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Identification of loci associated with women's reproductive traits and exploration of a shared genetic basis with obesity

Seong-ah Kwon[1] and Yoon Shin Cho[1,2,3*]

Abstract

Background The timing of menarche and menopause significantly affects women's health, with influences on cancer, cardiovascular disease, obesity, type 2 diabetes, and psychosocial problems. In addition, observational studies have reported that ages at menarche (AAM) and natural menopause (ANM) are correlated with obesity. To understand the genetic bases of these reproductive traits, we conducted a genome-wide association study (GWAS) of AAM and ANM in the Korean population. We also investigated the genetic correlation and causal relationship to explore the shared genetic architecture between reproductive traits and obesity in women.

Results Our GWA analyses of 45,608 and 21,599 adult women identified two and six genome-wide significant associations (P-value $< 5 \times 10^{-8}$) for AAM and ANM, respectively. Although most of the loci that we detected have been reported in previous studies, we have newly linked the *JHY* locus containing the SNP rs11605693 to AAM. Leveraging the GWAS results, we tested the shared genetic basis underlying AAM and ANM, which appear to be closely related to female hormone activity. Linkage disequilibrium score regression (LDSC) analysis did not identify a significant genetic correlation between the two traits. Our LDSC analyses indicated that AAM was inversely correlated with two obesity traits, body mass index (BMI) and waist circumference (WC). However, Mendelian randomization (MR) analyses did not provide evidence of a causal relationship between AAM and obesity traits.

Conclusions Overall, our study provides insights into the genetic architecture of women's reproductive traits and the shared genetic basis between AAM and obesity. Our MR analyses suggest that the genetic correlation between AAM and obesity traits results from the direct effects of genetic variants on both traits rather than a causal relationship between them.

Keywords Age at menarche, Age at menopause, Genome-wide association study, Genetic correlation, Mendelian randomization

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Background

Both menarche and menopause are significant milestones in a woman's life, representing the beginning and end of her reproductive capacity. Menarche is defined as the first menstrual period in a female adolescent [1] and typically occurs between 10 and 16 years of age (average, 12.4 years) [2]. In the Korean population, menarche occurs at 12.7 years of age on average [3]. After the first menstrual cycle, girls undergo physical changes such as breast and pubic hair development [4]. As evidence of aging, menopause can be defined as the end of a woman's menstrual cycle. Most women experience menopause between 40 and 58 years of age. The average age at menopause is 51 years in the US and UK and 49.9 years in Korea [2].

The ages at menarche (AAM) and natural menopause (ANM) have significant effects on women's health. Early menarche is associated with increased risk of breast cancer, cardiovascular disease, and obesity and type 2 diabetes and increased rates of psychosocial problems (e.g., depression, anxiety, and lower self-esteem during adolescence) [5, 6]. On the other hand, late menarche is related to a lower risk of hormone-related cancers, better bone health, and a higher risk of reproductive issues (e.g., infertility and irregular menstrual cycles) [6]. Early menopause may be linked to increased risk of osteoporosis and fractures, cardiovascular disease, and depression and anxiety [7]. On the other hand, late menopause is associated with increased risk of breast and endometrial cancer, reduced risk of osteoporosis, and improved longevity [8].

In addition to environmental factors and lifestyle, genetic factors influence both AAM and ANM. Relatively high heritabilities of AAM (53–74%) [9, 10] and ANM (49–87%) [10, 11] have been reported in twin and family studies. To understand the genetic basis of AAM, several genome-wide association studies (GWASs) have been conducted and identified about 400 genetic loci [12–16]. Most loci for AAM have been identified in women of European ancestry, while only about 30 distinct loci reaching genome-wide significance have been discovered in East Asians [15, 17, 18]. The recent GWAS meta-analysis of AAM, including 799,845 women – 166,890 of East Asian ancestry - implicated 665 genes, providing valuable insights into the biological determinants of puberty timing [19].

To date, GWASs for ANM have reported approximately 290 genetic loci [20–22]. The majority of these loci were identified in women of European descent [10, 16, 23–26], with only 16 new ANM loci discovered in East Asian women [15]. Despite these efforts, additional genetic loci need to be identified to better understand the genetic basis of these two reproductive traits in East Asians.

Although both menarche and menopause are related to the female sex hormone cycle known as the menstrual cycle, the association of AAM with ANM is uncertain. Some studies reported that women with early menarche also have early menopause [27–30], while others demonstrated an inverse association (early menarche = late menopause) or no relationship between the two traits [31–34]. A population study of 336,788 women in Norway reported that the association of AAM with ANM was weak and non-linear and that the duration of the reproductive period decreased with an increasing AAM [35]. Given the contradictory results of epidemiological studies of the relationship between menarche and menopause timing, further study of the shared genetic architecture of AAM and ANM may be valuable.

Numerous observational studies have demonstrated an effect of obesity on the timing of menarche and menopause. An inverse association between AAM and obesity traits has been reported in populations of diverse ancestries [36–39]. Long-term studies have also shown that the relationship between early menarche and increased obesity risk persists over time. Girls who reach menarche at an earlier age are reportedly more likely to have a higher BMI and greater fat mass in adulthood [40]. However, it is unclear whether obesity is associated with ANM. In some observational studies, no significant association between obesity and ANM was observed [41, 42]. On the other hand, other studies have reported a positive association between obesity and ANM [43, 44].

Understanding the effects of menarche and menopause timing on women's health is crucial because these traits have severe effects on health. In this regard, we first aimed to understand the genetic factor(s) influencing AAM and ANM. For this purpose, we conducted a GWAS to detect new genetic loci of these two traits in the Korean population. We also investigated genome-wide genetic correlations to better understand the shared genetic bases of AAM and ANM. Additionally, we tested the causal relationship to gain insight into how these two reproductive traits and obesity may influence each other genetically.

Methods

Study subjects

Subjects were recruited from three population-based cohorts of the Korean Genome and Epidemiological Study (KoGES) [45], comprising the Korea Association Resource Study (KARE) cohort [46], the Health EXAminee shared control study (HEXA) cohort [47, 48], and the CArdioVascular disease Association Study (CAVAS) cohort (formerly Health2 or the RURAL cohort) [46]. Of the 72,291 individuals in the KoGES cohorts, we used 46,323 adult women (older than 40 years old) in the present study (Table 1). Individual data on AAM and ANM were obtained through self-report at the time of the subject recruitment.

Table 1 Clinical characteristics of in study cohort subjects. The numbers for each variable represent the average for that variable

Variable	AAM	ANM	BMI	WC	WHR
N	45,608	21,599	46,314	46,284	46,238
Age (year)	54.1	54.4	54.1	54.1	54.1
BMI (kg/m^2)	24.0	24.0	24.0	24.0	24.0
Height (cm)	160.4	160.4	160.4	160.4	160.4
Weight (kg)	61.9	61.8	61.9	61.9	61.9
WHR	0.9	0.9	0.9	0.9	0.9
WC (cm)	81.3	81.2	81.3	81.3	81.3
Hip (cm)	94.1	94.1	94.1	94.1	94.1

N, number of female subjects; AAM, age at menarche; ANM, age at natural menopause; BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio

Genotyping, quality control, and imputation

In this study, genotype data were obtained from the National Biobank of Korea (NBK), Korea National Institute of Health (https://biobank.nih.go.kr/cmm/main/mainPage.do). Genotyping of KoGES subjects was performe d using the Korea Biobank Array (KBA) chip [49]. Both sample and SNP quality controls (QC) were performed using the PLINK v1.9 (https://zzz.bwh.harvard.edu/plink/) program [50]. For sample QC, we removed subjects with genotype call rates < 97%, excessive heterozygosity (het > 30% or het < 20%), high numbers of singletons (singleton > 15), gender mismatches (F < 0.8 in male and F > 0.2 in female), and second-degree relatives (IBS distance > 0.75). To infer the population structure in the study dataset, principal component analysis (PCA) was carried out by the PLINK v1.9 [50] using 169,326 SNPs, a subset of pruned markers that are in approximate linkage equilibrium. To visualize population structure, PCA plots were generated in R packages using the eigenvec values calculated from the PLINK PCA.

For the quality control of genetic variants, we excluded single-nucleotide polymorphisms (SNPs) with a call rate < 95%, minor allele frequency (MAF) < 0.01, and Hardy-Weinberg equilibrium (HWE) $P < 1 \times 10^{-6}$ [48, 51]. To extend SNP coverage, SNP imputation was performed using the IMPUTE4 program for phased genotype data with Eagle v2.3 software. The reference genome of East Asians in the 1000 Genomes Project Phase 3 [52] and the Korean reference genome [53] were used as a reference panel for SNP imputation. After imputation, SNPs with an INFO score < 0.8 and MAF < 0.01 were excluded [51]. In total, 8,056,211 SNPs remained for subsequent analyses.

Statistical analyses

GWA analyses were conducted using the KBA dataset of female subjects from the KoGES for the two reproductive traits of women (i.e., AAM and ANM) and obesity traits (i.e., body mass index [BMI], waist circumference [WC], and waist-to-hip ratio [WHR]). The number of subjects included in the GWAS were 45,608 for AAM, 21,599 for ANM, 46,314 for BMI, 46,284 for WC, and 46,238 for WHR (Table 1). The associations of the reproductive traits with genetic variants across the whole genome were tested by linear regression analysis with adjustment for age at recruitment, recruitment area, and BMI while the obesity traits were tested with adjustment for age and recruitment area. All association analyses were performed via an additive model using PLINK v1.9 (https://zzz.bwh.harvard.edu/plink/) [50]. To assess population structure in the dataset, the genomic inflation factor (λ_{gc}) of association analyses was calculated by dividing the median of the resulting χ^2 test statistics by the expected median of the χ^2 distribution.

To visualize GWA analysis results, Manhattan plots and Q-Q plots were created by the qqman package implemented in R using the PLINK output. Miami plots were generated by the gap package implemented in R using data for two different GWAS results. Regional plots were generated by LocusZoom, a web-based plotting tool, using the GWA analysis output. LocusZoom was accessed from a web interface at http://csg.sph.umich.edu/locuszoom.

Linkage disequilibrium score regression analysis

Genetic correlation refers to the proportion of variance shared by two separate traits due to genetic causes. In this context, the correlation between the genetic influences on one trait and those on another trait estimates the degree of pleiotropy or causal overlap [54].

To estimate the shared genetic architecture between the two traits of interest, a genetic correlation score (r_g) was calculated using linkage disequilibrium score regression (LDSC) software (https://github.com/bulik/ldsc) [55]. In the LDSC analysis, LD scores were extracted from an East Asian reference. Summary statistics obtained from the GWA analyses of the reproductive traits as well as the obesity traits were used in the r_g calculation for testing pairwise traits.

Mendelian randomization analysis

A Mendelian randomization (MR) analysis was performed to investigate whether AAM, as the exposure, has a causal effect on obesity traits, considered as the outcome. The key assumptions of MR are as follows: (1) the genetic variants (instrumental variables, IVs) are strongly associated with the exposure; (2) the IVs are not associated with any confounding factors of the exposure–outcome relationship; and (3) the IVs influence the outcome only through their effect on the exposure [56, 57].

In this study, independent genome-wide significant SNPs (association P-value $< 5 \times 10^{-8}$ and $r^2 < 0.6$) [58] identified from GWA analyses of AAM were selected as IVs to investigate potential causal relationships with

obesity traits. SNPs associated with known confounding factors (e.g., type 2 diabetes, dyslipidemia, and hypertension) were excluded prior to the MR analysis. To avoid horizontal pleiotropy, which may cause substantial bias in MR analysis, SNPs showing a direct effect on the outcome through other pathways independent of the exposure were also excluded.

One-sample MR analysis was performed using individual-level data from the KoGES dataset, applying a Two-Stage Least Squares (2SLS) approach implemented in the ivreg function of the R package AER (version 4.3.0). Two-sample MR analysis was also performed using GWAS summary statistics from Biobank Japan (BBJ), which included approximately 70,000 Japanese females [15, 59], in addition to the GWAS results from the KoGES dataset. An inverse-variance weighting (IVW) approach, implemented in the MendelianRandomization package in R software (version 4.3.0), was applied for the two-sample MR analysis.

Results

Identification of genetic loci for AAM and ANM

To identify genetic variants associated with the two reproductive traits of women, GWASs were conducted using the KBA dataset from the KoGES cohorts. PCA was performed prior to the GWAS to look for evidence of population substructure in the dataset. One distinct cluster was detected in the PCA plots, suggesting that there was no population structure in the KBA dataset (Supplementary Fig. 1). Based on this observation, subsequent GWA analyses were conducted without the adjustment of PCs.

Our GWA analysis identified two independent SNPs (P-value $< 5 \times 10^{-8}$) showing genome-wide significant associations with AAM (Table 2 and Fig. 1). The SNP rs2181193 (P-value $= 1.92 \times 10^{-14}$, $\beta = 0.10$) (Supplementary Fig. 2A) is an intron variant located in *LIN28B* that has been reported in previous genetic studies of AAM [16, 17, 60, 61]. It has been known that *LIN28B* expression in the pituitary gland affects gene expression and regulates pubertal development, implying the functional role of this gene in AAM [62]. Another SNP for AAM, rs11605693 (P-value $= 8.53 \times 10^{-9}$, $\beta = 0.08$), located downstream of *JHY*, was newly identified in this study (Table 2 and Fig. 2A). *JHY* is predicted to be involved in axoneme assembly and brain development [63].

In the GWAS of 21,599 women from the KoGES dataset, six independent variants exhibited a genome-wide significant association (P-value $< 5 \times 10^{-8}$) with ANM (Table 2 and Fig. 1). The SNP rs117737301 (P-value $= 1.27 \times 10^{-19}$, $\beta = -0.53$) is an upstream transcript variant of *HMCES* that was previously associated with ANM in East Asian populations [15, 64]. A genetic variant at chr4:99915490 (P-value $= 6.37 \times 10^{-12}$, $\beta =$

Table 2 GWAS results of genetic variants showing significant association (P-value $< 5 \times 10^{-8}$) with AAM and ANM.

Traits	CHR	SNP	BP	MIA	MJA	MIAF	BETA	SE	*P*-value	Near gene	Functioanl consequence	Variant details
AAM	6	rs2181193	105442327	T	A	0.25	0.10	0.01	1.92×10^{-14}	*LIN28B*	Intron variant	-
	11	rs11605693	122837037	C	T	0.25	0.08	0.01	8.53×10^{-9}	*JHY*	Downstream variant	-
ANM	3	rs117737301	128997608	C	A	0.10	-0.53	0.06	1.27×10^{-19}	*HMCES*	Upstream transcript variant	-
	4	chr4:99915490	99915490	G	GT	0.37	-0.25	0.04	6.37×10^{-12}	*EIF4E/METAP1*	Intergenic variant	-
	6	rs6923688	10929286	G	A	0.22	0.25	0.04	4.56×10^{-9}	*SYCP2L*	Intron variant	-
	8	rs3750243	37888017	C	G	0.32	0.31	0.04	1.16×10^{-16}	*EIF4EBP1*	Upstream transcript variant	-
	12	rs2277339	57146069	G	T	0.23	-0.30	0.04	3.20×10^{-13}	*PRIM1*	Missense variant	p.Asp5Ala
	15	rs17803620	89804043	T	C	0.31	-0.21	0.04	3.69×10^{-8}	*FANCI*	Missense variant	p.Ala86Val

Note: Information for the SNP ID and chromosomal position is based on NCBI genome build 37/hg19. Abbreviations are as follows: GWAS, genome-wide association study; AAM, age at menarche; ANM, age at natural menopause; CHR, chromosome; SNP, single nucleotide polymorphism; BP, base-pair (physical position); MIA, minor allele; MJA, major allele; MIAF, minor allele frequency; SE, standard error

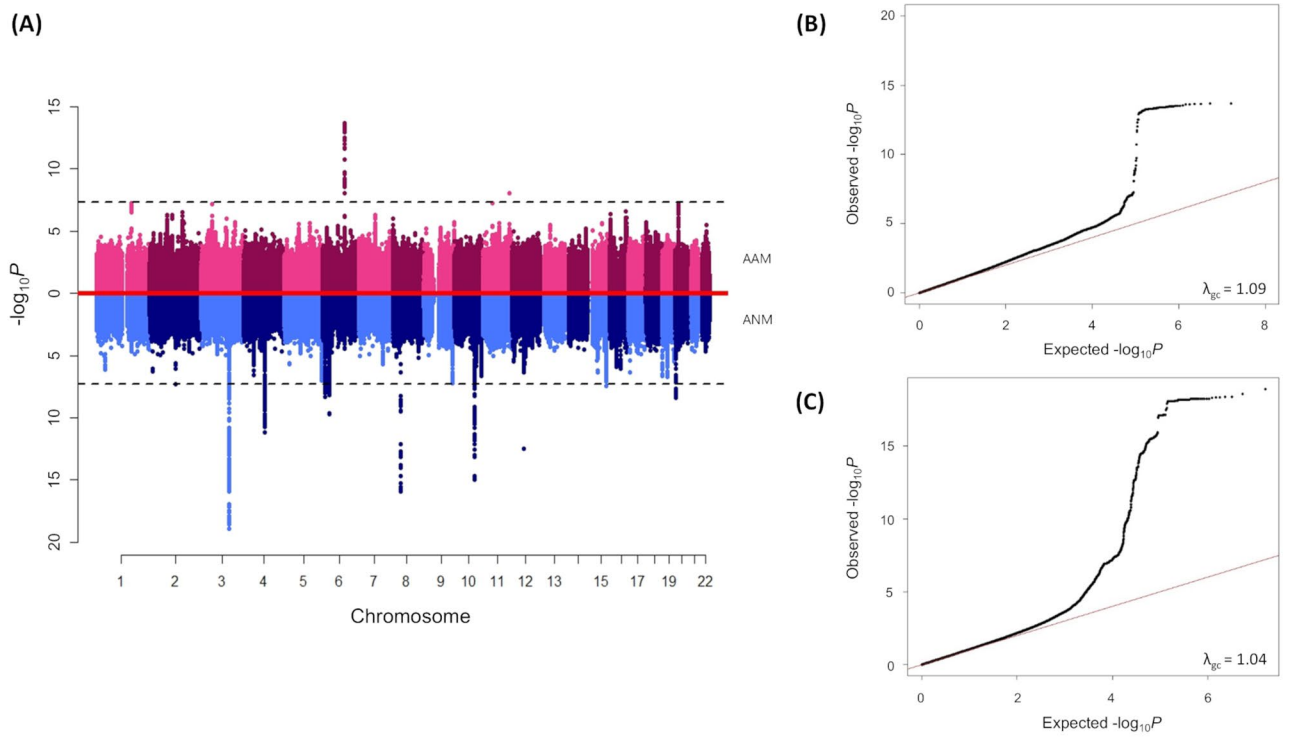

Fig. 1 Miami plot and Q–Q plots of ages at menarche (AAM) and natural menopause (ANM). (**A**) In the Miami plot, the upper panel indicates the GWA analysis results of AAM and the bottom panel indicates those of ANM. The $-\log_{10}$(association *P*-value) for each SNP across the whole genome is represented by a dot in the plot. The horizontal lines indicate the genome-wide significant association *P*-value (5.0×10^{-8}). Q–Q plots of (**B**) AAM and (**C**) ANM. In the Q–Q plots, the x- and y-axes represent the expected and observed *P*-values, respectively

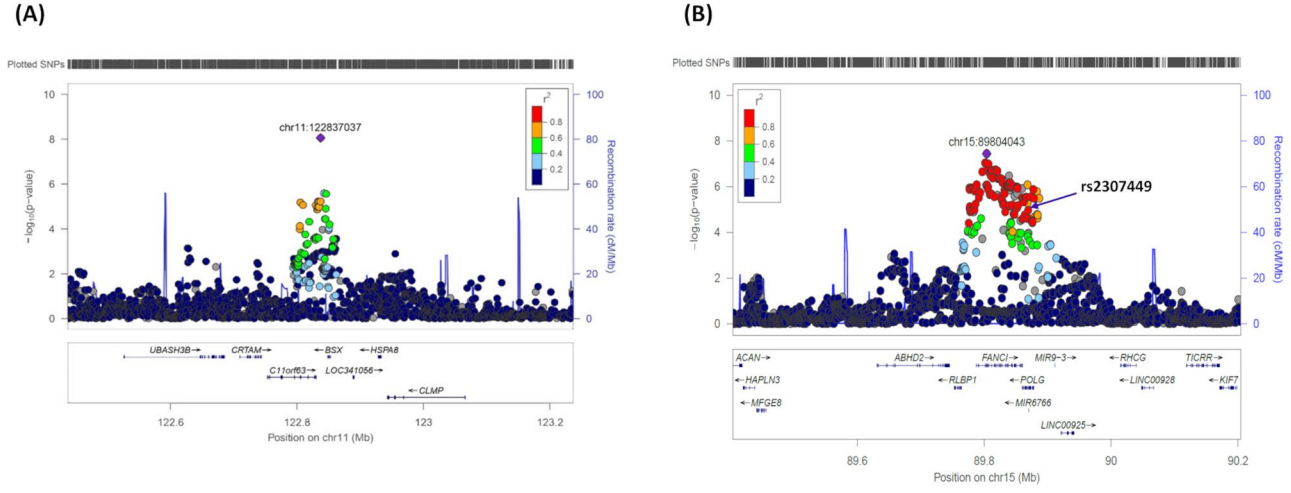

Fig. 2 Regional plots of (**A**) rs11605693 associated with age at menarche and (**B**) rs17803620 associated with age at natural menopause. In each plot, SNPs are marked with a circle denoting their chromosomal location within the genomic region 500 kb either side of the lead SNP (indicated by purple diamonds). The y-axis on the left indicates the association analysis results denoted as $-\log_{10}$(association *P*-value) for each SNP. The y-axis on the right indicates the recombination rate (cM/Mb) within the locus, estimated from 1000 Genomes Phase 3 ASN data, which is indicated by the blue line. The magnitude of the pairwise linkage disequilibrium (LD) between the lead SNP and other SNPs is represented by colors from high (red) to low (blue). At the bottom of each plot, genes are displayed in the region. The genomic positions are based on GRCh37/hg19

−0.25) is located between *EIF4E* and *METAP1*. The *EIF4E* locus has been linked to ANM in the Japanese population [15]. The SNP rs6923688 (*P*-value = 4.56×10^{-9}, β = 0.25) is in the intron of *SYCP2L*. The association of *SYCP2L* with menopause timing has been reported in previous studies of European [16, 23] and East Asian [65] ancestries. The SNP rs3750243 (*P*-value = 1.16×10^{-16}, β = 0.31) is an upstream transcript variant of *EIF4EBP1* while

rs2277339 (P-value = 3.20×10^{-13}, β = −0.30) is a missense variant of *PRIM1*. *EIF4EBP1* and *PRIM1* have also been linked to ANM in GWASs in Japanese [15] and in European [23] and East Asian [65] populations, respectively (Supplementary Fig. 2B). The SNP rs17803620 (P-value = 3.69×10^{-8}, β = −0.21), a missense variant of *FANCI*, appears to be in a strong linkage disequilibrium with rs2307449 in the *POLG* locus ($r^2 = 0.965$), previously identified for an ANM association in a European population [23] (Fig. 2B). However, the association between this locus and ANM has not been detected in East Asians.

The genomic inflation factors (λ_{gc}) were calculated as 1.09 for AAM and 1.04 for ANM in our GWA analyses. These values, which are close to 1, indicate that our GWAS were well controlled for type 1 errors related to population structure.

Quantification of the genome-wide genetic correlation between AAM and ANM

Considering that the reproductive milestones AAM and ANM are controlled by women's sex hormone cycle, we hypothesized that there would be shared genetic factors underlying the two traits. To test this hypothesis, we conducted LDSC and observed no significant genome-wide genetic correlation between AAM and ANM (r_g = 0.17, P-value = 0.10) (Table 3 and Fig. 3). This result is in agreement with a previous study suggesting no genetic correlation between menarche and menopause [66]. It also supports epidemiological studies that show no relationship between the two traits [31–33].

Quantification of the genome-wide genetic correlation between women's reproductive traits and obesity traits

Based on epidemiological studies demonstrating a significant correlation between women's reproductive traits and obesity, we conducted the LDSC analysis to determine whether the correlation is due to a shared genetic basis between these traits. Prior to the LDSC analysis, summary statistics of obesity traits (BMI, WC, and WHR) were also obtained from GWA analyses of about 46,300 female individuals from the KoGES cohorts (Supplementary Tables 1 and Supplementary Figs. 3 and 4). Our LDSC analyses using the GWAS results of reproductive traits and obesity traits revealed a significant genetic correlation of AAM with BMI ($r_g = -0.23$, P-value = 9.00×10^{-4}) and WC ($r_g = -0.16$, P-value = 0.04). However, no significant genetic correlations were detected for ANM and obesity traits (BMI, WC, and WHR) (Table 3 and Fig. 3). These results strongly suggest that the observations from physiological, clinical, and epidemiological studies are likely due to genetic factors shared between women's reproductive traits and obesity [37, 41, 67].

Table 3 LDSC analysis results between women's reproductive traits and obesity traits.

Trait 1	Trait 2	r_g	SE	P-value
AAM	ANM	0.17	0.11	0.10
	BMI	-0.23	0.07	9.00×10^{-4}
	WC	-0.16	0.08	0.04
	WHR	-0.11	0.08	0.17
ANM	BMI	0.04	0.08	0.62
	WC	0.04	0.09	0.67
	WHR	-0.03	0.09	0.71

Abbreviations are as follows: LDSC (Linkage disequilibrium score regression); rg, genetic correlation; SE, standard error; AAM, Age at menarche; ANM, Age at natural menopause; BMI, Body mass index; WC, Waist Circumference; WHR, Waist hip ratio

Inference of a causal relationship between AAM and obesity traits

Genetic correlations between separate traits are believed to be achieved either through the direct effects of variants on both traits (pleiotropy) or through the causal effect of one trait on the other. To clarify the genetic basis underlying the observed genetic correlation between AAM and obesity traits (BMI and WC) in this study, we explored the causal relationship between these traits.

In the KoGES dataset, obesity measures obtained at the time of subject recruitment reflect adult obesity and do not account for childhood obesity. Therefore, we performed MR analyses to investigate the causal effect of AAM on adult obesity, excluding testing of childhood obesity's causal effect on AAM. In this study, two independent SNPs for AAM (rs2181193 and rs11605693) were initially selected based on our IV selection criteria. As they were not directly associated with confounding factors such as T2D, dyslipidemia, and hypertension, nor with the outcome traits (obesity traits), these SNPs were used as IVs for the subsequent MR analyses (Supplementary Table 2).

Our one-sample MR analysis, applying a Two-Stage Least Squares (2SLS) method, revealed that the genetically determined risk factor of AAM did not significantly affects the outcome of obesity traits (BMI and WC). Even when we performed two-sample MR using the IVW method with the BBJ dataset, no causal relationship between AAM and obesity traits was observed (Fig. 4).

Discussion

Menarche and menopause are crucial milestones in a woman's life. Early or late onset of menarche and menopause has been linked to various health conditions [5–8]. In this regard, genetic studies can provide insights into the biological mechanisms underlying these processes. At least 400 and 290 genetic loci have been reported for AAM and ANM, respectively, from numerous GWASs [22, 61]. In this study, we conducted GWA analyses to catalog genetic loci for AAM and ANM in the Korean

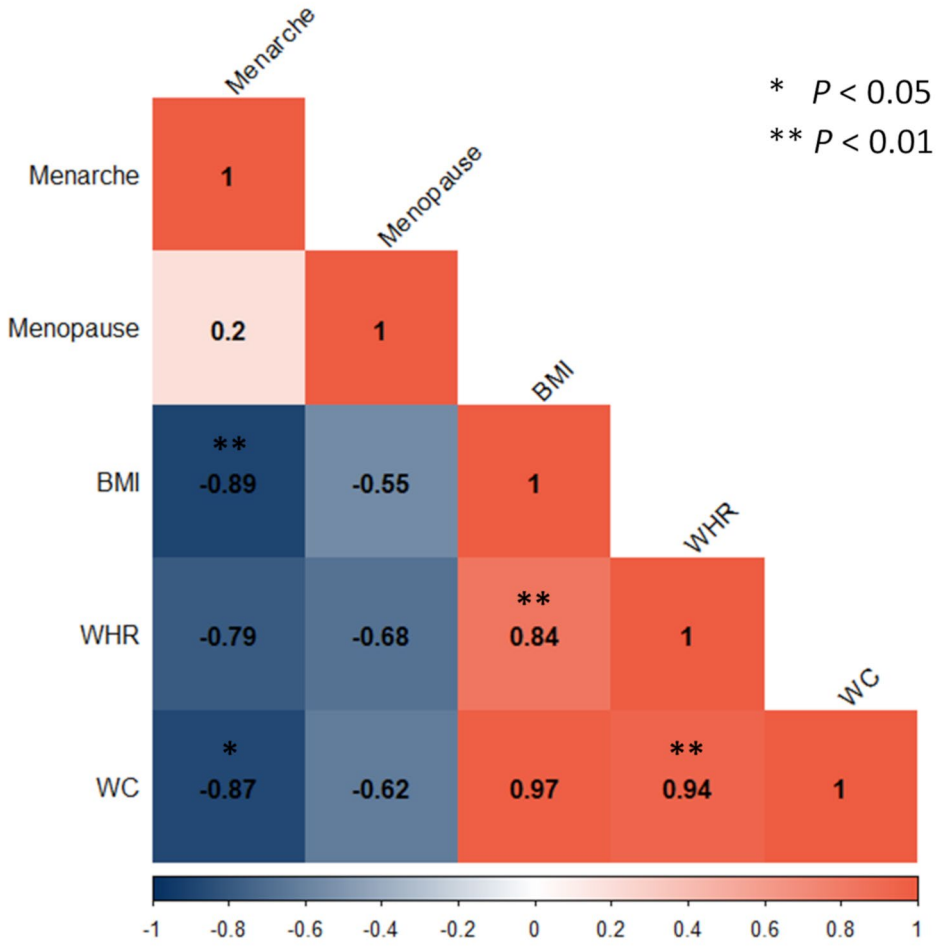

Fig. 3 Heat map of the genetic correlation between women's reproductive traits and obesity traits. Red- and blue-colored boxes represent positive and negative genetic correlations, respectively. Numbers in the boxes indicate the genetic correlation coefficients between the traits being compared. *Genetic correlations with *P*-values less than 0.05; **genetic correlations with *P*-values less than 0.01

Note: Abbreviations are as follows: BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference

population. To the best of our knowledge, this study is one of the largest GWAs conducted for AAM and ANM in an East Asian population. The genetic associations identified here were further tested to gain insight into the shared genetic architecture underlying these reproductive traits of women and obesity.

We identified two strong associations with AAM in loci for *LIN28B* (*lin-28 homolog B*) and *JHY* (*junctional cadherin complex regulator*). The protein encoded by *LIN28B* is a member of the lin-28 family, which is characterized by the presence of a cold-shock domain and a pair of CCHC zinc finger domains [68]. *LIN28B* is highly expressed in several tissues, including the pituitary, testes, fetal liver, and placenta. Specifically, rs2181193, the lead SNP of the association with AAM detected in this study, showed a significant association with the expression of *LIN28B* in the pituitary, further implying the close link between this gene and menarche timing. Indeed, it is believed that the onset of menarche results from reactivation of the hypothalamic-pituitary-gonadal axis, which is controlled by complex interactions among genetic and environmental factors [69]. An association of the *LIN28B* locus with AAM has been reported in multiple studies of East Asian [17, 61] and European [16, 60] descents. A previous study suggested the *LIN28B* gene as the first genetic regulator of the timing of human pubertal growth and development based on its association with earlier breast development in girls, earlier voice breaking and more advanced pubic hair development in boys, a faster tempo of height growth in girls and boys, and shorter adult height in women and men, in keeping with an earlier growth cessation [60].

The association of the rs11605693 locus with AAM is a new finding of this study. Although the association of this SNP with AAM has been detected in GWAS from BBJ, it did not reach genome-wide significance (P-value = 3.38×10^{-7}) [15]. GWA summary statistics from BBJ indicated that the effect direction and

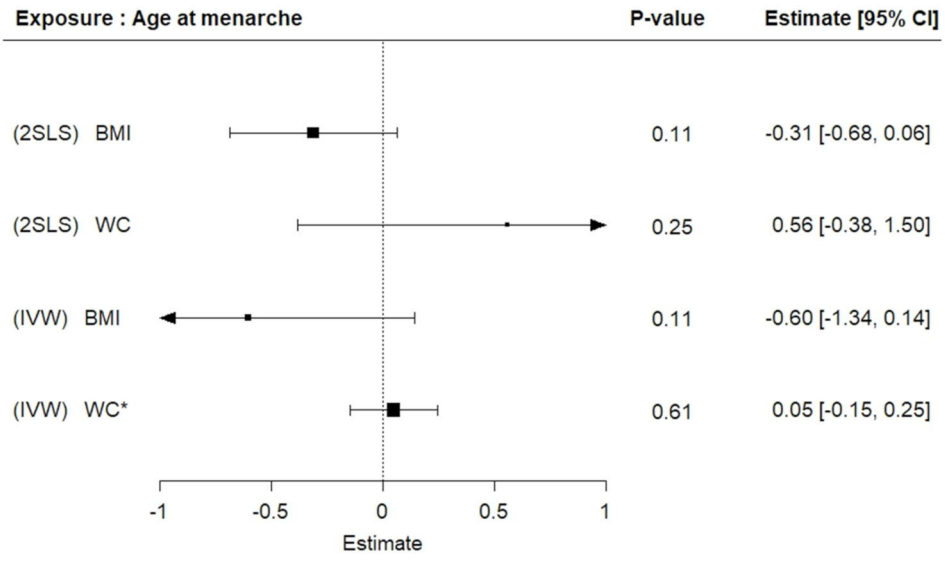

Fig. 4 Mendelian randomization results showing the causal effect of age at menarche (exposure) on obesity traits (outcome). A one-sample MR analysis was performed using individual-level data from the KoGES dataset, applying a Two-Stage Least Squares (2SLS) method. A two-sample MR analysis was conducted using GWAS summary statistics from Biobank Japan (BBJ) in addition to the GWAS results from the KoGES dataset applying an inverse-variance weighting (IVW) approach

Note: * Independent SNPs with association *P*-value less than 10^{-7} were used for IVW analysis of the causal relationship between AAM and WC. Abbreviations are as follows: AAM, age at menarche; BMI, body mass index; WC, waist circumference

size (β = 0.05, minor C allele frequency = 0.23) are consistent with our results (β = 0.08, minor C allele frequency = 0.25). These findings support our results.

The lead SNP rs11605693 downstream of *JHY* showed a significant association with the expression of *JHY* in the testes, tibial nerve, and subcutaneous adipose tissue. The protein encoded by *JHY* participates in several processes, including cerebrospinal fluid circulation, motile cilium assembly, and regulation of establishment of planar polarity [63]. The functional relevance of *JHY* in menarche timing needs to be elucidated through biological studies.

Genetic aspects of early menopause have been investigated by genome-wide linkage analyses, candidate gene association studies, and GWASs. These previous studies have revealed candidate genes involved in sex steroid hormone metabolism and biosynthesis pathways, in anti-Müllerian hormone signaling, in the vascular pathway, and in pathways affecting development such as the DNA damage repair and cell cycle regulation [70]. The six ANM genes identified in this study (i.e., *HMCES*, *EIF4E*, *SYCP2L*, *EIF4EBP1*, *PRIM1*, and *FANCI*) are likely involved in pathways affecting development. Of these genes, the associations of *HMCES*, *EIF4E*, *EIF4EBP1*, and *PRIM1* with ANM have been reported in East Asian populations [15, 64]. Like many genes associated with ANM, *PRIM1* is involved in DNA replication, suggesting its functional relevance in the timing of menopause [22]. The *SYCP2L* locus was previously associated with ANM in several studies [16, 23, 65] including the study in Japanese women [15].

The *FANCI* (*FA complementation group I*) gene encodes a protein that play a role in the repair of DNA double-strand breaks. This protein is predicted to be required for the maintenance of chromosomal stability [71]. The association of the *FANCI* locus with ANM has never been detected in East Asians. However, *POLG* (chr15:89,859,551 – 89,878,055), located in close proximity to *FANCI* (chr15:89,787,210 – 89,860,362), has been reported to be associated with ANM in the European population [23]. Two genes, *FANCI* and *PLOG*, are also in strong LD in both Europeans and East Asians ($r^2 = 0.86$). Therefore, it is presumed that the identification of two different genes representing the ANM association of 3q21.3 in the two ethnic groups is due to the genetic differences in allele frequencies of the two genes between two groups or different environmental factors between Korean and European populations. Interestingly, both *FANCI* and *POLG* play a role in DNA replication and repair [71, 72], highlighting the findings of previous study that these functions may be important in the timing of menopause [23].

In this study, we detected a significant genetic correlation between AAM and obesity traits. This result suggests that common genetic variants contribute to both traits, indicating horizontal pleiotropy. This finding may enhance our understanding of comorbidities and risk prediction related to AAM and obesity. However, a genetic correlation does not necessarily imply causation

between two different traits, highlighting the need for MR analysis to draw causal inferences.

Based on the results of our LDSC analyses, we tested the genetic causal relationship between AAM and obesity traits (BMI and WC). In this study, our MR approach was limited to testing the causal effect of AAM on obesity traits, as the available obesity measures in our dataset only represent adult obesity. Due to the lack of childhood obesity data, we could not test the genetic causal effect of obesity on the timing of menarche in this study. A two-sample MR analysis using GWAS results for childhood obesity from independent studies could help overcome this limitation. Finally, our MR analyses revealed that the genetically determined risk factor of AAM did not significantly affect the outcome of obesity traits, including BMI and WC.

Conclusion

Our study identifies genetic associations with menarche and menopause timing in Korean women and provides evidence of a shared genetic basis between AAM and obesity. MR analyses further suggest that the genetic correlation between AAM and obesity traits arises from the direct effects of genetic variants on both traits (pleiotropy) rather than a causal relationship between them. Overall, our findings may contribute to the development of more personalized strategies for women's healthcare.

Abbreviations

GWAS	Genome-wide association study
AAM	Ages at menarche
ANM	Ages at menopause
LDSC	Linkage disequilibrium score regression
BMI	Body mass index
WC	Waist circumference
WHR	Waist-to-hip ratio
KoGES	Korean Genome and Epidemiological Study
KARE	Korea Association Resource Study
HEXA	Health EXAminee shared control study
CAVAS	CArdioVascular disease Association Study
NBK	National Biobank of Korea
KBA	Korea Biobank Array
SNP	Single nucleotide polymorphism
MAF	Minor allele frequency
HWE	Hardy-Weinberg equilibrium
MR	Mendelian randomization
IVW	Inverse-variance weighting
GTEx	Genotype-Tissue Expression
eQTL	Expression quantitative trait loci

Supplementary Information

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Supplementary Figure 1: PCA plots of the dataset consisting of 46,323 adult women were generated using the first three principal components (PCs). The plots show PC1 on the x-axis and PC2 on the y-axis (**A**), PC1 on the x-axis and PC3 on the y-axis (**B**), and PC2 on the x-axis and PC3 on the y-axis (**C**). **Supplementary Figure 2**: Regional plots of (**A**) rs2181193 showing a strong association with age at menarche and of (**B**) rs117737301, chr4:99915490, rs6923688, rs3750243, and rs2277339 showing a strong association with age at natural menopause. In each plot, SNPs are marked with a circle denoting their chromosomal location within the genomic region 500 kb either side of the lead SNP (indicated by purple diamonds). The y-axis on the left indicates the association analysis results denoted as $-\log_{10}$(association *P*-value) for each SNP. The y-axis on the right indicates the recombination rate (cM/Mb) within the locus, estimated from 1000 Genomes Phase 3 ASN data, which is indicated by the blue line. The magnitude of pairwise linkage disequilibrium (LD) between the lead SNP and other SNPs is represented by colors from high (red) to low (blue). At the bottom of each plot, genes are displayed in the region. The genomic positions are based on GRCh37/hg19. Supplementary Figure 3: Manhattan plots of GWA analyses of BMI (**A**), WC (**B**), and WHR (**C**). In the Manhattan plot, the $-\log_{10}$(association *P*-value) for each SNP across the whole genome is depicted as a dot. The red line indicates the genome-wide significant *P*-value (5.0×10^{-8}). **Note**: Abbreviations are as follows: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio. **Supplementary Figure 4**: Quantile–quantile (Q–Q) plots of GWA analyses of BMI (**A**), WC (**B**), and WHR (**C**). In the Q–Q plot, the x- and y-axes represent the expected and observed *P*-values, respectively. **Note**: Abbreviations are as follows: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio

Supplementary Table 1: GWAS results of genetic variants showing a significant association with obesity traits (*P*-value $<5\times10^{-8}$). **Note**: Information for the SNP ID and chromosomal position is based on NCBI genome build 37/hg19. Abbreviations are as follows: GWAS, genome-wide association study; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; CHR, chromosome; SNP, single-nucleotide polymorphism; BP, base pair (physical position); MIA, minor allele; MJA, major allele; MIAF, minor allele frequency; SE, standard error

Supplementary Table 2: Associations of IVs (SNPs) selected for the exposure ($P<5\times10^{-8}$ & $r^2<0.6$) with confounding factors and outcome traits. Association results were obtained from the KoGES dataset, except for those of the outcome traits used in the IVW MR analysis, which were derived from the BBJ dataset. **Note**: Information for the SNP ID and chromosomal position is based on NCBI genome build 37/hg19. Abbreviations are as follows: MR, Mendelian randomization; CHR, chromosome; IV, instrumental variable; CHR, chromosome; SNP, single nucleotide polymorphism; BP, base-pair (physical position); AAM, age at menarche; T2D, type 2 diabetes; BMI, body mass index; WC, waist circumference; 2SLS, two-stage least squares; IVW, inverse-variance weighting; NA, not available in the BBJ dataset

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Author contributions

S.K. contributed to the manuscript preparation, table and figure creation, and statistical analysis. Y.S.C. contributed to the study design, data collection and synthesis, and manuscript preparation, revision, and submission.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (HIRB-2023-047) of Hallym University. Informed consent was obtained from all study subjects.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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