affecting menarche and menopausal timings and also the primary focus is on common-gene common-variant hypothesis, which brings in urgent need to shift our focus towards discovery and replication of rare variants, copy number variations, insertions and deletions and inversion variants which could have remained undetectable by these three genetic approaches. More extensive use of high-throughput technologies such as microarrays, exome and next-generation genetic and epigenetic sequencing can search for suitable genes underlying both traits.

A path-breaking step in future could be integration of candidate-gene, linkage, genome-wide, microarray-gene profiling and proteomic studies in a single pipeline via a system approach. Its use could be seen in a study by Elks *et al.* (2010) where a large-scale meta-analysis of previously identified candidate genes was conducted

and also by Liu *et al.* (2009) where they utilised GWAS, candidate-SNP study and haplotype-based analysis for menarcheal timing. Besides identification of genetic variants future studies should focus on exploring their epigenetic as local biologies underlying these traits might have contributed through epigenetic mechanisms. The present era of studies are limited to selective ethnicities and thus warrants the inclusion of diverse ethnic groups to bring out the role of their local biologies, this can be enhanced by integration of large international consortiums and amalgamating efforts and data of different research groups for increasing the efficiency of epidemiological research.

CONCLUSION

Despite overflowing number of researches on menarche and menopausal timings, these represent only a tip of the iceberg. Besides the three discussed approaches there is a need for integration and incorporation of new high-throughput technologies in future studies for a better understanding of the mechanisms behind menarche and menopause. However, major concern remains the actual translation of these genomic findings into clinical practices.

REFERENCES

Adair, C.S. and P. Gordon-Larsen, 2001. Maturational timing and overweight prevalence in US adolescent girls. *Am J. Public Health*, 91: 642.

Albright, D.L., Voda, A.M, Smolensky, MH, His, B.P., M. Decker, 1990. Seasonal characteristics of and age at menarche. *Prog Clin Biol Re.s*, 341: 709-720.

Anderson, C.A., Duffy, D.L., Martin, N.G., Visscher P.M., 2007. Estimation of variance components for age at menarche in twin families. *Behav Genet.,* 37:668–677.

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, D.M., Maraskovsky, E., Billingsley, W.L., Dougall, W.C., Tometsko, M.E., Roux, E.R., Teepe, M.C., DuBose, R.F., Cosman, D. and L. Galibert, 1997. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. *Nature*, 390: 175–179.

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., Must, A., 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.

Atsma, F., Bartelink, M.L., Grobbee, D.E. and Y.T. 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.

Barrette-Conor, E. and D.Goodman-Gruen, 1995. Prospective study of endogamous sex hormones and fatal CVD in postmenopausal women. *BMJ*. 311: 1193-1196.

Boot, A.M., van der Sluis, I.M., de Muinck Keizer-Schrama, S.M., van Meurs, J.B., Krenning, E.P., Pols, H.A., and , A.G., Uitterlinden, 2004. Estrogen receptor alpha gene polymorphisms and bone mineral density in healthy children and young adults. *Calcif. Tissue Int*., 74 (6): 495–500.

Braem M.G., Voorhuis, M., van der Schouw, Y.T., Peeters, P.H.M., Leo J. Schouten, L.J., Eijkemans,M.J.C., Broekmans, F.J., and N. Charlotte Onland-Moret, 2013. Interactions between Genetc Variants inAMH and AMHR2 may modify age at natural menopause. *PLoS One,* 8(3):e59819. doi: 10.1371/ journal. pone. 0059819.

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

Calle, 2005. Age at natural menopause and cause-specific mortality. *Am. J. Epidemiol*. 162 (11): 1089–1097.

Carty, C.L. Spencer, K.L. Setiawan, V.W. Fernandez-Rhodes, L., Malinowski J. , Buyske, S., Young, A., Jorgensen, N.W., Cheng,I., Carlson, C.S., Brown-Gentry,K., Goodloe,R., Park,A., Parikh, N.I., Henderson,B., Le Marchand,L., Wactawski-Wende, J., Fornage, M., Matise,T.C., Hindorff,L.A., Arnold, A.M., Haiman,C.A., Franceschini, N., Peters, U., and D.C. Crawford , 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*, 28(6): 1695–1706.

Castrillon, D.H., Miao, L., Kollipara, R., Horner, J.W., 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., Hur J.Y., Kim, Y.T., Kim, S.H., Lee, K.W. and T. Kim, 2010. Age at menarche in a Korean population: secular trends and influencing factors. *European Journal of Pediatrics,* 169(1): 89-94.

Cooper R.S, Tayo, B. and X. Zhu, 2008. Genome-wide association studies: implications for multiethnic samples. *Hum Mol Genet.,* 17: 151–155.

Cooper, G.S., Ephross, S.A., Weinberg, C.R., Baird, D.D., Whelan, E.A. and D.P. Sandler, 1999. Menstrual and reproductive risk factors for ischemic heart disease. *Epidemiology,* 10 (3): 255–259.

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, 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.

de Bruin, J.P. Bovenhuis, H. van Noord, P.A.H. Pearson, P.L. van Arendonk, J.A.M. teVelde, 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. Shu, X.O., 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.

Di Vall, S.A. and S. Radovick, 2008. Pubertal development and Menarche. *Ann. N.Y. Acad.Sci.*, 1135: 19-28.

Dossus, L., Allen, N., Kaaks, K., Bakken, K., Lund, E., *et al.*, 2010, Reproductive risk factors and endometrial cancer: the European Prospective Investigation into cancer and nutrition. *Int. J. Cancer.* 127: 427-451.

Dvornyk, V. and W. Ul-Haq, 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.

Ebling, F.J.P., 2005. The neuroendocrine timing of puberty. *Reproduction*. 129: 675-683.

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.

Freedman, D.S., Khan, L.K., Serdula, M.K., Dietz, W.H., Srinivasan, S.R. and G.S. Berenson, 2002. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa Heart study, *BMC Pediatr*. 3: 3.

Freeman EW, Sammel MD, Lin H. and C.R. Gracia, 2012. Anti-Mullerian Hormone as a Predictor of Time to Menopause in Late Reproductive Age Women. *J Clin Endocrinol Metab.,* 97: 1673–1680.

Gama, A., 2008. Age at menarche in Portuguese rural women from Oleiros. *Annals of Human Biology*, 35 (6): 639-655.

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.

Gold, E.B., Bromberger, J., Crawford, S., Samuels, S., Greendale, G.A., Harlow, S.D. and J. Skurnick, 2001. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am. J. Epidemiol.,* 153 (9): 865–874.

Golub, M.S., Collman, G.W., Foster, P.M. Kimmel, C.A., Rajpert-De Meyts, E., Reiter, E.O., Sharpe, R.M., Skakkebaek, N.E. and J. Toppari, 2008. Public health implications of altered puberty timing. *Pediatrics*, 121(Suppl. 3) : S218-230.

Gorai, I., Tanaka, K., Inada, M., Morinaga, H., Uchiyama, Y., Kikuchi, R., Chaki, O. and F. Hirahara, 2003. Estrogen-metabolizing gene polymorphisms, but not estrogen receptor alpha gene polymorphisms, are associated with the onset of menarche in healthy postmenopausal Japanese women. *J. Clin. Endocrinol. Metab*. 88 (2):799–803.

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

Grimm, C., Tempfer, C.B., Walch, K., Reinthaller, A., Tomovski, C., Huber, J.C., Leodolter, S. and L.A. Hefler, 2005. The influence of a Vitamin D receptor gene polymorphism on the timing of female reproductive functions in humans. *Maturitas,* 51 (2): 135–139.

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. Genomewidelinkage 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 and R. R., 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.

Harlow, B.L., Cohen, C.S., Otto, M.W., Spiegelman, D. and D.W. Cramer, 2004. Early life menstrual characterstics and pregnancy experiences among women with and without major depression: the Harvard study of moods and cycles. *J. Affect Disord*, 79: 167-176.

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

Hattersley A.T. and M.I. McCarthy, 2005. What makes a good genetic association study? *Lancet,* 366: 1315–1323.

Hayward, C.S., Kelly, R.P. and P. Collins, 2000. The roles of gender, the menopause and hormone replacement on cardiovascular function. *Cardiovasc Res,* 46: 28–49.

Hayward, C., Killen, J.D., Wilson, D.M., Hammer, L.D., Litt, I.F., Kraemer, H.C, Haydel F., Varady, A. and C.B. Taylor, 1997. Psychiatric risk associated with early puberty in adolescent girls. *J Am Acad Child Adolesc Psychiatry*, 36: 255–262.

He, C. and J.M., Murabito, 2012. Genome wide association studies of age at menarche and age at natural menopause. *Molecular and Cellular Endocrinology, http://dx.doi.org/10.1016/j.mce.2012.05.003*

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., Zhang, C., Hunter, D.J., Hankinson, S.E., Louis, G.M., Hediger, M.L. and F.B. Hu, 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, 2009b. 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., Grimm, C., Heinze, G., Schneeberger, C., Mueller, M.W., Muendlein, A., Huber, J.C., Leodolter, S. and C.B. Tempfer, 2005. Estrogen-metabolizing gene polymorphisms and age at natural menopause in Caucasian women. *Hum. Reprod*. 20 (5): 1422–1427.

Hefler, L.A., Worda, C., Huber, J.C. and C.B. Tempfer, 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., Hirschhorn, K., 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 and Genomics*. 35:69-75

Hsu, Y.H., Chen, X. and X. Xu, 2010. A powerful multi-phenotype approach on genomewide association studies to identify novel pleiotropic genes that affect multiple quantitative traits. In: *International Genetic Epidemiology Society Meeting*, Boston, MA.

Hsu, Y.H., Chen, X., Murabito, J.M., Elks, C., Estrada, K. and T.B. Harris, 2011. Genomewide bivariate association analysis identified novel candidate genes for ages at menarche, natural menopause, and bone mineral density. *Endocrine Society meeting,* Boston, MA.

Hu, F.B., Grodstein, F., Hennekens, C.H., Colditz, G.A., Johnson, M., Manson, J.E., Rosner, B. and M.J. Stampfer,1999. Age at natural menopause and risk of cardiovascular disease. *Arch. Intern. Med*. 159 (10): 1061–1066.

Hwang J.Y., Shin, C., Frongillo, E.A., Shin, K.R. and Jo, I., 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.

Ito, M., Yamada, M., Hayashi, K., Ohki, M., Uetani, M. and T. Nakamura, 1995. Relation of early menarche to high bone mineral density. *Calcif. Tissue Int*. 57(1), 11–14.

Jacobsen, B.K., Heuch, I. and G. Kvale, 2003. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. *Am. J. Epidemiol*. 157 (10): 923–929.

Jacobsen, B.K., Heuch, I. and G. Kvale, 2007. Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. *Am. J. Epidemiol.* 166 (12): 1431–1437.

Kaaks, R., Lukanova, A. and M.S. Kurzer, 2002. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol. Biomarkers Prev*. 11 (12): 1531–1543.

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.

Kannel, W.B., Hjortland, M.C., McNamara, P.M. and T. Gordon, 1976. Menopause and risk of cardiovascular disease: the Framingham study. *Ann. Intern. Med*. 85 (4):447–452.

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.

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. and P.H. 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.

Kok, H.S., van Asselt, K.M., van der Schouw Y.T., van der Tweel, I, Peeters, P.H., Wilson, P.W., Pearson, P.L., and D.E. Grobbee, 2006. Heart disease risk determines menopausal age rather than the reverse. *J Am Coll Cardiol*., 47: 1976–1983.

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.

Kritz-Silverstein D. and E. Barrett-Connor, 1993. Early menopause, number of reproductive years, and bone mineral density in postmenopausal women, *Am J Public Health*, 83:983–988.

Kulik-Rechberger B., Skorupski P., Bogusiewicz M., Miotla P., and T. Rechberger, 2007. Polimorfizm genu CYP17 a wiek menarche [Polymorhism of CYP17 gene and age of menarche]. *Ginekol Pol* 78: 929–932.

Kurjak A. and S. Kupesic ,1995. Ovarian senescence and its significance on uterine and ovarian perfusion. *Fertil Steril*., 64: 532–537.

Kvale, G., 1992. Reproductive factors in breast cancer epidemiology. *Acta Oncol*. 31 (2): 187–194.

La Vecchia C, Negri E, Bruzzi P, Dardanoni G, Decarli A, Franceschi S, Palli D and R. Talamini, 1992. The role of age at menarche and at menopause on breast cancer risk: combined evidence from four case-control studies. *Ann Oncol*, 3: 625–629.

Lai, J., Vesprini, D., Chu, W., Jernstrom, H. and S.A. Narod, 2001. CYP gene polymorphisms and early menarche. *Mol. Genet. Metab.* 74 (4): 449–457.

Lakshman R, Forouhi N, Luben R, Bingham S, Khaw K, Wareham N, and K.K. Ong, 2008. Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. *Diabetologia*, 51(5): 781–786.

Lakshman, R., Forouhi, N.G., Sharp, S.J., Luben, R., Bingham, S.A., Khaw, K.T., Wareham, N.J. and K.K. Ong, 2009. Early age at menarche associated with cardiovascular disease and mortality. *J. Clin. Endocrinol. Metab*. 94(12): 4953–4960.

Lappalainen, T., Jarvelin, M.R., Eriksson, J.G., Raitakari, O., Salomaa, V., Sovio, U., Hartikainen, A.L., Pouta, A., McCarthy, M.I., Osmond, C., Kajantie, E., Lehtimaki, T., Viikari, J., Kahonen, M., Tyler-Smith, C., Freimer, N., Hirschhorn, J.N., Peltonen, L. and A. Palotie, 2010. Distinct variants at LIN28B influence growth in height from birth to adulthood. *Am. J. Hum. Genet.* 86 (5): 773–782.

Lisabeth, L.D., Beiser. A.S., Brown, D.L., Murabito, J.M, Kelly-Hayes, M. and P. A. Wolf, 2009. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. *Stroke* 40:1044–1049.

Liu, P., Lu, Y., Recker, R.R., Deng, H.W. and V. Dvornyk, 2010. Association analyses suggest multiple interaction effects of the methylenetetrahydrofolate reductase polymorphisms on timing of menarche and natural menopause in white women. *Menopause* 17 (1): 185–190.

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.

Long, J., Zheng, W., Xiang, Y.B., Lose, F., Thompson, D., Tomlinson, I., Yu, H., Wentzensen, N., Lambrechts, D., T. Dork, *et al.*, 2012 Genome-wide association study identifies a possible susceptibility locus for endometrial cancer. *Cancer Epidemiol Biomarkers Prev*., 21:980–987.

Long, J.R., Shu, X.O., Cai, Q., Cai, H., Gao, Y.T., Jin, F. and W. Zheng, 2006. Polymorphisms of the CYP1B1 gene may be associated with the onset of natural menopause in Chinese women. *Maturitas.* 55 (3): 238–246.

Long, J.R., Xu, H., Zhao, L.J., Liu, P.Y., Shen, H., Liu, Y.J., Xiong, D.H., Xiao, P., Liu, Y.Z., Dvornyk, V., Li, J.L., Recker, R.R. and H.W. Deng, 2005. The oestrogen receptor alpha gene is linked and/or associated with age of menarche in different ethnic groups. *J. Med. Genet*,. 42 (10):796–800.

Lu, Y., Liu, P., Recker, R.R., Deng, H.W. and V. Dvornyk, 2010. TNFRSF11A and TNFSF11 are associated with age at menarche and natural menopause in white women. *Menopause.* 17(5): 1048-1054.

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.

Manuck, S.B., Craig, A.E., Flory, J.D., Halder, I. and R.E. Ferrell, 2011. Reported early family environment covaries with menarcheal age as a function of polymorphic variation in estrogen receptor-a. *Dev Psychopathol.,* 23: 69–83.

Mitchell, E.S., Farin, F.M., Stapleton, P.L., Tsai, J.M., Tao, E.Y., Smith-DiJulio, K. and N.F. Woods, 2008. Association of estrogen-related polymorphisms with age at menarche, age at final menstrual period, and stages of the menopausal transition. *Menopause* 15 (1), 105–111.

Mondul, A.M., Rodriguez, C., Jacobs, E.J. and E.E., Calle, 2005. Age at Natural Menopause and Cause-specific Mortality. *Am J Epidemiol*., 162 (11): 1089-1097.

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.

Morris, D.H., Jones, M.E., Schoemaker, M.J., Ashworth, A. and A.J. Swerdlow, 2011. Familial concordance for age at menarche: analyses from the Breakthrough Generations Study. *Paediatr Perinat Epidemiol,* 25: 306–311.

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.

Murabito, J.M., Yang, Q., Fox, C.S. and L.A. Cupples, 2005b. Genome-wide linkage analysis to age at natural menopause in a community-based sample: the Framingham Heart Study. *Fertil. Steril*. 84 (6): 1674–1679.

Murray, A., Bennett, C.E., Perry, J.R., Weedon, M.N., Jacobs, P.A., Morris, D.H., Orr, N., Schoemaker, M.J., Jones, M., Ashworth, A. and A.J. Swerdlow, 2011. Common genetic variants are significant risk factors for early menopause: results from the Breakthrough Generations Study. *Hum. Mol. Genet*. 20 (1): 186–192.

Must, A., Phillips, S.M., Naumova, E.N., Blum, M., Harris, S., Dawson-Hughes, B. and W.M. Rand, 2002. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol*, 155: 672–679.

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., Elks, C.E., Li, S., Zhao, J.H., Luan, J., Andersen, L.B., Bingham, S.A., Brage, S., Smith, G.D., Ekelund, U., Gillson, C.J., Glaser, B., Golding, J., Hardy, R., Khaw, K.T., Kuh, D., Luben, R., Marcus, M., McGeehin, M.A., Ness, A.R., Northstone, K., Ring, S.M., Rubin, C., Sims, M.A., Song, K., Strachan, D.P., Vollenweider, P., Waeber, G., Waterworth, D.M., Wong, A., Deloukas, P., Barroso, I., Mooser, V., Loos, R.J. and

N.J.Wareham, 2009. Genetic variation in LIN28B is associated with the timing of puberty, *Nat. Genet*. 41 (6): 729–733.

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

Osei-Hyiaman, D., Santoshi, T., Ueji, M., Hideto, T. And K. Kano, 1998. Timing of menopause, reproductive years and bone mineral density: a cross sectional study of postmenopausal Japanese women, *Am. J. Epidemiol*, 148: 1055-1061.

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.

Paganini-Hill A. and V.W. Henderson, 1994. Estrogen deficiency and risk of Alzheimer disease in women, *Am J Epidemiol*. 140(3): 256-261.

Paganini-Hill, A. and V.W. Henderson, 1996. Estrogen deficiency and risk of Alzheimer disease, *Arch Intern Med.* 156(19), 2213-2217.

Paganini-Hill, A., Atchison, K.A., Gornbein, J.A., Nattiv, A., Service, S.K. and S.C. White, 2005. Menstrual and reproductive factors and fracture risk: the Leisure World Cohort Study, *J. Women's Health* (Larchmt) 14(9): 808–819.

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.

Pearson, T.A. and T.A. Manolio, 2008. How to interpret a genome-wide association study. *JAMA*, 299: 1335–1344.

Peeters, P.H., Verbeek, A.L., Krol, A., Matthyssen, M.M. and F. de Waard, 1995. Age at menarche and breast cancer risk in nulliparous women. *Breast Cancer Res. Treat*., 33 (1): 55–61.

Perry, J.R., Corre, T., Esko, T., Chasman, D.I., Fischer, K., Franceschini, N., *et al.*, 2013. A genome-wide association study of early menopause and the combined impact of identified variants. *Hum Mol Genet.,* 22(7): 1465-1472.

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.

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

Riener, E.K., Keck C., Worda C., Hefler L.A. and C..B. Tempfer, 2004. Body mass index but not a polymorphism of the interleukin-1 receptor antagonist (IL-1 RA) gene is associated with age at natural menopause. *Gynecol Obstet Invest.,* 58: 117–120.

Riestra, P., Garcia-Anguita, A., Torres-Cantero, A., Bayonas, M.J., de Oya, M. and C. Garces, 2011. Association of the Q223R polymorphism with age at menarche in the leptin receptor gene in humans. *Biol Reprod.* 84: 752–755.

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.

Salehi, F., Dunfield, L., Philips, K.P., Krewshi, D., and B.C. van der hyden, 2008. Risk factors for ovarian cancer: An overview with emphasis on hormonal factors. *J. Toxicol. Environ. Health Sci.,* Part B 11: 301.

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

Silman, A.J., 2003. Risk factors for Collis'fracture in men and women: results from the European prospective osteoporosis study. *Osteoprosis Int*., 14: 213-218.

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.

Sizonenko, P.C., 1989. Physiology of puberty. *J Endocrinol Invest*; 12: 59–63.

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. *J. Clin. Endocrinol. Metab.* 83 (6): 1875–1880.

So, T., Lee, S.W. and M. Croft, 2006. Tumor necrosis factor/tumor necrosis factor receptor family members that positively regulate immunity. *Int J Hematol,* 83:1–11.

Spencer, K. L., Malinowski, J., Carty, C. L., Franceschini, N., Fernández-Rhodes, L., Young, A. and D. C. Crawford, 2013. Genetic variation and reproductive timing: African American women from the Population Architecture using Genomics and Epidemiology (PAGE) Study.,*PloS ONE*,8(2), e55258. doi:10.1371/journal.pone.0055258.

Stavrou, I., Zois, C., Chatzikyriakidou, A., Georgiou, I. and A. Tsatsoulis, 2006. Combined estrogen receptor alpha and estrogen receptor beta genotypes influence the age of menarche. *Hum. Reprod*. 21 (2): 554–557.

Stavrou, I., Zois, C., Ioannidis, J. P. and A. Tsatsoulis, 2002. Association of polymorphisms of the oestrogen receptor alpha gene with the age of menarche. *Hum. Reprod*. 17 (4): 1101–1105.

Stice, E., Presnell, K. and S.K. Bearman, 2001. Relation of early menarche to depression, eating disorders, substance abuse and comorbid psychopathology among adolescent girls. *Dev Psychol* 3: 608.

Stockl, D., Meisinger, C., Peters, A., Thorad, B., Huth, C., Heier, M., Rathmann, W., Kowall, B., Stckl, H. and A. Doring, 2011. Age at menarche and its association with the metabolic syndrome and its components: results from the KORA F4 study. PLoS ONE, 6:e26076.

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.

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 Japanese Population. *PloS ONE* 8(5): e63821. Doi:10.1371/journal.pone.0063821.

Taylor KC, Small CM, Epstein MP, Sherman SL, Tang W, Wilson MM, Bouzyk M. and M. Marcus, 2010. Associations of progesterone receptor polymorphisms with age atmenarche and menstrual cycle length. *Horm Res Paediatr*., 74:421–427.

Tempfer, C.B., Riener, E.K., Keck, C., Grimm, C., Heinze, G., Huber, J.C., Gitsch, G. and L.A. Hefler, 2005. Polymorphisms associated with thrombophilia and vascular homeostasis and the timing of menarche and menopause in 728 white women. *Menopause* 12 (3):325–330.

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

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.

Treolar, S.A., Do, K.A. and Martin, N.G. 1998. Genetic influences on the age at menopause. *Lancet,* 352: 1084–1085.

van Asselt, K.M., Kok, H.S., Putter, H., Wijmenga, C., Peeters, P.H., van der Schouw, Y.T., Grobbee, D.E., teVelde, 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 der Graaf, Y., de Kleijn, M.J. and Y.T. van der Schouw, 1997. Menopause and cardiovascular disease. *J. Psychosom. Obstet. Gynaecol.* 18 (2): 113–120.

van der Schouw Y.T., van der Graaf, Y., Steyerberg, E.W., Eijkemans, J.C. and J.D. Banga, 1996. Age at menopause as a risk factor for cardiovascular mortality. *Lancet*; 347: 714–718.

van Dorp, W., van den Heuvel-Eibrink, M.M., Stolk, L., Pieters, R., Uitterlinden, A.G., Visser, J.A. and J.S. Laven, 2013. *Hum Reprod*. 28(4): 1069-76.

van Asselt, K.M., Kok, H.S., Pearson, P.L., Dubas, J.S., Peeters, P.H., TeVelde, E.R. and P. A.van Noord, 2004a. Heritability of menopausal age in mothers and daughters. *Fertil. Steril.* 82 (5): 1348–1351.

van Asselt, K.M., Kok, H.S., Peeters, P.H., Roest, M., Pearson, P.L., teVelde, E.R., Grobbee, D.E. and Y.T. van der Schouw, 2003. Factor V Leiden mutation accelerates the onset of natural menopause, *Menopause,* 10 (5): 477–481.

van Asselt, K.M., Kok, H.S., van Der Schouw, Y.T., Grobbee, D.E., teVelde, E.R., Pearson, P.L. and P.H. Peeters, 2004c. Current smoking at menopause rather than duration determines the onset of natural menopause. *Epidemiology* 15 (5): 634–639.

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

Visser, J.A., Schipper, I., Laven, J.S. and A.P. Themmen, 2012. Anti-Mullerian hormone: an ovarian reserve marker in primary ovarian insufficiency. *Rev Endocrinol* 8: 331–41.

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.

Widen, E., Ripatti, S., Cousminer, D.L., Surakka, I., *et al*., 2010. Distinct variants at LIN28B influence growth in height from birth to adulthood. *Am J Hum Genet.*, 86(5): 773-82.

Wise, P.M., Krajnal, K.M. and M.L., Kashon, 1996. Menopause: the aging of multiple pacemakers. *Science*. 273: 67-70.

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 Organization. WHO definition of Health, Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948. In: *Grad, Frank P. (2002). "The Preamble of the Constitution of the World Health Organization". Bulletin of the World Health Organization. 80 (12): 982.*

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(12): 3129–3133.

Xu, W.H., Xiang, Y.B., Ruan, Z.X., Zheng, W., Cheng, J.R., Dai, Q., Gao, Y.T. and X.O. Shu, 2004. Menstrual and reproductive factors and endometrial cancer risk: results from a population-based case-control study in urban Shanghai. *Int. J. Cancer* 108 (4): 613–619.

Yan, J., Kim, Y.S., Yang, X.P., Li, L.P., Liao, G., Xia, F. and A.M. Jetten, 2007. The ubiquitin-interacting motif containing protein RAP80 interacts with BRCA1 and functions in DNA damage repair response. *Cancer Res*. 67: 6647–6656.

Zerbetto, I., Gromoll, J., Luisi, S., Reis, F.M., Nieschlag, E., Simoni, M. and F. Petraglia, 2008. Follicle-stimulating hormone receptor and DAZL gene polymorphisms do not affect the age of menopause. *Fertil Steril,* 90: 2264–2268.

Zhang, F., Xiong, D.H., Wang, W., Shen, H., Xiao, P., Yang, F., Recker, R.R. and H.W. Deng, 2006. HDC gene polymorphisms are associated with age at natural menopause in Caucasian women. *Biochem. Biophys. Res. Commun*., 348 (4): 1378–1382.

Zhang, J., Lathbury, L.J. and L. A. Salamonsen, 2000. Expression of the chemokine eotaxin and its receptor, CCR3, in human endometrium. *Biol Reprod.,* 62: 404–411.

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.