WEB APPENDIX

AGES: The Reykjavik Study cohort comprises a random sample of the individuals born 1907-1935 and living in Reykjavik during 1967 (71% recruitment rate). Between 2002-2006 survivors of the original cohort were invited to be re-examined and 1,849 women participated in the AGES-Reykjavik Study for genotyping. This study was approved by the National Bioethics Committee, the Data Protection Authority, and the MedStar Institutional Review Board. Written informed consent was obtained from all participating subjects.

AMISH: The Old Order Amish cohort is drawn from a founder population in Lancaster County, PA, which can be defined by one 14-generation pedigree. The characteristics of the women in this study have been described previously (1-5). Institutional Review Board (IRB) approval was obtained from the University of Maryland, Baltimore and all participants gave informed consent. Age at menarche was self-reported, and women pregnant or 6 months postpartum were excluded. Genotyping was conducted on either the Affymetrix 500k or 6.0 genotyping chip at the UMB Genomics Core Facility (Baltimore MD 21201). A (n-1)-degree-of-freedom t test was used to assess the significance of the measured genotype. The polygenic component was modeled using the relationship matrix derived from the complete 14-generation pedigree structure, to properly control for the relatedness of all subjects in the study.

ARIC: The Atherosclerosis Risk in Communities (ARIC) Study is a predominantly bi-racial population-based cohort recruited from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban areas of Minneapolis, Minnesota; and Washington County, Maryland, USA (50). The 15,792 men and women in ARIC were between 45-64 years of age at baseline and were then followed up through time (http://www.cscc.unc.edu/aric/). Caucasian women with genotype information and a self-reported age at menarche at baseline (between 9

and 17 years of age) were included in this meta-analysis (n=4,775). This study was approved by each IRB at each field site, and by the Public Health and Nursing IRB of the University of North Carolina. Written and informed consent was provided by all participants.

Genotyping was performed using an Affymetrix 6.0 Array. Genetic variants with a call rate ≤95, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value $\leq 1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL software. Adjustments were also made for study site and population stratification using principal components.

B58C-T1DGC and -WTCCC: The 1958 British Birth Cohort (B58C, also known as the National Child Development Study) is a population based sample of births in England, Wales, and Scotland during one week in 1,958 and followed until 44-55 years of age. Age at menarche was derived from an examination at age 16 (6).

Genotyping was performed as part of the Type 1 Diabetes Genetics Consortium (T1DGC) and the Wellcome Trust Case Control Consortium (WTCCC) (7-9). In sum, 1,584 women passed quality controls and had information on menarche.

COLAUS: The Cohorte LAUSannoise (CoLaus) is a random sample of Swiss adults, aged 35-75 years old living in Lausanne, Switzerland in 2003-2006 (10). Individuals without two prior generations of European origin were excluded. Baseline questionnaire ascertained age at menarche within the nearest year. All participants gave informed consent and the study was approved the Local Ethics committees.

After applying quality controls and missing data, 2,874 women were available for genome-wide analysis for menarche before excluding any women with menarche before 9 years or after 17 years of age.

DECODE: The deCODE Genetics Study is study of 39,728 Icelanders as part of a nationwide cancer screening program since 1964 through the Cancer Detection Clinic, Icelandic Cancer Society. Age at menarche was self-reported was assessed through a questionnaire and items

about the age at previous birthday before menarche, and ranged between 8-20 years of age. This study was approved by the Data Protection Commission as well as the National Bioethics Committee of Iceland. Written and informed consent was obtained from all participants and personal identifiers were encrypted.

Genetic information was available for 15,864 men and women in the study (Illumina 317K/370K SNP chip) after excluding extreme menarcheal ages (<9, >17 years). As part of quality control, only individuals with a genotype yield greater than 98% were included.

DNBC: The Danish National Birth Cohort (DNBC) is a population-based sample of 101,042 pregnancies recruited between 1996 and 2002 (11). Participating women retrospectively reported menarche by computer-assisted telephone interviews. DNBC was approved by the Danish Scientific Ethical Committee as well as the Danish Data Protection Agency. Genome-wide data was available for 3,840 mothers and children (Illumina Human660w-Quadv1_A chip) as part of the Gene Environment Association Studies (GENEVA) Consortium. 1,748 women had both genetic data (genotype yield >=95%) and information on menarche (9-17 years). Prior to imputation genetic variants with a call rate £98%, minor allele frequency £0.01, or Hardy-Weinberg Equilibrium p-value £0.001 were excluded. Imputation was conducted using the MACH software package and the HapMap Phase II CEU sample as the reference panel. Age at menarche was regressed on imputed allele dosages with adjustment for birth year using MACH2QTL.

EGCUT: The Estonian cohort from the Estonian Genome Center, University of Tartu (EGCUT) is a population-based biobank. EGCUT methods can be found elsewhere (12). All participants signed the biobank consent form and the project was conducted in accordance to the Estonian Gene Research Act. The EGCUT samples used in this analysis are a random subset of the total cohort with genotyped information, which is over 43,000 Estonians >18 years of age. Self-reported age at menarche between 9-17 years was available for 983 females in this subset.

Genotyping was performed according to the Illumina protocol (www.illumina.com) for the Ilumina HumanHap 370K CNV array. Genetic variants with a call rate ≤98%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with IMPUTEv1.0 and SNPTEST software.

EPIC-Cohort: The European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) is the parent cohort of the EPID Obesity case-cohort study, and was conducted in 1993-1997 in Norfolk, United Kingdom among men and women 39-79 years of age (13). Age at menarche in years was ascertained at baseline by questionnaire. This study was approved by the Norwich Local Research Ethics Committee, and all subjects gave their written and informed consent.

The EPIC Obesity case-cohort study comprises 625 obese and 1,215 control women with menarche and genome-wide information; although on the controls are used in this analysis.

ERF: The Erasmus Rucphen Family (ERF) is a family-based cohort and is based on one extended family and its descents in a population isolate in the Netherlands. Detailed information about ERF can be found elsewhere (14). The Medical Ethics Committee of the Erasmus Medical Center in Rotterdam approved the study. All participants gave informed consent. Self-reported age at menarche between 9-17 years and imputed data were available for 1103 women in ERF.

Genotyping was performed using Illumina 6K, 318K, 370K, and Affymetrix 250K arrays. Genetic variants with a call rate ≤98%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL software.

FHS: The Framingham Heart Study (FHS) has been described previously and consists of several multi-generational population-based cohorts (15, 16). Women were asked to report their age at menarche at the second Offspring examination (1979-1982), at the first Third Generation examination, or at an Osteoporosis Study examination (if previous report was unavailable from

the Offspring examination, n=214). There were 3801 women with self-reported age at menarche between 9-17 years from these sources.

Genotyping was performed using Affymetrix 500K + 50K arrays. Genetic variants with a call rate ≤97%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and R-packages. Birth decade was adjusted for instead of birth year.

HBCS: The Helsinki Birth Cohort Study (HBCS) is a birth cohort that consists of 8760 subjects born in Helsinki between 1934 and 1944. Age at menarche was collected on the 1075 women who participated in a clinical trial between 2000 and 2002. Genotoype information from Illumina 670 Wuad arrays (modified from the Illumina Infinium 610K array) was only available for 976 women. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL.

All subjects gave informed consent and the study was approved by the local Ethical Committee and the National Data Protection Board (when relevant).

Health 2000 controls: The Health 2000 Cohort-Control Subsample (GENMETS controls) is a population-based survey that was conducted by the National Institute for Health and Welfare in Finland from 2000-2001. Information on age at menarche was collected by reproductive health survey. From a sub-cohort of 6,000 individuals greater than 30 years old, a case-control study was created for genetic analysis. Controls were matched to metabolic syndrome subjects by sex, age and residence. All subjects gave informed consent and the study was approved by the local Ethical Committee and the National Data Protection Board (when relevant).

Similar to HBCS and NFBC, genotyping was performed on an Illumina 670 Quad array (modified from Illumina Infinium 610K arrays). Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded.

Imputation and analysis were performed with MACH and ProbABEL.

InCHIANTI: The InCHIANTI study is a population-based study of older populations in the Chianti region of Tuscany, Italy (17). The study consistented of individuals in the population registries of Greve in Chianti and Bagno a Ripoli 21-102 years of age, and included some related individuals. The study was approved by the Italian National Institute of Research as well as the Care of Aging Institutional Review Board.

Corrections for family structure based on the genetic data were applied all analyses.

INDIANA: The Indiana University premenopausal Caucasian women peak BMD study (Indiana) began in 1988 with twin pairs. Over time it has expanded to include sister pairs at least 20 years of age from Indiana, USA. Exclusion criteria included irregular menses, pregnancy or lactation 3 months prior to enrollment, history of chronic disease, current medication to affect bone density, or inability to measure bone density. Age at menarche was self-reported at study visit (n=1,497).

Genotyping was performed using Illumina HumanHap 610 Quad version 1B array. Genetic variants with a call rate $\leq$95%, minor allele frequency $\leq$0.01, or Hardy-Weinberg Equilibrium p-value $\leq 1 \times 10^{-4}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL software.

INGI-VB: The Italian Network of Isolated Populations (INGI)-Val Borbera (VB) is a population-based cohort from population isolate from the Val Borbera Valley in the Appennine Mountains in Northwest Italy (18). Healthy participants were between 8 and 102 years old and had at least one grandfather from the valley. 910 women reported their age at menarche as being between 9 and 17 years (no exclusions). The study, including the overall plan and the informed consent form was reviewed and approved by the institutional review boards of San Raffaele Hospital in Milan and by the Regione Piemonte Ethical committee.

Genotyping was performed using Illumina 370k Quad v3 array. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-4}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL software.

KORA F3 and S4: Cooperative Health Research in the Region of Augsburg (KORA) contains a series of independent population-based cross-sectional cohorts from Southern Germany (19). This study contains data from the follow-up examination of the KORA S3 study, the KORA F3 study (10-year follow up after recruitment from 1994 to 1995) and from the KORA S4 study (1999-2001). The study was approved by the local ethics committee. All participants gave informed consent. Age at menarche between 9-17 years was self-reported by 809 women in KORA F3 and 898 women in KORA S4.

Genotyping for KORA F3 was performed using the Affymetrix 500K array (Sty I and Nsp I). Genotyping for KORA S4 was performed with the Affymetrix 6.0 array. Imputation and analysis were performed with MACH and R software.

KORCULA: CROATIA-Korcula (KORCULA) is a family-based cohort from the isolated island of Korcula, which includes 508 female participants with age at menarche 9-17 years and available genetic data.

Genotyping was performed using Illumina HAP 370K CNV array. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-4}$ were excluded. Imputation and analysis were performed with MACH and R-packages/ProbABEL software.

NFBC: The Northern Finland Birth Cohort 1966 (NFBC) is a population-based cohort from the two northernmost provinces of Finaland: Oulu and Lapland. Mothers who delivered babies in the areas in the year of 1966 were enrolled (http://kelo.oulu.fi/NFBC/pub/). At the age of 31 participants self-reported their age at menarche and a sub-sample of the full cohort was invited for a clinical visit that included genotyping. 2,648 women reported their age at menarche

between 9 and 17 years and had available genotype information. The study has been described in detail previously (20-22).

Genotyping was performed using Illumina HAP 370K CNV Duo array. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL software.

NHS-BrCa and -T2D: The Nurses' Health Study cohorts have been described previously in detail (23). Participants were between 30-55 years old and reported their ages at menarche in the initial questionnaire in 1976. The study was approved by the IRB of Brigham and Women's Hospital in Boston, MA. Informed consent was obtained from all participants.

NHS-BrCa is a nested case-control study of breast cancer derived from the 32,826 women in the blood subcohort who were free of diagnosed breast cancer at blood collection and followed for incidence disease until June 1, 2004. The 2,287 NHS participants included in the present analysis were from this nested breast cancer case-control study and were self-described Caucasians with genotype data available from the National Cancer Institute's Cancer Genetic Marker of Susceptibility (CGEMS) project (24). Genotyping was performed using Illumina HumanHap 550K array. Genetic variants with a call rate ≤90%, or minor allele frequency ≤0.01 were excluded. Imputation and analysis were performed with MACH and ProbABEL software.

NHS-T2D is a nested case-control study of type 2 diabetes (25). The 3,098 women included in this analysis reported an age at menarche (9-17 years) and had available genetic information. The study is a component of the Gene Environment-Association Studies, and genotyping was performed using Affymetrix 6.0 array. Genetic variants with a call rate ≤98%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-4}$ were excluded. Imputation and analysis were performed with MACH and ProbABEL software.

NTR: The Netherlands Twin Register (NTR) is part of a longitudinal study of health assessed every 2-3 years (26). Genotype information was collected on 1,940 NTR participants as part of a

case-control study on major depression disorder (27). Females retrospectively reported their age at menarche, as was available on 1,051 female participants.

ORCADES: The Orkney Complex Disease Study (ORCADES) is a family-based study of the isolated Scottish archipelago of Orkney. Participants come from one of ten islands in the area, and gave their informed consent. Pregnant women were excluded from the study. Age at menarche was reported between 9 to 17 years for 348 women with available genetic information. The study was approved by the Research Ethics Committee in Orkney and Aberdeen.

Genotyping was performed using Illumina HumanHap 300 Beadchip. Genetic variants with a call rate $\leq$97%, minor allele frequency $\leq$0.01, or Hardy-Weinberg Equilibrium p-value $\leq 1x10^{-5}$ were excluded. Imputation and analysis were performed with MACH and R-packages/ProbABEL software.

QIMR: This study is composed of two separate cohorts: the Adult and Adolescent cohorts. Recruitment for the Adult cohorts occurred in 1980-1982 as part of the Canberra Study of twins aged 17-88 at the time, and in 1989 of twins born in 1964-1971 and their first degree relatives. In sum, the Adult cohorts provided 2,256 women with menarche data to the analysis. The adolescents of the Adolescent cohort were recruited as part of studies on melanoma and cognition, and menarche was obtained using a set protocol (28). The young age of assessment resulted in a larger amount of censored data for individuals younger than the mean age of menarche in their last interview. After quality control, missing data, and excluding extreme menarche values (<9, >17 years), 1,272 individuals were available for analysis in the Adolescent cohort.

Informed consent was obtained from the participants and their parents prior to data collection. Genotyping and imputation details have been presented elsewhere (29).

SNPs were removed if they had a call rate <95%, minor allele frequency < 0.01, or Hardy-

Weinberg Equilibrium p-value < 1 x 10^{-5}. Imputation was performed using MACH and association analysis was performed using MERLIN.

RAINE: The Recruitment of Western Australian Pregnancy (RAINE) cohort has been described in detail (30). Between 1989 and 1991, 2900 women were enrolled into a randomized controlled trial. Their 2,868 babies have been followed as prospective population-based cohort. Month and year of first period was recorded for each girl. A one-page questionnaire was given to the parent(s) of girls at the 10-year assessment. If the girls lived outside the Perth metropolitan area, or were not physically attending the 10-year follow-up, the questionnaire was posted along with other study material for the 10-year follow-up. The puberty questionnaire, information and consent forms given to the parents asked to prospectively record details of date of menarche and subsequent two menstrual periods, and return the questionnaire to the RAINE Study management in a supplied postage paid envelope. If the puberty questionnaire had not been returned by the time of the 14-year follow-up, mothers and the female participants were telephoned with a reminder to complete the questionnaire. Information was either collected over the phone or a copy of the questionnaire was posted. Telephone follow up allowed clarification of the recall of the date of menarche, whether date of menarche was a recent event or whether the information was retrieved from a diary, calendar or recalled from the memory of a coinciding event (such as Christmas day, school day, party). In sum, 614 participants reported an age at menarche between 9 and 17 years old between 2000-2006, were of European descent, and had available genetic information.

Genotyping was performed using Illumina 660w Quad array. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$5.7x10^{-7}$ were excluded. Imputation and analysis were performed with MACH and R software.

RS I-III: The Rotterdam Studies I, II, and III (RSI-III) are population-based cohorts of men and women aged 55 years old and older living in Ommoord, Netherlands (31, 32). Participants

reported their age at menarche by questionnaire. In RS I, II, and III there were 3,175, 1,119, and 1,112 women with menarche ages between 9 and 17 years and available genetic information.

Genotyping was performed using Illumina HumanHap 550K array. Genetic variants with a call rate ≤98%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and MACH2QTL software.

SAGE: The Study of Addiction: Genetics and Environment (SAGE) is based on three complementary population-based studies: the Collaborative Study on the Genetics of Alcoholism (COGA), the Family Study of Cocaine Dependence (FSCD), and the Collaborative Genetic Study of Nicotine Dependence (COGEND). The three substudies were reviewed and approved by institutional review boards at all data collection sites. All subjects gave informed consent. Women were asked to report their age at menarche. Data were available for 1,291 subjects for this analysis (passed quality control and reported menarche 9-17 years). Additional information can be found here:http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000092.v1.p1.

Genotyping was performed using Illumina Human 1Mv1_C array. Genetic variants with a call rate ≤98%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-4}$ were excluded. Imputation and analysis were performed with IMPUTE and SNPTEST software.

SARDINIA: The SardiNIA genome-wide association study consists of 4,305 individuals participating in the longitudinal study of aging-related traits in the Ogliastra region of Sardinia, Italy and has been described previously (33, 34). 2,158 women had information on age at menarche and genetic data. Protocol and informed consent from each participant, has been approved by both the US-IRB and Italian Ethical Committee.

Participants need to have at least two prior generations of Sardinians in their families to be randomly selected for genotyping (n=1,412 using the Affymetrix Mapping 500K Array Set;

n=2,893 using the Affymetrix Mapping 10K Array). MACH software was used for imputation and took advantage of the relatedness of individuals in the imputation of stretches of missing genetic information.

SPLIT: The Croatia-Split (SPLIT) is a population-based cohort from the Dalmatian City of Split, which includes 283 female participants with age at menarche 9-17 years and available genetic data.

Genotyping was performed using Illumina HAP 370K CNV array. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-4}$ were excluded. Imputation and analysis were performed with MACH and R-packages/ProbABEL software.

TWINSUK I-III: The TwinsUK I cohort consists of groups of twins recruited from the general population through national media, with similar disease-related and lifestyle characteristics as singletons of similar ages (35, 36). TwinsUK II and III cohorts come from the adult twin British registry (also known to representative of the general population (37). Age at menarche was retrospectively reported by questionnaire. All studies were approved by the Guy's and St. Thomas' Hospital Ethics Committee. Written informed consent was obtained from all participants.

Genotyping was obtained for 2,276, 671, and 1,016 women with menarche information in the three studies (I-III, respectively). Of note, the TwinsUK I sample were genotyped with the Infinium 610k assay at two centers. SNPs with call rates≤90%, Hardy -Weinberg p-values <10^{-4} and minor allele frequencies <1% were excluded. Subjects with genotyping errors more frequent than 2% were also removed. Imputation was done using the IMPUTE software.

VIS: The CROATIA-Vis (VIS) is a family-based cohort from the isolated island of Vis, which includes 502 female participants with age at menarche 9-17 years and available genetic data.

Genotyping was performed using Illumina HAP 300v1 array. Genetic variants with a call rate ≤95%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-4}$ were excluded. Imputation and analysis were performed with MACH and R-packages/ProbABEL software.

WGHS: The Women's Genome Health Study (WGHS) is a population-based cohort of female healthcare professionals ≥45 years old who participated in the Women's Health Study, a placebo-controlled randomized trial. WGHS has been described previously (38). Self-reported age at menarche was collected at baseline by questionnair. 22028 women with available menarche and genotyped data, and of European descent were included in this analysis.

Genotyping was performed using Illumina HumanHap300 Duo "+" array. Genetic variants with a call rate ≤98%, minor allele frequency ≤0.01, or Hardy-Weinberg Equilibrium p-value ≤$1x10^{-6}$ were excluded. Imputation and analysis were performed with MACH and MACHQ2TL software.

MULTIPLE TESTING

In Genome-Wide Association Studies (GWAS) studies, almost all SNPs are null, and the risk of committing a false positive is huge, so it is appropriate to control the Family Wise Error Rate (FWER). Bonferroni correction is the most common way to control FWER. The Bonferroni adjusted *P* value is simply the nominal *P* value multiplied by the total number of tests. It's popular because it is so easy to perform and can control the FWER for all possible data structure. However, Bonferroni correction is very conservative, and Holm (39) proposed a step-down procedure which is always more powerful than Bonferroni correction. Let m be the number of tests and $p_{(1)}$, ..., $p_{(m)}$ be the ordered *P* values. The Holm's adjusted *P* values are

$$P_{(j)}^{Holm} = \min\{p_j(m-j+1), 1\}, \qquad j = 1, \ldots, m$$

Note that when m is large, there will be little difference between Holm's procedure and Bonferroni correction.

An alternative criterion to adjust multiple testing is to control False Discovery Rate (FDR) (40), especially when there is a large portion of truly significant hypotheses, and thus FWER is too conservative.

Web Appendix Table 1. Frequency distribution for the hypotheses

	Not Rejected	Rejected	Total
True Hypotheses	U	V	m_0
False Hypotheses	T	S	$m - m_0$
Total	$m - R$	R	m

Web Appendix Table 1 is a two-by-two cross-tabulation of true status of the hypotheses and the testing results. Benjamini and Hochberg defined FDR to be $E[V/R]$, i.e. the expected proportion of false positives among all rejected hypotheses (40). When $R = 0$, set $V/R = 0$. They showed that when all hypotheses are truly null, i.e.$m_0 = m$, controlling FDR is equivalent to controlling FWER. While $m_0 < m$, controlling FDR is more liberal than controlling FWER, which indicates a potential gain in power. They proposed a simple step-down procedure, which can control FDR when the tests are independent. The procedure is to determine

$$k = argmax_{1 \le i \le m}\left[p_i \le \frac{i}{m} q^*\right]$$

and then rejects all H_i, $i = 1,...,k$, where q^* is the pre-specified FDR level. To mimic the *P* value to give a measure of significance to every single test, one can define a "FDR *P* value" to be

$$p_j^{FDR} = \min\{q^*: H_i \text{ is rejected at } FDR = q^*\} = \min\left\{\frac{p_j m}{j}, p_{j-1}^{FDR}\right\}$$

Where $j = m,...,1$ and p_{m+1}^{FDR} is defined to be 1.

Storey proposed a direct approach to estimate the pFDR (41), which is defined to be

$$pFDR = E\left[\frac{V}{R} | R > 0\right]$$

They use the term *Q* value, a *P* value counterpart to decide the significance level for each single test.

$$Q\ value_i = \min\{q^*: H_i\ is\ rejected\ at\ pFDR = q^*\}$$

We applied Bonferroni correction and Holm's step-down procedure to control FWER, as well as FDR and pFDR approaches to adjust multiple testing. We used expressions shown above to calculate adjusted *P* values for Bonferroni correction, Holm's step-down procedure and FDR ("FDR p-value"), *Q* values for pFDR were calculated by the R package *qvalue* (42).

CUMULATIVE GENETIC EFFECTS

We estimated a genetic risk scores (GRSs) for overall (BMI) and central adiposity (waist circumference/waist-hip-ratio) variants separately using three approaches. In two separate studies [the Atherosclerosis Risk in Communities Study (ARIC) with *n*=4,775 and the Women's Genome Health Study (WGHS) with *n*=22,863], we defined each GRS to be the sum of the menarche risk alleles (i.e. menarche decreasing) across all of variants previously described with the given phenotype. Both genotyped and imputed data were included in the GRSs. Waist circumference variant, rs545854, was missing in both studies. We then modeled the effect of each GRS on age at menarche in a linear regression model. First, adjustments were made for birth year and center (appropriate in ARIC) only (Web Figure 4A,D). Second, additional adjustments for population stratification were made using the same measure of population stratification as used for the individual SNP effect estimates (presented in Tables 1 and Web Tables 3-5). The results of this fully analysis are summarized in Figure 3.

Lastly, in order to estimate the association between cumulative genetic risk and age at menarche in the entire sample (up to *n*=92,105) we used the publically available R package Genetics ToolboX (GTX) (43, 44) and the fixed-effect SNP-effects from Tables 1 and Web Tables 3-5. Whereas in the previous two approaches, 69 and 25 variants were included in the BMI and waist circumference/waist-hip-ratio GRSs, respectively, in this approach we included only SNPs that were independent (r^2<0.2). This yielded a subset of 48 and 25 SNPs for the BMI

and waist circumference/waist-hip-ratio GRSs, respectively.

PATHWAY AND INTERACTION ANALYSES

In order to explore if loci associated both with AAM and adiposity-related phenotypes cluster in specific biological pathways we did three sets of analyses.

First, we used the Gene Group Functional Profiling (g:Profiler) web tool to look for statistical enrichment using databases of functional evidence (e.g. Gene Ontology and biological pathways) around the chromosomal regions represented by a set of marker SNPs (http://biit.cs.ut.ee/gprofiler/index.cgi) (45, 46). To this aim, we investigated four sets of markers based on our study findings: 1-2) published waist circumference and BMI loci significantly associated with age at menarche (P<0.05/95, or P<0.05 if it was previously described) with and without the inclusion of suggestive signals (all additional associations P<0.05 with inverse effects on BMI and age at menarche), 3) published BMI loci not associated with age at menarche, and 4) published waist circumference, waist-hip-ratio loci not associated with age at menarche. The nearest gene to the tested SNP was entered into g:Profiler. We also entered chromosomal regions (±150kb and ±300kb) around each SNP, but did not get any significant results.

Second, we used the DAPPLE web tool to search for protein-protein interactions between genes within a defined region around the input SNPs (http://www.broadinstitute.org/mpg/dapple/dapple.php) (47). DAPPLE builds direct and indirect interaction networks from proteins encoded for by genes in the specified chromosomal regions and estimates the significance of the identified networks based on permutation. We used three lists of marker SNPs to search a window of 300kb up and downstream of each input SNP with 10,000 permutations and specifying a common interactor binding degree cutoff of 2. These lists were: 1) published waist circumference and BMI loci significantly associated with age at

menarche (P<0.05/95, or P<0.05 if it was previously described), 2) published BMI loci not significantly associated with age at menarche, and 3) published waist circumference and waist-hip-ratio loci not associated with age at menarche. Additionally, we re-ran the analyses entering the closest candidate gene to each signal, but these did not reveal any direct interactions.

Lastly, we examined pathways previously suggested to associate with BMI by GIANT (48). The GIANT-consortium had identified these pathways by utilizing MAGENTA gene-set enrichment analysis of GWAS meta-analysis results for adult BMI. We compared the genes listed in these pathways (all residing within 300kb of genome-wide significant BMI loci) with the loci additionally implicated significantly (P<0.05/95) or suggestively (P<0.05) with age at menarche in the current study.

POWER ANALYSIS

QUANTO 1.2.4 (49) was used to calculate power to detect nominal associations and those below a Bonferroni correction for 95 tests over a range of conditions (http://hydra.usc.edu/gxe/). We based our expected effect size on the range of effect sizes of the adiposity variants on age at menarche reported by Elks *et al.* (8.4 to 18.2 days, or 0.02 to 0.05 year change per allele (48)), a common lower bound of sample size (~86,000), and the distribution of continuous age at menarche of the Atherosclerosis Risk in Communities Study (mean=12.9 years, standard deviation=1.5 years). QUANTO 1.2.4 was then used to calculate power within a range of observable effect sizes and common (>1%) minor allele frequencies (Web Figure 6) seen among 13 nominally significant variants after quality controls in this study.

We had over 80% power to detect a true effect at most of these loci given the minor allele frequency (MAF) and a type I error rate of 5% (Web Figure 6A). However, 2 BMI-SNPs with biologically consistent effects for menarche and BMI associations had low MAF (4% for rs13107325 and 7% for rs11847697) and therefore low power. When a Bonferroni multiple

testing correction was applied for 95 tests, only the most common variants and those with strong effects (≥20% and ≥14-day change per allele) would have greater than 80% power (Web Figure 6B).

ADDITIONAL STUDY ACKNOWLEDGMENTS

AMISH: The Amish study was supported by NIH research grants U01 HL72515, U01 HL84756 and R01 088119, the University of Maryland General Clinical Research Center, grant M01 RR 16500, the Clinical Nutrition Research Unit of Maryland (P30 DK072488), and the Baltimore Veterans Administration Medical Center Geriatrics Research. The authors also want to acknowledge Alan R. Shuldiner and Elizabeth A. Streeten for their work on this study.

ARIC: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors would like to thank the staff and participants of the ARIC study for their important contributions.

B58C: We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust (Grant Number 068545/Z/02; http://www.b58cgene.sgul.ac.uk/). Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z. The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for Health Research Cambridge

Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895).

COLAUS: The CoLaus study was supported by research grants from the Swiss National Science Foundation (grant no: 33CSCO-122661) from GlaxoSmithKline and the Faculty of Biology and Medicine of Lausanne, Switzerland. The authors also express their gratitude to the participants in the Lausanne CoLaus study and to the investigators who have contributed to the recruitment, in particular research nurses Yolande Barreau, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection.

EGCUT: EGCUT received financing by (ENGAGE, OPENGENE), targeted financing from Estonian Government SF0180142s08, Estonian Research Roadmap through Estonian Ministry of Education and Research (3.2.0304.11-0312), Center of Excellence in Genomics (EXCEGEN) and Development Fund of University of Tartu (SP1GVARENG). We acknowledge EGCUT personnel, especially Mr V. Soo. Data analyzes were carried out in part in the High Performance Computing Center of University of Tartu.

ERF: The study was supported by grants from The Netherlands Organisation for Scientific Research (NWO), Erasmus MC and the Centre for Medical Systems Biology (CMSB). We are grateful to all general practitioners for their contributions, to Petra Veraart for her help in genealogy, Jeannette Vergeer for the supervision of the laboratory work and Peter Snijders for his help in data collection.

INGI-VB: The Italian Network of Isolated Populations (INGI)-Val Borbera (VB) study was funded by the Fondazione Compagnia di San Paolo, Cariplo Foundation and Health Ministry grant “Ricerca Finalizzata 2008”. We thank the inhabitants of the Val Borbera that made this study possible, the local administrations, the Tortona and Genova archdiocese and the ASL-Al, Novi Ligure (Al) for support. We particularly thank Clara Camaschella (Vita e Salute University,

Milano) who supervised data collection and phenotype analysis, Federico Caligaris-Cappio (Oncology-Hsr) and the internal medicine MDs of the San Raffaele Hospital, Maria Rosa Biglieri, Diego Sabbi and Silvia Bione (IGM,CNR) for their contribution to clinical data collection. We thank Massimo Ginestri (Asl-Al) for help with laboratory data analysis and Fiammetta Viganò for technical support.

KORA F3 and S4: The KORA Augsburg studies were financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany and supported by grants from the German Federal Ministry of Education and Research (BMBF). Part of this work was financed by the German National Genome Research Network (NGFN). Our research was supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.

KORCULA: The CROATIA-Korcula study was funded by grants from the Medical Research Council (UK), European Commission Framework 6 project EUROSPAN (Contract No. LSHG-CT-2006-018947) and Republic of Croatia Ministry of Science, Education and Sports research grants to I.R. (108-1080315-0302). We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools, Institute for Anthropological Research in Zagreb and Croatian Institute for Public Health.

The SNP genotyping for the CROATIA-Korcula cohort was performed in Helmholtz Zentrum München, Neuherberg, Germany.

NHS-BrCa and NHS-T2D: The NHS BrCa GWA scan was performed as part of the Cancer Genetic Markers of Susceptibility initiative of the NCI. We particularly acknowledge the contributions of R. Hoover, A. Hutchinson, K. Jacobs and G. Thomas. The current research is supported by CA 40356 and U01-CA98233 from the National Cancer Institute.

The NHS/HPFS type 2 diabetes (T2D) GWAS (U01HG004399) is a component of a collaborative project that includes 13 other GWAS funded as part of the Gene Environment-Association Studies (GENEVA) under the NIH Genes, Environment and Health Initiative (GEI) (U01HG004738, U01HG004422, U01HG004402, U01HG004729, U01HG004726, U01HG004735, U01HG004415, U01HG004436, U01HG004423, U01HG004728, RFAHG006033) with additional support from individual NIH Institutes (NIDCR: U01DE018993, U01DE018903; NIAAA: U10AA008401, NIDA: P01CA089392, R01DA013423; NCI: CA63464, CA54281, CA136792, Z01CP010200). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Genotyping was performed at the Broad Institute of MIT and Harvard, with funding support from the NIH GEI (U01HG04424), and Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438) and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease”(HHSN268200782096C). Additional funding for the current research was provided by the National Cancer Institute (NCI, P01CA087969, P01CA055075), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, R01DK058845).

We acknowledge the study participants in the NHS for their contribution in making this study possible.

ORCADES: ORCADES was supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the Medical Research Council Human Genetics Unit and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We would like to acknowledge the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney.

QIMR: We thank the twins and their families for their participation. We also thank Dixie Statham, Ann Eldridge, Marlene Grace, Kerrie McAloney, Lisa Bowdler, Steven Crooks, Peter Visscher, Allan McRae, Sarah Medland, Dale Nyholt, Scott Gordon, Andrew Heath and Pamela Madden. Funding was provided by the Australian National Health and Medical Research Council (241944, 339462, 389927, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 552485, 552498), the Australian Research Council (A7960034, A79906588, A79801419, DP0770096, DP0212016, DP0343921), the FP-5 GenomEUtwin Project (QLG2-CT-2002-01254), and the U.S. National Institutes of Health (NIH grants AA07535, AA10248, AA13320, AA13321, AA13326, AA14041, MH66206). A portion of the genotyping on which this study was based (Illumina 370K scans on 4300 individuals) was carried out at the Center for Inherited Disease Research, Baltimore (CIDR), through an access award to our late colleague Dr. Richard Todd (Psychiatry, Washington University School of Medicine, St Louis). Statistical analyses were carried out on the Genetic Cluster Computer, which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003). E.M.B is supported by NHMRC grant.

RAINE: The authors are grateful to the Raine Foundation, to the Raine Study participants and their families, and to the Raine Study research staff for cohort coordination and data collection. The authors gratefully acknowledge the NH&MRC for their long term contribution to funding the study over the last 20 years and also the following Institutions for providing funding for Core Management of the Raine Study: The University of Western Australia (UWA), Raine Medical Research Foundation, UWA Faculty of Medicine, Dentistry and Health Sciences, The Telethon Institute for Child Health Research, Women and Infants Research Foundation

The authors gratefully acknowledge the assistance of the Western Australian Genetic Epidemiology Resource and the Western Australian DNA Bank (both National Health and Medical Research Council of Australia National Enabling Facilities). The authors also

acknowledge the support of the National Health and Medical Research Council of Australia (Grant ID 572613 and ID 003209) and the Canadian Institutes of Health Research (Grant ID 166067). We gratefully acknowledge the assistance of the Wind Over Water Foundation, the Telethon Institute for Child Health Research, and the Raine Medical Research Foundation of the University of Western Australia.

SAGE: Study of Addiction: Genetics and Environment (SAGE) funding was provided through the NIH Genes, Environment and Health Initiative [GEI] (U01 HG004422). SAGE is one of the genome-wide association studies funded as part of the Gene Environment Association Studies (GENEVA) under GEI. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01 HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Support for collection of datasets and samples were provided by the Collaborative Study on the Genetics of Alcoholism (COGA; U10 AA008401), the Collaborative Genetic Study of Nicotine Dependence (COGEND; P01 CA089392), and the Family Study of Cocaine Dependence (FSCD; R01 DA013423, R01 DA019963). Funding support for genotyping, which was performed at the Johns Hopkins University Center for Inherited Disease Research, was provided by the NIH GEI (U01HG004438), the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease" (HHSN268200782096C).

SARDINIA: The SardiNIA team was supported by Contracts NO1-AG-1-2109 and HHSN271201100005C from the NIA, and in part by the Intramural Research Program of the National Institute on Aging (NIA), National Institutes of Health (NIH). The SardiNIA authors are grateful to the many volunteers who generously participate in the study, to Monsignore Piseddu, Bishop of Ogliastra, to the Mayors and administrations of the four towns involved and the Head

of Public Health Unit ASL4 in Ogliastra.

SPLIT: The CROATIA-Split study is funded by grants from the Medical Research Council (UK), and Republic of Croatia Ministry of Science, Education and Sports research grants to I.R. (108-1080315-0302). We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools, Institute for Anthropological Research in Zagreb and Croatian Institute for Public Health. The SNP genotyping for the CROATIA-Split cohort was performed by AROS Applied Biotechnology, Aarhus, Denmark.

TwinsUK: The study was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F2-2008-ENGAGE and the European Union FP-5 GenomEUtwin Project (QLG2-CT-2002-01254) and Framework 6 Project EUroClot. The study also receives support from the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London We thank the staff from the TwinsUK, the DNA Collections and Genotyping Facilities at the Wellcome Trust Sanger Institute for sample preparation; Quality Control of the Twins UK cohort for genotyping (in particular Amy Chaney, Radhi Ravindrarajah, Douglas Simpkin, Cliff Hinds, and Thomas Dibling); Paul Martin and Simon Potter of the DNA and Genotyping Informatics teams for data handling; Le Centre National de Génotypage, France, led by Mark Lathrop, for genotyping; Duke University, North Carolina, USA, led by David Goldstein, for genotyping; and the Finnish Institute of Molecular Medicine, Finnish Genome Center, University of Helsinki, led by Aarno Palotie.

VIS: The CROATIA-Vis study was funded by grants from the Medical Research Council (UK), European Commission Framework 6 project EUROSPAN (Contract No. LSHG-CT-2006-018947) and Republic of Croatia Ministry of Science, Education and Sports research grants to I.R. (108-1080315-0302). We would like to acknowledge the staff of several institutions in

Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools, Institute for Anthropological Research in Zagreb and Croatian Institute for Public Health.

The SNP genotyping for the CROATIA-Vis cohort was performed in the core genotyping laboratory of the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh, Scotland.

WGHS: The WGHS is supported by HL043851 and HL69757 from the National Heart, Lung, and Blood Institute and CA 047988 from the National Cancer Institute, with funding for genotyping provided by Amgen.

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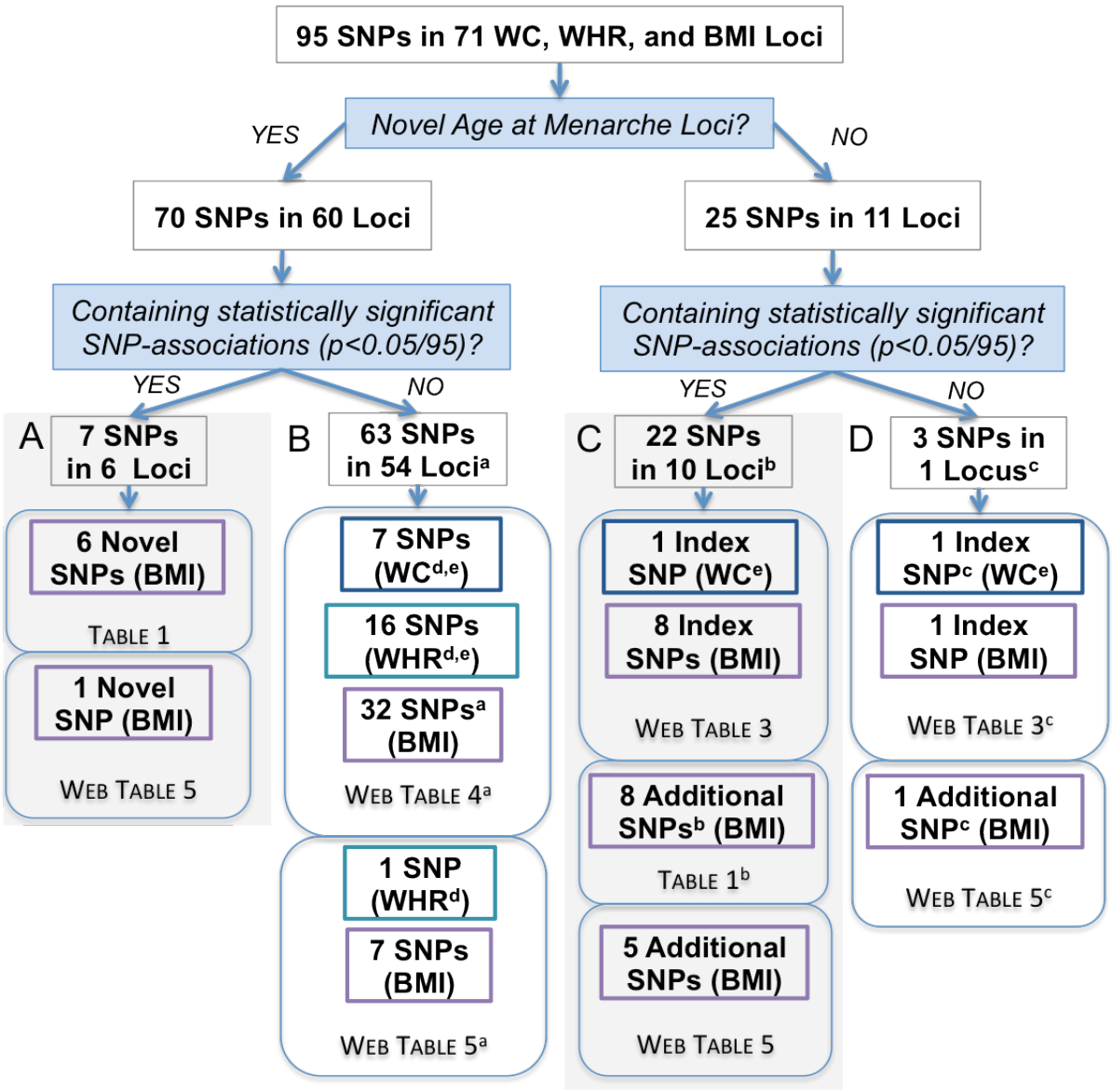
WEB FIGURES

Web Figure 1A-D. Strategy for SNP Selection and Presentation



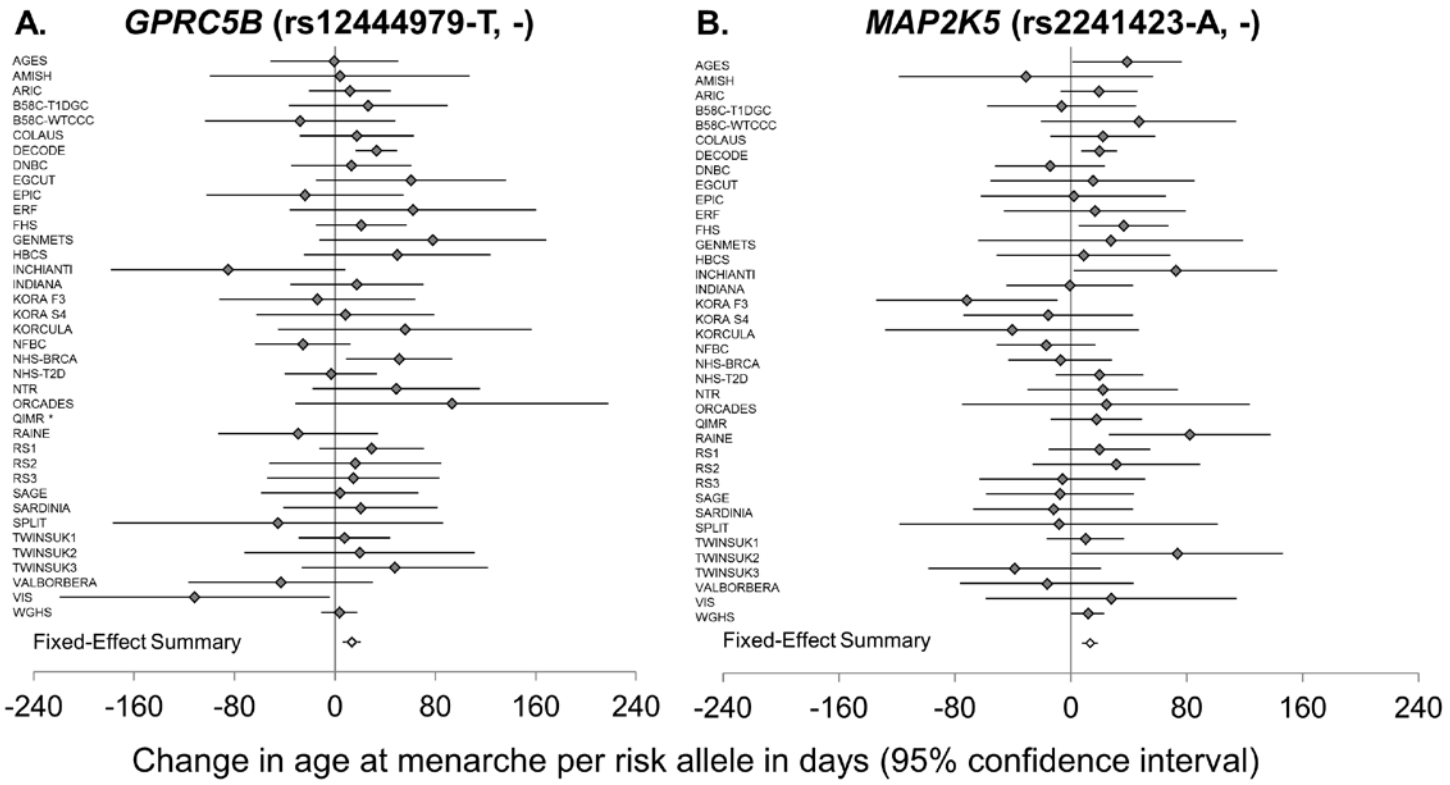
Abbreviations: AAM, Age at menarche; BMI, body mass index; SNP, single nucleotide polymorphism; WC, Waist circumference; WHR, Waist-hip-ratio

[a]Note that when the number loci is less than the number of SNPs as in Tables 1, and Web Table 4, some SNPs have been removed due to signal dependence and placed in Web Table 5. Two exceptions are detailed as follows. Loci redundancies are due, in part, to our methodologic approach to generating a list of candidate adiposity SNPs. In sum, 15 SNPs in linkage disequilibrium (LD; r^2<0.2) with other SNPs in Table 1 (7 BMI SNPs) and Web Table 4 (1 WHR adjusted for BMI, and 7 BMI SNPs) are therefore presented in Web Table 3. In Web Table 4 the *MC4R* locus was considered to associate with two adiposity phenotypes: WC (rs489693) and BMI (rs12970134). Therefore, one additional BMI-SNP (rs12970134) at the *MC4R* locus is included in Web Table 4 (55 SNPs in 54 loci). In contrast, both the variants at *NRXN3* were considered to represent BMI (rs10150332 and rs10146997). Due to their tight LD (r^2<0.2), the former is shown in Web Table 4 and the latter in Web Table 5. Phenotypic categorizations at these two loci were based on the reported change in WC effect after adjusting for BMI at these loci.

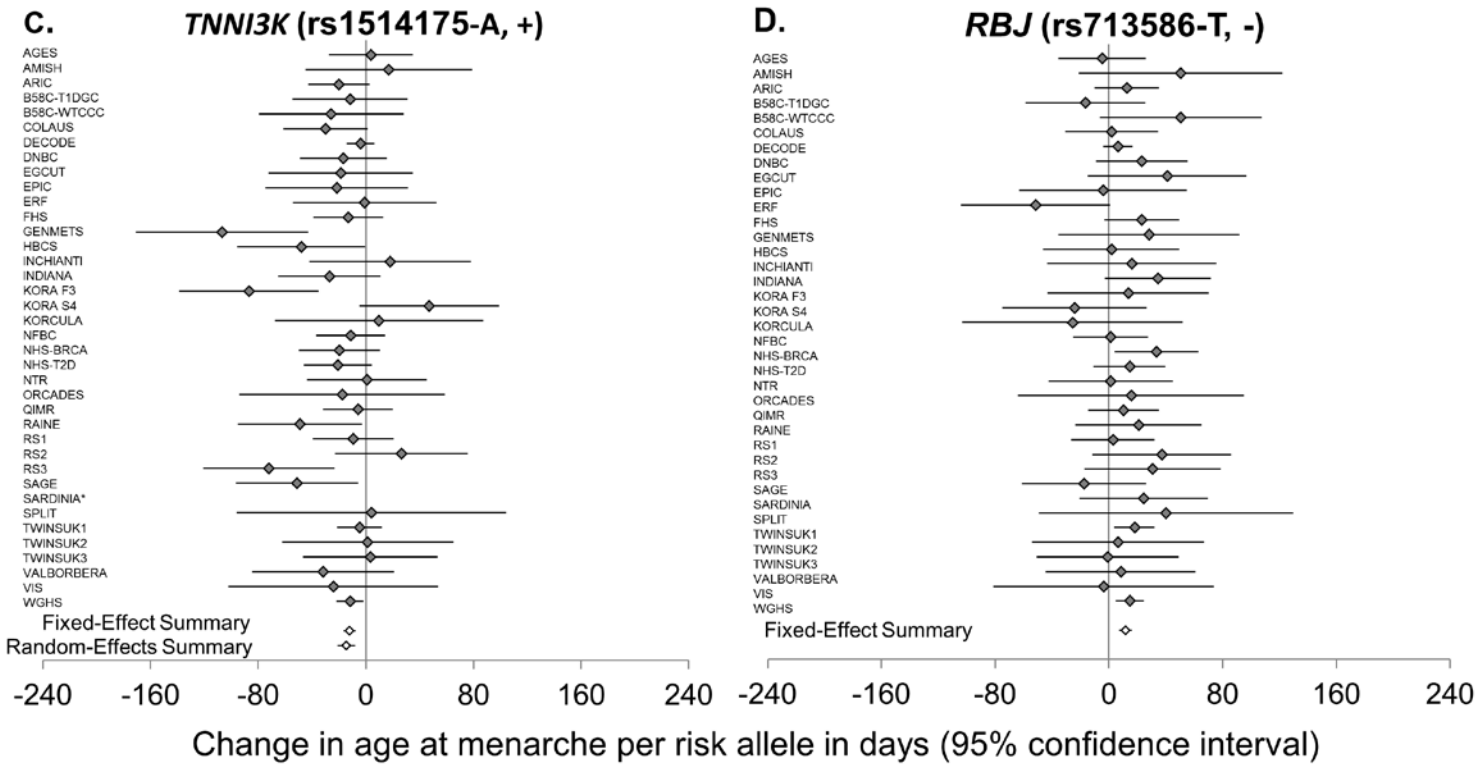
[b]Table 1 is shown here to contain eight additional SNPs, of which two are located at *BDNF* (rs7481311 and rs6265) and represent independent genetic signals based on our linkage disequilibrium criteria (r^2<0.2). Therefore panel C is recorded to represent 10 loci in total.

[c]Each of the SNP-associations at previously reported age at menarche loci shown in panel D did not have evidence below a Bonferroni correction for multiple testing (P<0.05/95), but were nominally significant (P<0.05). Of these three SNPs, two SNPs (rs7647305 at *ETV5* in Web Table 4*;* rs6499640 at *FTO* in Web Table 5) were in linkage disequilibrium (r^2<0.2) with at least one other SNP at the same locus with significant evidence of association (P<0.05/95). The lack of significance using these specific SNP markers may be an artifact of these SNPs being weaker markers of the underlying genetic effect at *ETV5* and *FTO*. For this reason panel D is only recorded to represent one locus (*MSRA*).
[d]Adjusted for BMI.
[e]Unadjusted for BMI.

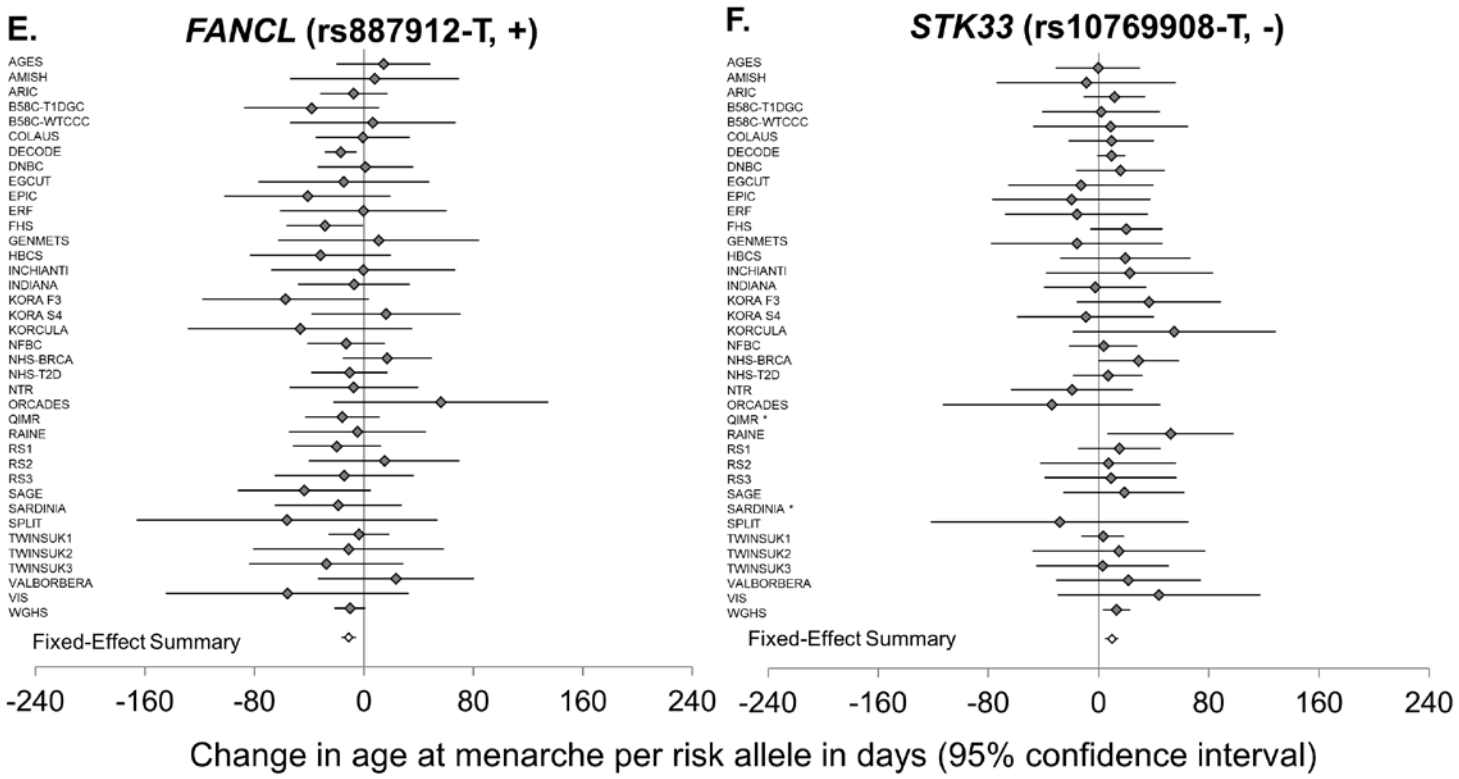
Web Figure 2A-B. BMI-Age at Menarche-SNPs at Six Novel Loci by Decreasing Magnitude of Effect



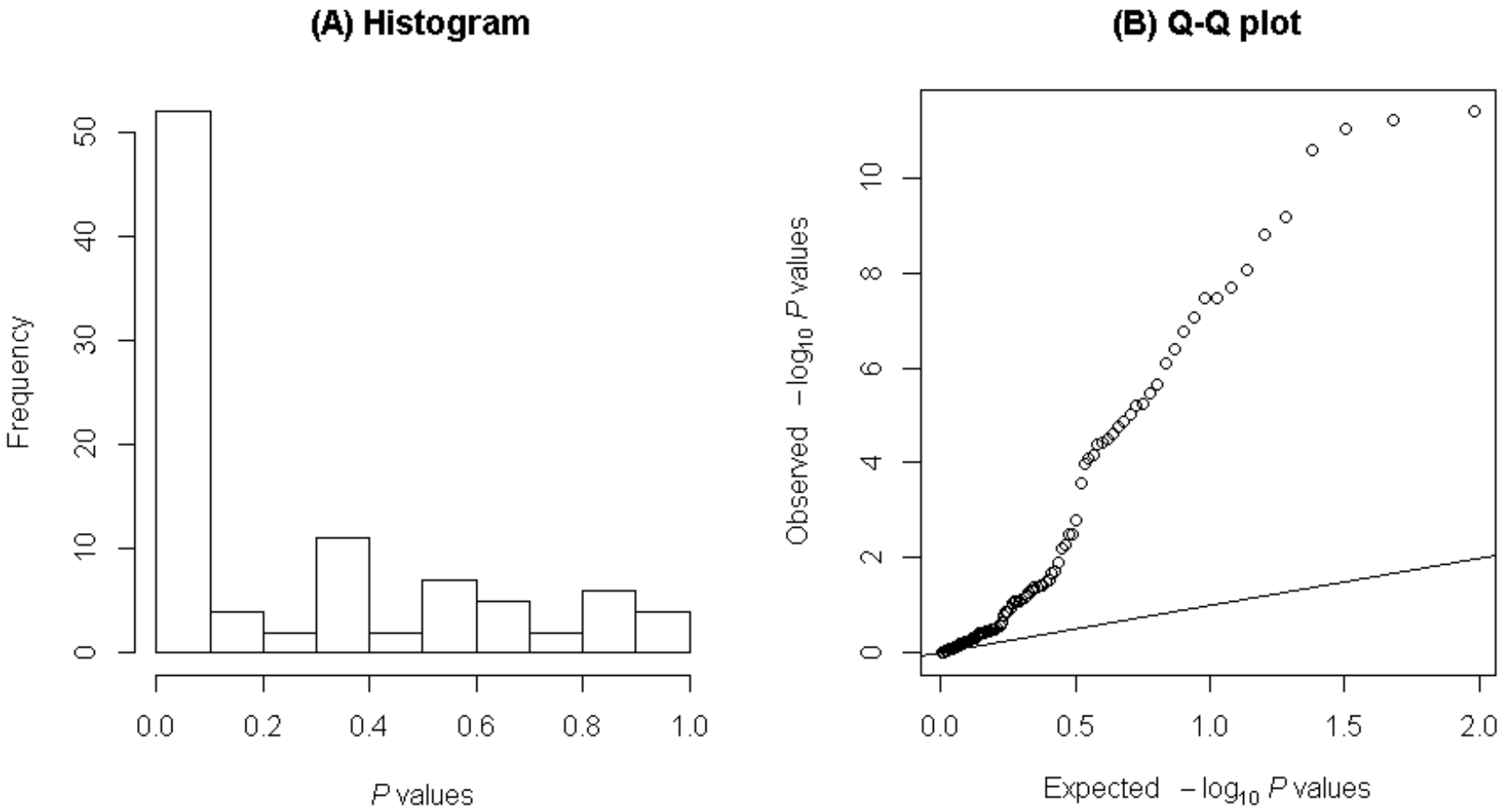
Web Figure 2C-D. BMI-Age at Menarche-SNPs at Six Novel Loci by Decreasing Magnitude of Effect



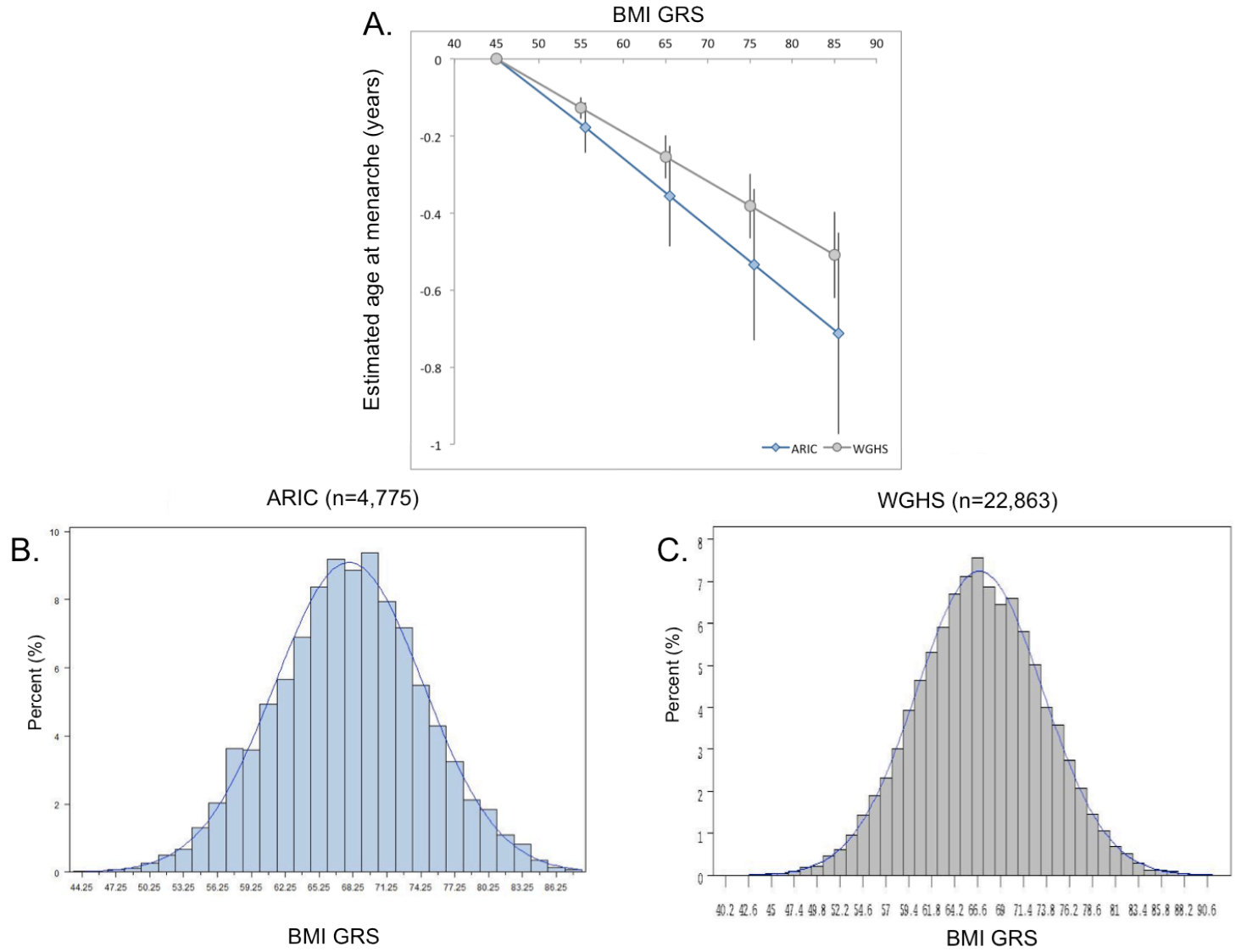
Web Figure 2E-F. BMI-Age at Menarche-SNPs at Six Novel Loci by Decreasing Magnitude of Effect



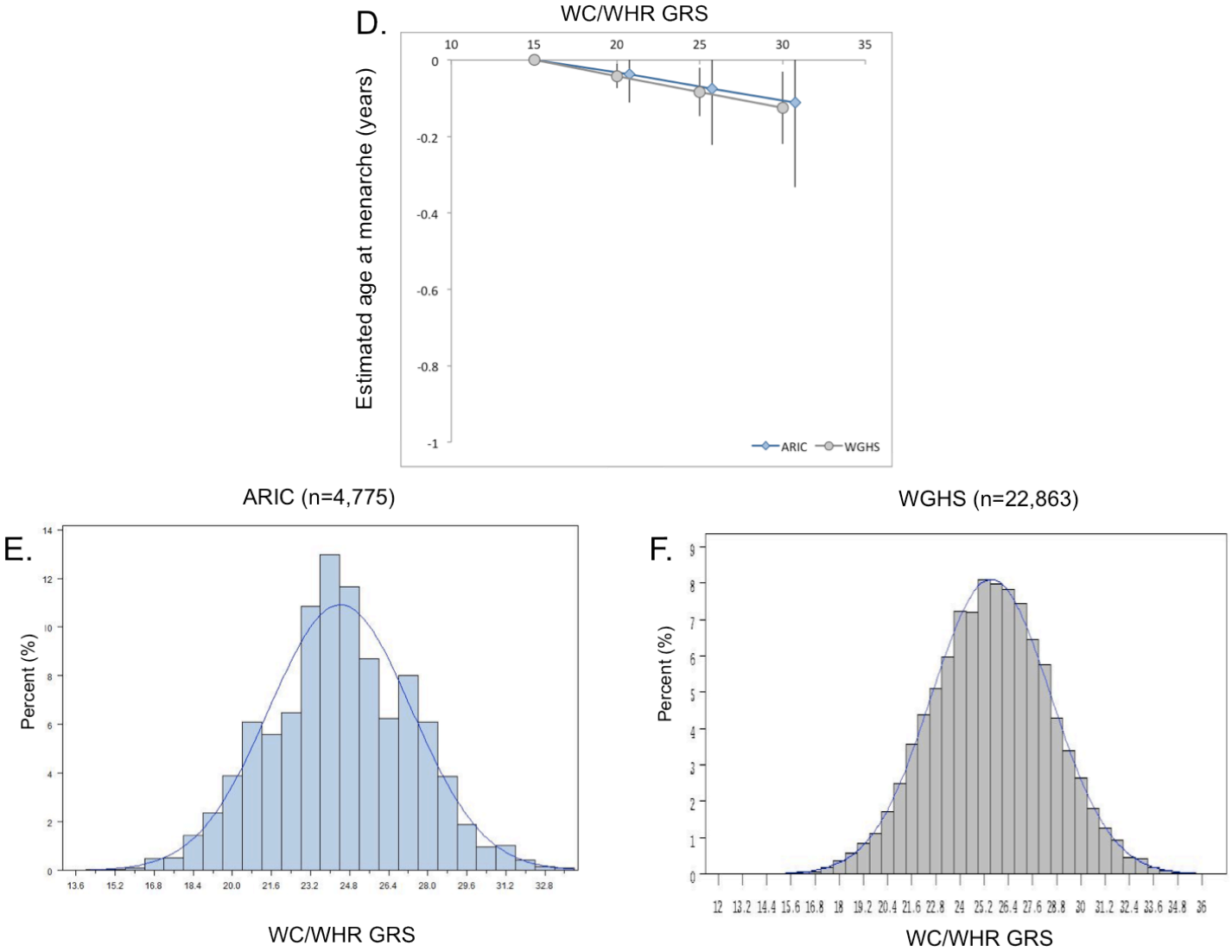
Web Figure 3A-B. Histogram (A) and Q-Q Plot (B) of the Distribution of *P* Values Among 95 Adiposity-SNPs



Web Figure 4A-C. Distribution and estimated decline in age at menarche in years per one risk allele increase in a genetic risk score (GRS) of BMI (A-C) and waist circumference/waist-hip-ratio genetic variants (D-F) in the Atherosclerosis Risk in Communities (ARIC) Study and the Women's Genome Health Study (WGHS).

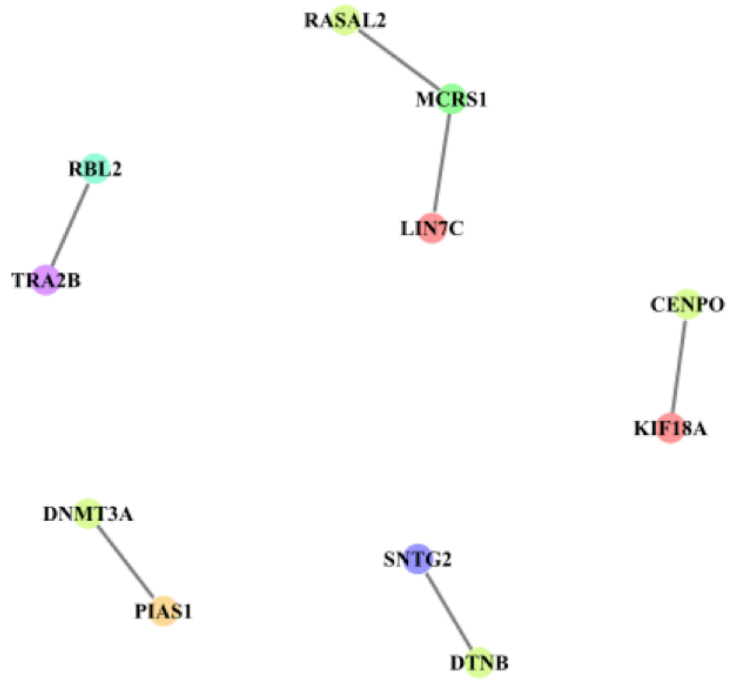


Web Figure 4D-F. Distribution and estimated decline in age at menarche in years per one risk allele increase in a genetic risk score (GRS) of BMI (A-C) and waist circumference/waist-hip-ratio genetic variants (D-F) in the Atherosclerosis Risk in Communities (ARIC) Study and the Women's Genome Health Study (WGHS).



Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; GRS, genetic Risk Score; WC, waist circumference; WGHS, Women's Genome Health Study; WHR, waist-hip-ratio.
Note: One BMI SNP was missing from both studies (rs545854) and therefore is not included in the BMI GRS.

Web Figure 5. DAPPLE Interaction Analysis of Waist Circumference and BMI SNPs Associated Significantly with Age at Menarche (±300kb Window From Each Marker SNP)



Direct Interactions (P=0.034)

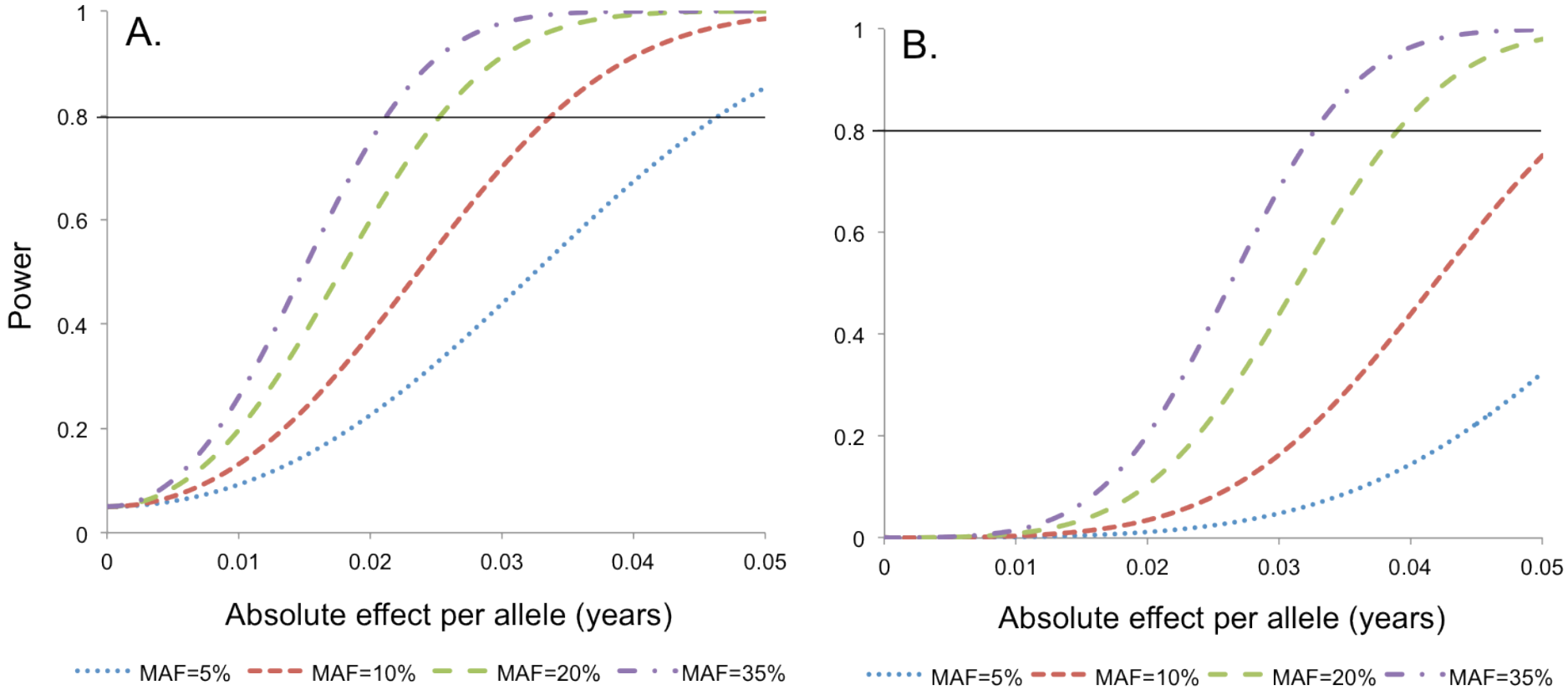
- *MCRS1 -- LIN7C*
- *MCRS1 -- RASAL2*
- *CENPO -- KIF18A*
- *SNTG2 -- DTNB*
- *DNMT3A -- PIAS1*
- *RBL2 -- TRA2B*

Indirect Interactions (P≥0.05)

GENE	REGION	$P_{uncorrected}$	$P_{corrected}$
SNTG2	rs2867125, rs6548238, rs7561317	0.032	0.032

[a]Neither rs545854 nor rs7826222 were recognized.

Web Figure 6A-B. Estimated Power to Detect Effects on Age at Menarche With a Set Sample of 86,000 Women at Nominal Significance (A; *P*<0.05) and After Bonferroni Adjustment for Multiple Tests (B; *P*<0.05/95)[a]



[a]Estimates of statistical power were based on a distribution of age at menarche of 12.9 years (standard deviation=1.5), additive gene effects, a sample of 86,000 unrelated individuals, and nominal significance (*P*<0.05). Because a range of effect sizes (8.4-18.2 day or 0.02-0.05 year-changes per allele) have been noted for age at menarche and only variants >1% minor allele frequency were excluded, both parameters were allowed to vary.

WEB TABLES

Web Table 1. Characteristics of Participating Studies of Women of European Descent in the ReproGen Consortium by Continent of Study Origin

Full Study Name	Abbreviation	N	Type	Isolate	Country of Origin	Mean Birth Year (SD)	Data Collection Period	Mean Age (SD)	Mean AAM (SD)	Specific Menarche Questions
European Studies										
Age, Gene/Environment Susceptibility Study	AGES	1,849	Population-based cohort	Yes	Iceland	1927 (5.6)	2002-2006	76.3 (5.5)	13.6 (1.3)	"At what age did your menstrual periods begin?"
1958 British Birth Cohort- Type 1 Diabetes Genetics Consortium	B58C-T1DGC	1,021	Population-based cohort	No	England, Wales, Scotland	1958	1974	16.1 (0.2)	12.7 (1.4)	"At what age did she [your daughter] have her first menstrual period?" with response categories "before 11th birthday" (coded as 10), "when aged 11", "aged 12", "aged 13", "aged 14", "aged 15 or more", "not yet commenced" (coded as 16), "commenced but don't know when" (excluded), "don't know if commenced" (excluded).
1958 British Birth Cohort- Wellcome Trust Case Control Consortium	B58C-WTCCC	563	Population-based cohort	No	England, Wales, Scotland	1958	1974	16.1 (0.2)	12.8 (1.3)	"At what age did she [your daughter] have her first menstrual period?" with response categories "before 11th birthday"

										(coded as 10), "when aged 11", "aged 12", "aged 13", "aged 14", "aged 15 or more", "not yet commenced" (coded as 16), "commenced but don't know when" (excluded), "don't know if commenced" (excluded).
Cohorte LAUSannoise	COLAUS	2,797	Population-based cohort	No	Switzer-land	1951 (10.8)	2003-2006	53.4 (10.8)	13.2 (1.6)	"At what age did you have your first period?"
deCODE Genetics Study	DECODE	15,864	Population-based cohort	No	Iceland	1948 (17.0)	1970-2008	48.1 (7.1)	13.2 (1.3)	“How old were you when your menstruation started?”
Danish National Birth Cohort	DNBC	1,748	Population-based cohort	No	Denmark	1970 (4.4)	1996-2002	30.0 (4.3)	13.3 (1.3)	"How old were you when you had your first menstrual period?"
Estonian Genome Center, University of Tartu	EGCUT	983	Population-based cohort	Yes	Estonia	1963 (16.0)	2003-2010	41.2 (16.5)	13.4 (1.5)	"How old you were when you had your first menstruation?"
European Prospective Investigation into Cancer and Nutrition- Obesity case-cohort study (Controls)	EPIC-COHORT	1,215	Nested Case Control	No	England, Wales, Scotland, Northern Ireland	1936 (9.1)	1993-1997	58.7 (9.0)	12.9 (1.8)	"How old were you when you had your first menstrual period?"
Erasmus Rucphen Family study	ERF	1,103	Family-based cohort	Yes	Nether-lands	1957 (14.4)	2002	47.5 (14.3)	13.1 (1.7)	"At what age did your menstrual periods begin?"
Health2000 cohort-control subsample	Health 2000 (GENMETS) controls	465	Controls	No	Finland	1948 (11.6)	2000-2001	51.9 (11.6)	13.4 (1.6)	"How old were you when your periods started?"

Helsinki Birth Cohort Study	HBCS	976	Population-based cohort	Yes	Finland	1941 (2.9)	2000-2002	61.5 (3.0)	12.8 (1.5)	"At what age did your menstrual periods start?"
InCHIANTI Study	INCHIANTI	597	Population-based cohort	No	Italy	1930 (15.4)	1998-2000	68.2 (15.5)	13.3 (1.5)	"How old were you when you had your first menstrual period?"
Italian Network of Isolated Populations-Val Borbera	INGI-VB	910	Population-based cohort	Yes	Italy	1951 (18.4)	2005-2008	54.4 (18.3)	12.9 (1.5)	"What was your age at menarche?"
Cooperative Health Research in the Region of Augsburg	KORA F3	809	Population-based cohort	No	Germany	1942 (10.1)	2004-2005	61.8 (10.1)	13.7 (1.5)	"At what age did you have your first menstruation/period (menarche)?"
Cooperative Health Research in the Region of Augsburg	KORA S4	898	Population-based cohort	No	Germany	1946 (8.8)	1999-2001	53.5 (8.8)	13.5 (1.5)	"At what age did you have your first menstruation/period (menarche)?"
CROATIA-Korcula	KORCULA	508	Population-based cohort	Yes	Croatia	1952 (14.0)	2007	54.9 (13.2)	13.7 (1.6)	"Age at menarche?__"
Northern Finland Birth Cohort 1966	NFBC	2,648	Population-based cohort	Yes	Finland	1966	1997-1998	31.2 (0.4)	12.9 (1.3)	"How old were you when you started menstruating?"
Netherlands Twin Register	NTR	1,051	Family-based cohort	No	Nether-lands	1961 (13.7)	1991-2008	44.6 (13.6)	13.2 (1.4)	“How old were you when you had your first menstrual period?”
Orkney Complex Disease Study	ORCADES	348	Population-based cohort	Yes	Scotland	1955 (15.6)	2005-2007	52.7 (15.3)	12.8 (1.4)	"How old were you when you had your first menstrual period?"
Rotterdam Study 1	RS1	3,175	Population-based cohort	No	Nether-lands	1922 (9.4)	1989-1993	69.6 (9.3)	13.5 (1.6)	"How old were you when you had your first menstrual period?"
Rotterdam Study 2	RS2	1,119	Population-based cohort	No	Nether-lands	1935 (8.2)	2000-2001	65.1 (8.4)	13.3 (1.6)	"How old were you when you had your first menstrual period?"

Rotterdam Study 3	RS3	1,112	Population-based cohort	No	Nether-lands	1951 (6.1)	2006-2008	56.2 (6.1)	13.1 (1.6)	"How old were you when you had your first menstrual period?"
SardiNIA genome-wide association study	SARDINIA	2,158	Family-based cohort	Yes	Italy	1958 (17.4)	2001-2008	43.9 (17.2)	13.2 (1.6)	“At what age did your menstrual periods begin?”
CROATIA-Split	SPLIT	283	Population-based cohort	No	Croatia	1960 (14.0)	2009-2010	49.8 (13.9)	13.5 (1.5)	"Age at menarche?__"
Twins United Kingdom Cohort I	TWINSUK1	2,276	Family-based cohort	No	England, Wales, Scotland, Northern Ireland	1951 (12.7)	1992-2001	58.2 (12.7)	13.0 (1.6)	“How old were you when you had your first menstrual period?”
Twins United Kingdom Cohort II	TWINSUK2	671	Family-based cohort	No	England, Wales, Scotland, Northern Ireland	1954 (14.6)	1992-2001	55.4 (14.6)	13.1 (1.6)	“How old were you when you had your first menstrual period?”
Twins United Kingdom Cohort III	TWINSUK3	1,016	Family-based cohort	No	England, Wales, Scotland, Northern Ireland	1947 (11.6)	1992-2001	62.4 (11.6)	12.9 (1.5)	“How old were you when you had your first menstrual period?”
CROATIA-Vis	VIS	502	Population-based cohort	Yes	Croatia	1947 (15.8)	2003-2004	56.6 (15.8)	13.6 (1.6)	"Age at menarche?__"
Non-European Studies										
Old Order Amish Cohort	AMISH	557	Family-based cohort	Yes	United States	1953 (16.2)	1997-2009	49.1 (3.7)	13.1 (1.3)	“How old were you when you had your first menstrual period?”
Atherosclerosis Risk in Communities Study	ARIC	4,775	Population-based cohort	No	United States	1934 (5.8)	1987-1989	53.9 (5.7)	12.9 (1.5)	"How old were you when you had your first menstrual period?"

Framingham Heart Study	FHS	3,801	Population-based cohort	No	United States	1951 (15.8)	1970-1983, 2002-2005	42.5 (10.1)	12.8 (1.5)	"Age at start of menses? ___, How old were you when you had your first menstrual period (menses)?, About how old were you when you had your first menstrual period?"
Indiana University premenopausal Caucasian women peak BMD study	INDIANA	1,497	Family-based cohort	No	United States	1965 (8.1)	1994-2004	33.3 (7.2)	12.6 (1.4)	"At what age did your periods begin? ___Years old."
Nurses' Health Study	NHS-BRCA	2,270	Nested case control	No	United States	1931 (6.4)	1976	56.8 (6.4)	12.5 (1.4)	"At what age did your menstrual periods begin?"
Nurses' Health Study	NHS-T2D	3,090	Nested case control	No	United States	1932 (6.9)	1976	55.7 (6.7)	12.5 (1.4)	"At what age did your menstrual periods begin?"
Queensland Institute of Medical Research	QIMR	3528	Family-based cohort	No	Australia	1965 (19.0)	1982-2010	32.1 (11.4)	13.1 (1.3)	"How old were you when you had your first menstrual period?"
Western Australian Pregnancy cohort	RAINE	614	Population-based cohort	No	Australia	1990 (0.8)	2000-2006	12.7 (1.1)	12.7 (1.1)	"What date did your daughter have her first period? __/__/__"
Study of Addiction: Genetics and Environment	SAGE	1,291	Population-based cohort	No	United States	1963 (55.6)	1997-2006	38.4 (9.1)	12.8 (1.6)	"At what age did you have your first menstrual period?"
Women's Genome Health Study	WGHS	22,028	Population-based cohort	No	United States	1939 (7.2)	1992-1994	54.7 (7.1)	12.4 (1.4)	"At what age did your menstrual periods begin?" with response categories "9 or younger; 10; 11; 12; 13; 14; 15; 16; 17 or older."
	Overall[a]	92,116								

Abbreviations: CI, Confidence interval; SD, Standard deviation

[a]The overall total is an estimate of the maximum sample size available from each study. However, due to variable quality control measures at each SNP, this sum contains 11 more samples than the largest SNP meta-analysis in this study (n=92,105).

Web Table 2. Summary of 95 Candidate Adiposity SNPs Available in the Literature as of August 11, 2011

SNP ID	Chromosome: Position[a] (bp)		Nearest Genes	Reference	Coded Allele	Previous Effect Size[b]	Phenotype	*P*-value	Notes on Effect Shown
rs3934834	1	995,669		Johansson et al.	G	0.11	BMI	$6x10^{-7}$	
rs2568958	1	72,537,704	*NEGR1*	Thorleifson et al.	A	3.77 (% SD)	BMI, weight	$1x10^{-11}$	BMI
rs2815752	1	72,585,028	*NEGR1*	Willer et al./Speliotes et al.	A	0.13	BMI	$2x10^{-22}$	BMI from Speliotes et al.
rs1514175	1	74,764,232	*TNNI3K*	Speliotes et al.	A	0.07	BMI	$8x10^{-14}$	
rs1555543	1	96,717,385	*PTBP2*	Speliotes et al.	C	0.06	BMI	$4x10^{-10}$	
rs10783050	1	96,809,671		Thorliefson et al.	C	2.6 (% SD)	BMI	$4x10^{-6}$	
rs984222	1	119,305,366	*TBX15-WARS2*	Heid et al.	G	0.034	WHR	$9x10^{-25}$	
rs1011731	1	170,613,171	*DNM3-PIGC*	Heid et al.	G	0.028	WHR	$1x10^{-17}$	
rs543874	1	176,156,103	*SEC16B*	Speliotes et al.	G	0.22	BMI	$4x10^{-23}$	
rs10913469	1	176,180,142	*SEC16B, RASAL2*	Thorleifson et al.	C	3.36 (% SD)	BMI, weight	$6x10^{-8}$	BMI
rs2605100	1	217,710,847	*LYPLAL1*	Lindgren et al.	G	0.040 (z-score)	WHR[c]	$3x10^{-8}$	Women
rs4846567	1	217,817,340	*LYPLAL1*	Heid et al.	G	0.034	WHR	$5x10^{-33}$	Women
rs6429082	1	233,666,752	*TBCE*	Lindgren et al.	C	NR	WC[c]	$3x10^{-7}$	
rs2867125	2	612,827	*TMEM18*	Speliotes et al.	C	0.31	BMI	$3x10^{-49}$	
rs6548238	2	624,905	*TMEM18*	Willer et al.	C	0.26	BMI	$1x10^{-18}$	
rs7561317	2	634,953	*TMEM18*	Thorleifson et al.	G	6.12 (% SD)	BMI, weight	$4x10^{-12}$	BMI
rs713586	2	25,011,512	*RBJ*	Speliotes et al.	C	0.14	BMI	$6x10^{-22}$	
rs887912	2	59,156,381	*FANCL*	Speliotes et al.	T	0.10	BMI	$2x10^{-12}$	
rs2890652	2	142,676,401	*LRP1B*	Speliotes et al.	C	0.09	BMI	$1x10^{-10}$	
rs10195252	2	165,221,337	*GRB14*	Heid et al.	T	0.033	WHR	$4x10^{-24}$	
rs824931	2	222,509,943		Johansson et al.	G	0.07 kg	BMI	$3x10^{-6}$	
rs6784615	3	52,481,466	*NISCH-STAB1*	Heid et al.	T	0.043	WHR	$4x10^{-10}$	
rs6795735	3	64,680,405	*ADAMTS9*	Heid et al.	C	0.025	WHR	$2x10^{-16}$	Women
rs1024889	3	70,546,020		Johansson et al.	G	0.12 (kg)	BMI	$6x10^{-6}$	Women
rs13078807	3	85,966,840	*CADM2*	Speliotes et al.	G	0.10	BMI	$4x10^{-11}$	
rs1875517	3	118,790,257		Fox et al.	NR	NR	WC	$2x10^{-6}$	
rs7647305	3	187,316,984	*SFS10, ETV5, DGKG*	Thorleifson et al.	C	4.42 (% SD)	BMI, weight	$7x10^{-11}$	BMI
rs9816226	3	187,317,193	*ETV5*	Speliotes et al.	T	0.14	BMI	$2x10^{-18}$	
rs1152846	3	189,903,591		Johansson et al.	G	-0.09 (kg)	BMI, weight	$3x10^{-6}$	BMI
rs10938397	4	44,877,284	*GNPDA2*	Willer et al./Speliotes et al.	G	0.18	BMI	$4x10^{-31}$	BMI from Speliotes

									et al.
rs13107325	4	103,407,732	*SLC39A8*	Speliotes et al.	T	0.19	BMI	$2x10^{-13}$	
rs2383393	4	180,901,647		Johansson et al.	G	0.1 (kg)	BMI	$2x10^{-6}$	Women
rs4701252	5	21,814,911	*CDH12*	Heard-Costa et al.	NR	NR	WC	$2x10^{-6}$	
rs2112347	5	75,050,998	*FLJ35779*	Speliotes et al.	T	0.10	BMI	$2x10^{-13}$	
rs4836133	5	124,360,002	*ZNF608*	Speliotes et al.	A	0.07	BMI	$2x10^{-9}$	
rs6861681	5	173,295,064	*CPEB4*	Heid et al.	A	0.022	WHR	$2x10^{-9}$	
rs12517906	5	180,103,425	*MGAT1*	Johansson et al.	G	-0.16 (kg)	BMI, weight	$6x10^{-6}$	BMI; Women
rs1294421	6	6,688,148	*LY86*	Heid et al.	G	0.028	WHR	$2x10^{-17}$	
rs2076529	6	32,471,933	*BTNL2*	Heid et al.	C	0.020	WHR	$4x10^{-7}$	
rs206936	6	34,410,847	*NUDT3*	Speliotes et al.	G	0.06	BMI	$3x10^{-8}$	
rs6905288	6	43,866,851	*VEGFA*	Heid et al.	A	0.026	WHR	$2x10^{-26}$	
rs987237	6	50,911,009	*TFAP2B*	Lindgren et al./Speliotes et al.	G	0.13	WC[c]/BMI	$3x10^{-20}$	BMI from Speliotes et al.
rs1555967	6	51,267,954	*PKHD1*	Heard-Costa et al.	NR	NR	WC	$3x10^{-6}$	
rs9491696	6	127,494,332	*RSPO3*	Heid et al.	G	0.042	WHR	$2x10^{-32}$	Women
rs2275215	6	129,903,085	*LAMA2*	Liu et al.	T	-0.09 (SD)	BMI	$4x10^{-7}$	
rs1055144	7	25,837,634	*NFE2L3*	Heid et al.	T	0.040	WHR	$1x10^{-24}$	
rs1106683	7	131,104,065		Fox et al.	NR	NR	BMI	$1x10^{-7}$	
rs1106684	7	131,104,205		Fox et al.	?	NR	BMI	$2x10^{-6}$	
rs545854[d]	8	9,897,490	*MSRA*	Lindgren et al.	G	0.04 (z-score)	WC[c]	$9x10^{-9}$	
rs4471028	8	75,457,530	*GDAP1*	Fox et al.	NR	NR	WC	$2x10^{-7}$	
rs1927702	9	15,976,716		Johansson et al.	G	0.08 (kg)	BMI	$6x10^{-6}$	Women
rs10968576	9	28,404,339	*LRRN6C*	Speliotes et al.	G	0.11	BMI	$3x10^{-13}$	
rs10458787	10	4,645,565		Liu et al.	G	0.09 (% SD)	BMI	$1x10^{-6}$	
rs7081678	10	32,030,629	*ZEB1*	Heid et al.	A	0.027	WHR	$6x10^{-6}$	
rs7932813	11	7,664,857	*OVCH2*	Heard-Costa et al.	NR	NR	WC	$5x10^{-6}$	
rs10769908	11	8,440,665	*STK33*	Willer et al.	C	NR	BMI	$1x10^{-6}$	
rs4929949	11	8,561,169	*RPL27A*	Speliotes et al.	C	0.06	BMI	$3x10^{-9}$	
rs7481311	11	27,539,705	*BDNF*	Thorleifson et al.	T	3.15 (% SD)	BMI, weight	$8x10^{-6}$	BMI
rs4923461	11	27,613,486	*BDNF*	NR	NR	NR	BMI	NR	
rs925946	11	27,623,778	*BDNF*	Thorleifson et al.	T	3.85 (% SD)	BMI, weight	$9x10^{-10}$	
rs6265	11	27,636,492	*BDNF*	Thorleifson et al.	G	4.58 (% SD)	BMI, weight	$5x10^{-10}$	BMI
rs10767664	11	27,682,562	*BDNF*	Speliotes et al.	A	0.19	BMI	$5x10^{-26}$	
rs3817334	11	47,607,569	*MTCH2*	Speliotes et al.	T	0.06	BMI	$2x10^{-12}$	
rs10838738	11	47,619,625	*MTCH2*	Willer et al.	G	0.07	BMI	$5x10^{-9}$	
rs1458095	11	80,663,196		Johansson et al.	G	0.19 (kg)	BMI	$7x10^{-6}$	Women
rs718314	12	26,344,550	*ITPR2-SSPN*	Heid et al.	G	0.030	WHR	$2x10^{-17}$	Women

rs7138803	12	48,533,735	*FAIM2*	Thorliefson et al./Speliotes et al.	A	0.12	WC/BMI	$2x10^{-12}$	BMI from Speliotes et al.
rs1443512	12	52,628,951	*HOXC13*	Heid et al.	A	0.031	WHR	$6x10^{-16}$	Women
rs4771122	13	26,918,180	*MTIF3*	Speliotes et al.	G	0.09	BMI	$9x10^{-10}$	
rs1333026	13	65,018,785		Fox et al.	NR	NR	BMI	$8x10^{-6}$	
rs11847697	14	29,584,863	*PRKD1*	Speliotes et al.	T	0.17	BMI	$6x10^{-11}$	
rs10150332	14	79,006,717	*NRXN3*	Speliotes et al.	C	0.13	BMI	$3x10^{-11}$	
rs10146997	14	79,014,915	*NRXN3*	Heard-Costa et al.	G	0.65	WC[c]	$5x10^{-8}$	
rs2241423	15	65,873,892	*MAP2K5*	Speliotes et al.	G	0.13	BMI	$1x10^{-18}$	
rs12324805	15	80,139,255	*RKHD3*	Willer et al.	C	NR	BMI	$7x10^{-6}$	
rs12444979	16	19,841,101	*GPRC5B*	Speliotes et al.	C	0.17	BMI	$3x10^{-21}$	
rs7498665	16	28,790,742	*SH2B1, ATP2A1*	Willer et al./Thorliefson et al.	G	3.63 (% SD)	BMI/BMI, weight	$3x10^{-10}$	BMI from Thorliefson et al.
rs7359397	16	28,793,160	*SH2B1*	Speliotes et al.	T	0.15	BMI	$2x10^{-20}$	
rs6499640	16	52,327,178	*FTO*	Thorleifson et al.	A	5.25 (% SD)	BMI, weight	$4x10^{-13}$	BMI
rs1558902	16	52,361,075	*FTO*	Heard-Costa et al./Speliotes et al.	A	0.39	WC[c]/BMI	$5x10^{-120}$	BMI from Speliotes et al.
rs1121980	16	52,366,748	*FTO*	Loos et al.	?	0.06 (ln BMI)	BMI	$4x10^{-8}$	
rs8050136	16	52,373,776	*FTO*	Thorleifson et al.	A	8.04 (% SD)	BMI, weight	$1x10^{-47}$	BMI
rs9939609	16	52,378,028	*FTO*	Frayling et al./Willer et al.	A	0.33	BMI	$4x10^{-51}$	BMI from Willer et al.
rs571312	18	55,990,749	*MC4R*	Speliotes et al.	A	0.23	BMI	$6x10^{-42}$	
rs17782313	18	56,002,077	*MC4R*	Loos et al./Willer et al.	C	0.2	BMI	$5x10^{-18}$	
rs489693	18	56,033,767	*MC4R*	Heard-Costa et al.	NR	NR	WC	$4x10^{-7}$	
rs12970134	18	56,035,730	*MC4R*	Chambers et al./Thorliefson et al.	A	4.38 (% SD)	WC/BMI, weight	$1x10^{-12}$	BMI from Thorliefson et al.
rs3803915	19	2,111,529		Johansson et al.	C	0.13 (kg)	BMI	$5x10^{-6}$	
rs29941	19	39,001,372	*KCTD15*	Thorleifson et al./Speliotes et al.	G	0.06	BMI/BMI, weight	$3x10^{-9}$	BMI from Speliotes et al.
rs11084753	19	39,013,977	*KCTD15*	Willer et al.	G	NR	BMI	$2x10^{-8}$	
rs2287019	19	50,894,012	*QPCTL*	Speliotes et al.	C	0.15	BMI	$2x10^{-16}$	
rs3810291	19	52,260,843	*TMEM160*	Speliotes et al.	A	0.09	BMI	$2x10^{-12}$	
rs1878047	19	56,465,614		Johansson et al.	G	-0.06 (kg)	BMI	$5x10^{-6}$	
rs2145270	20	6,569,685	*BMP2*	Willer et al.	T	NR	BMI	$6x10^{-6}$	
rs4823006	22	27,781,671	*ZNRF3-KREMEN1*	Heid et al.	A	0.023	WHR	$3x10^{-11}$	Women

Abbreviations: BMI, body mass index; kg, kilograms; ln, Natural Logarithm, NR, None reported; SD, Standard deviation; WC, waist circumference; WHR, waist-hip ratio

[a]Positions from Build 36.

[b]Unless otherwise noted effect sizes are in unitless changes in WHR, cm changes in WC, and kg/m^2 changes in BMI.

[c]Central adiposity measures (WC or WHR) were unadjusted for BMI and/or not found to be independent of BMI in secondary analyses.

[d]Previously reported SNP, rs7826222, has merged into rs545854.

Web Table 3. SNPs Previously Reported to Associate With Waist Circumference or BMI and Age at Menarche from Elks *et al.*, 2010

SNP ID	Chromosome: Position[a] (bp)		Nearest Genes	Studies	N	Alleles		Coded Freq-uency	Fixed Effects					Hetero-geneity *P* value
						Coded	Other		Estimate (days)	SE (days)	95% CI		*P* value	
Waist Circumference (WC)[b]														
rs987237	6	50,911,009	*TFAP2B*	38	92,104	A	G	0.82	13.2	3.2	7.0	19.4	**$3.3x10^{-5}$**	0.95
rs545854[c]	8	9,897,490	*MSRA*	9	32,335	C	G	0.81	16.2	5.8	4.8	27.6	$5.2x10^{-3}$	0.23
Body Mass Index (BMI)[d]														
rs2815752	1	72,585,028	*NEGR1*	38	92,081	A	G	0.61	-13.4	2.4	-18.2	-8.6	**$3.5x10^{-8}$**	0.41
rs10913469	1	176,180,142	*SEC16B, RASAL2*[e]	37	88,557	T	C	0.81	16.7	3.1	10.6	22.8	**$8.5x10^{-8}$**	0.81
rs6548238	2	624,905	*TMEM18*[e]	37	89,688	T	C	0.16	19.1	3.4	12.4	25.7	**$2.1x10^{-8}$**	0.40
rs7647305	3	187,316,984	*SFS10, ETV5, DGKG*[e]	38	92,064	T	C	0.21	8.7	3.0	2.9	14.5	$3.3x10^{-3}$	0.62
rs10938397	4	44,877,284	*GNPDA2*	37	88,074	A	G	0.57	13.5	2.6	8.4	18.6	**$1.7x10^{-7}$**	0.93
rs4923461	11	27,613,486	*BDNF*	33	89,535	A	G	0.80	-13.0	3.1	-19.0	-7.0	**$2.3x10^{-5}$**	0.44
rs7138803	12	48,533,735	*FAIM2*	37	89,837	A	G	0.38	-11.7	2.5	-16.6	-6.9	**$2.2x10^{-6}$**	0.29
rs9939609	16	52,378,028	*FTO*[e]	37	89,904	A	T	0.40	-16.9	2.4	-21.7	-12.2	**$4.2x10^{-12}$**	0.22
rs11084753	19	39,013,977	*KCTD15*	36	86,300	A	G	0.34	10.8	2.8	5.4	16.3	**$1.0x10^{-4}$**	0.60

Abbreviations: CI, Confidence interval; SE, Standard error; SNP ID, Reference Single Nucleotide Polymorphism Identification Number
P values in bold represent SNP-associations below the Bonferroni threshold of $P<0.05/95$.
[a]Positions from Build 36.
[b]Unadjusted for BMI.
[c]Previously SNP ID, rs7826222, has changed into rs545854.
[d]This table is an updated version of Supplemental Table 13 from Elks *et al.*, 2010. Therefore the SNPs in this table represent loci (*NEGR1, SEC16B, TMEM18, ETV5, BDNF, FTO,* and KCTD15) that are also described in Table 1 (i.e. represented by SNPs that were not previously been associated with both adiposity and menarche). Additional SNP-associations at three of these loci (*TMEM18, BDNF,* and *FTO*) are reported in Web Table 5, because they were in linkage disequilibrium with four SNPs in Table 1 ($r^2 \geq 0.2$) and had not been described previously.
[e]SNPs at *SEC16B, TMEM18*, *ETV5,* and *FTO* are also previously reported to genome-wide significantly associate with age at menarche ($P<5x10^{-8}$): rs633715, rs2947411, rs2002675, and rs9939609 (presented above), respectively.

Web Table 4. SNPs Previously Reported to Associate With Waist Circumference, Waist-Hip Ratio, or BMI but not With Age at Menarche That Did Not Reach Statistical Significance ($P \geq 0.05/95$)

SNP ID	Chromosome: Position[a] (bp)		Nearest Genes	Studies	N	Alleles			Fixed Effects					
						Coded	Other	Coded Freq-uency	Estimate (days)	SE (days)	95% CI		*P* value	Hetero-geneity *P* value
Waist Circumference (WC)[b]														
rs6429082[c]	1	233,666,752	*TBCE*	33	89,452	T	C	0.46	7.2	2.4	2.4	11.9	0.0031	0.59
rs1875517	3	118,790,257		38	92,080	A	G	0.43	-2.1	2.4	-6.8	2.6	0.38	0.86
rs4701252	5	21,814,911	*CDH12*	31	57,845	T	C	0.83	9.1	5.0	-0.6	18.8	0.068	0.69
rs1555967	6	51,267,954	*PKHD1*	37	89,957	A	G	0.24	1.9	3.1	-4.2	8.1	0.53	0.04
rs4471028	8	75,457,530	*GDAP1*	38	92,091	T	G	0.57	0.0	2.4	-4.7	4.7	0.99	0.43
rs7932813	11	7,664,857	*OVCH2*	38	91,927	A	G	0.83	-3.3	3.4	-10.0	3.5	0.34	0.11
rs489693	18	56,033,767	*MC4R*	38	92,092	A	C	0.32	1.2	2.6	-3.8	6.3	0.63	0.70
Waist-Hip Ratio (WHR)[b]														
rs984222	1	119,305,366	*TBX15-WARS2*	33	89,547	C	G	0.38	-0.1	2.5	0.0	0.0	0.97	0.50
rs1011731	1	170,613,171	*DNM3-PIGC*	32	87,317	A	G	0.57	-0.5	2.4	-5.3	4.3	0.85	0.51
rs2605100[c]	1	217,710,847	*LYPLAL1*[d]	32	87,350	A	G	0.31	1.4	2.6	-3.7	6.6	0.59	0.78
rs10195252	2	165,221,337	*GRB14*	32	85,913	T	C	0.57	-0.3	2.5	-5.1	4.6	0.92	0.30
rs6784615	3	52,481,466	*NISCH-STAB1*	32	87,341	T	C	0.95	1.1	5.9	-10.5	12.7	0.86	0.07
rs6795735	3	64,680,405	*ADAMTS9*	32	87,365	T	C	0.41	2.3	2.4	-2.5	7.1	0.36	0.24
rs6861681	5	173,295,064	*CPEB4*	32	87,311	A	G	0.32	4.4	2.8	-1.1	9.9	0.12	0.79
rs1294421	6	6,688,148	*LY86*	32	87,100	T	G	0.38	1.4	2.5	-3.6	6.3	0.58	0.64
rs2076529	6	32,471,933	*BTNL2*	23	55,048	T	C	0.58	-0.4	3.0	-6.2	5.4	0.88	<0.01
rs6905288	6	43,866,851	*VEGFA*	30	79,680	A	G	0.56	-2.2	3.1	-8.3	4.0	0.48	0.52
rs9491696	6	127,494,332	*RSPO3*	33	89,202	C	G	0.50	1.2	2.4	-3.6	6.0	0.63	0.54
rs1055144	7	25,837,634	*NFE2L3*	32	87,391	T	C	0.19	-1.1	3.2	-7.4	5.1	0.72	<0.01
rs7081678	10	32,030,629	*ZEB1*	32	88,994	A	G	0.08	7.2	4.8	-2.3	16.6	0.14	0.20
rs718314	12	26,344,550	*ITPR2-SSPN*	33	89,460	A	G	0.75	-4.3	2.9	-10.1	1.4	0.14	0.52
rs1443512	12	52,628,951	*HOXC13*	33	89,530	A	C	0.22	-2.0	2.9	-7.7	3.8	0.50	0.07
rs4823006	22	27,781,671	*ZNRF3-KREMEN1*	32	86,963	A	G	0.57	-0.7	2.5	-5.6	4.2	0.78	0.47
Body Mass Index (BMI)														
rs3934834	1	995,669		32	81,506	T	C	0.16	-0.9	3.8	-8.4	6.5	0.81	0.77
rs10783050	1	96,809,671	[d]	37	88,558	T	C	0.64	2.3	2.5	-2.6	7.2	0.36	0.99
rs2890652	2	142,676,401	*LRP1B*	38	91,847	T	C	0.82	2.9	3.3	-3.6	9.3	0.38	0.20
rs824931	2	222,509,943		38	92,048	T	C	0.65	5.9	2.5	0.9	10.8	0.020	0.03
rs1024889	3	70,546,020		37	89,908	A	G	0.68	-6.0	2.6	-11.1	-0.9	0.020	0.04

rs13078807	3	85,966,840	*CADM2*	37	88,567	A	G	0.79	1.8	3.1	-4.2	7.8	0.56	0.76
rs1152846	3	189,903,591		38	92,091	T	C	0.24	-0.1	2.8	0.0	0.0	0.96	0.88
rs13107325	4	103,407,732	*SLC39A8*	37	88,562	T	C	0.07	-11.7	5.7	-22.9	-0.6	0.04	0.19
rs2383393	4	180,901,647		38	91,997	A	G	0.40	-1.1	2.5	-6.0	3.9	0.67	0.87
rs2112347	5	75,050,998	*FLJ35779*	38	92,039	T	G	0.64	-2.2	2.5	-7.1	2.7	0.39	0.90
rs4836133	5	124,360,002	*ZNF608*	37	90,040	A	C	0.48	2.2	2.6	-2.9	7.2	0.40	0.22
rs12517906	5	180,103,425	*MGAT1*	36	86,375	T	C	0.15	-0.7	3.5	-7.5	6.1	0.84	0.91
rs206936	6	34,410,847	*NUDT3*	38	92,037	A	G	0.80	-6.1	3.0	-12.0	-0.2	0.043	0.88
rs2275215	6	129,903,085	*LAMA2*	37	89,922	T	C	0.73	-2.7	2.7	-8.1	2.7	0.32	0.27
rs1106683	7	131,104,065	[d]	37	89,904	A	G	0.15	-6.2	3.5	-13.0	0.7	0.077	0.56
rs1927702	9	15,976,716		38	91,935	T	C	0.57	2.5	2.4	-2.2	7.2	0.30	0.55
rs10968576	9	28,404,339	*LRRN6C*	37	88,578	A	G	0.68	0.7	2.7	-4.6	5.9	0.81	0.98
rs10458787	10	4,645,565		37	87,781	A	G	0.23	-1.7	3.1	-7.8	4.5	0.59	0.25
rs10838738	11	47,619,625	*MTCH2*[d]	37	88,560	A	G	0.65	4.5	2.5	-0.5	9.4	0.079	0.25
rs1458095	11	80,663,196		38	92,072	T	C	0.09	-9.0	4.3	-17.5	-0.5	0.038	0.74
rs4771122	13	26,918,180	*MTIF3*	38	91,603	A	G	0.77	7.5	3.0	1.6	13.4	0.012	0.05
rs1333026	13	65,018,785		38	92,085	A	G	0.16	3.4	3.4	-3.3	10.1	0.32	0.34
rs11847697	14	29,584,863	*PRKD1*	37	88,518	T	C	0.04	-17.9	6.6	-30.8	-5.0	0.0063	0.69
rs10150332	14	79,006,717	*NRXN3*[d]	37	88,565	T	C	0.78	6.0	3.0	0.0	11.9	0.047	0.01
rs12324805	15	80,139,255	*RKHD3*	36	86,322	A	C	0.67	-5.1	2.6	-10.2	0.1	0.053	0.02
rs7498665	16	28,790,742	*SH2B1, ATP2A1*[d]	38	91,853	A	G	0.60	2.1	2.4	-2.7	6.9	0.39	0.88
rs12970134	18	56,035,730	*MC4R*[d]	37	88,573	A	G	0.27	1.1	2.8	-4.3	6.6	0.69	0.70
rs3803915	19	2,111,529		36	90,328	A	C	0.11	8.7	4.1	0.7	16.7	0.033	0.65
rs2287019	19	50,894,012	*QPCTL*	36	89,334	T	C	0.20	4.0	3.3	-2.4	10.4	0.22	0.36
rs3810291	19	52,260,843	*TMEM160*	36	86,923	A	G	0.66	-8.9	2.8	-14.5	-3.4	0.0016	0.42
rs1878047	19	56,465,614		38	92,085	A	G	0.63	-1.6	2.5	-6.5	3.2	0.51	0.22
rs2145270	20	6,569,685	*BMP2*	38	91,838	T	C	0.63	2.8	2.6	-2.2	7.9	0.27	0.29

Abbreviations: CI, Confidence interval; SE, Standard error; SNP ID, Reference Single Nucleotide Polymorphism Identification Number

[a]Positions from Build 36.

[b]Adjusted for BMI, unless otherwise noted.

[c]Unadjusted for BMI.

[d]Additional SNP-associations at *LYPLAL1, PTBP2,* intergenic region on chromosome 7, *MTCH2, NRXN3, SH2B1,* and *MC4R* are reported in Web Table 5, because they were in linkage disequilibrium with the noted SNPs ($r^2 \geq 0.2$).

Web Table 5. SNPs Previously Reported to Associate With Waist-Hip Ratio or BMI but not With Age at Menarche that are Within 500kb and in Linkage Disequilibirum[a] (r^2≥0.2) With Other Candidate SNPs

				LD[a]				Alleles			Fixed Effects					
SNP ID	Chromosome: Position[b] (bp)		Nearest Genes	SNP ID	r^2	Studies	N	Coded	Other	Coded Frequency	Estimate (days)	SE (days)	95% CI		*P* value	Heterogeneity *P* value
Waist-Hip Ratio (WHR)[c]																
rs4846567	1	217,817,340	*LYPLAL1*	rs2605100	0.64	33	89,518	T	G	0.30	-1.3	2.7	-6.5	3.9	$6.3x10^{-1}$	0.56
Body Mass Index (BMI)																
rs1555543	1	96,717,385	*PTBP2*	rs10783050	0.37	37	89,908	A	C	0.41	-3.4	2.4	-8.2	1.4	$1.6x10^{-1}$	0.52
rs2867125	2	612,827	*TMEM18*	rs7561317	1.00	38	92,075	T	C	0.17	19.3	3.2	13.0	25.6	**$1.6x10^{-9}$**	0.56
rs1106684	7	131,104,205		rs1106683	0.88	37	89,625	C	G	0.85	6.1	3.6	-1.0	13.2	$9.0x10^{-2}$	0.54
rs4929949	11	8,561,169	*RPL27A*	rs10769908	0.97	38	91,649	T	C	0.47	10.1	2.4	5.3	14.9	**$4.1x10^{-5}$**	0.98
rs925946	11	27,623,778	*BDNF*	rs7481311	0.57	38	92,073	T	G	0.31	-11.8	2.6	-16.8	-6.7	**$5.9x10^{-6}$**	0.92
rs10767664	11	27,682,562	*BDNF*	rs6265	0.77	37	88,544	A	T	0.79	-14.2	3.1	-20.2	-8.2	**$3.6x10^{-6}$**	0.30
rs3817334	11	47,607,569	*MTCH2*	rs10838738	0.84	37	89,931	T	C	0.41	-4.2	2.4	-9.0	0.6	$8.4x10^{-2}$	0.33
rs10146997[d]	14	79,014,915	*NRXN3*	rs10150332	1.00	37	88,573	A	G	0.79	6.2	3.0	0.2	12.1	$4.2x10^{-2}$	0.01
rs7359397	16	28,793,160	*SH2B1*	rs7498665	1.00	38	92,105	T	C	0.40	-2.4	2.4	-7.2	2.3	$3.2x10^{-2}$	0.87
rs6499640[e]	16	52,327,178	*FTO*	rs8050136	0.21	37	89,848	A	G	0.62	-5.5	2.5	-10.4	-0.5	$2.9x10^{-2}$	0.44
rs1558902[e]	16	52,361,075	*FTO*	rs8050136	0.93	38	92,014	A	T	0.41	-17.5	2.6	-22.5	-12.5	**$6.2x10^{-12}$**	0.42
rs1121980[e]	16	52,366,748	*FTO*	rs8050136	0.84	37	89,612	A	G	0.43	-17.2	2.6	-22.2	-12.2	**$2.6x10^{-11}$**	0.22
rs571312[e]	18	55,990,749	*MC4R*	rs12970134	0.81	38	92,026	A	C	0.24	5.4	2.9	-0.3	11.0	$6.4x10^{-2}$	0.94
rs17782313[e]	18	56,002,077	*MC4R*	rs12970134	0.81	36	86,337	T	C	0.76	-5.1	3.0	-10.9	0.7	$8.3x10^{-2}$	0.90

Abbreviations: CI, Confidence interval; LD, Linkage disequilibrium; SE, Standard error; SNP ID, Reference Single Nucleotide Polymorphism Identification Number

P values in bold represent SNP-associations below the Bonferroni threshold of *P*<0.05/95.

[a]LD data from HapMap Build 22 data.

[c]Adjusted for BMI.

[d]Previoulsy associated with waist circumference, but the signal went away after adjustment for BMI.

[e]In LD with each other: *FTO* (r^2>0.21) and *MC4R* (r^2=1.00).

Web Table 6. Study-Specific Estimates for BMI-Age at Menarche-SNPs at Six Novel Loci by Decreasing Magnitude of Effect

Study[a] by locus	Effect per allele (days)	SE (days)	Lower 95% CI	Upper 95% CI
***GPRC5B* (rs12444979-T)**				
AGES	-0.5	25.9	-51.3	50.3
AMISH	3.9	52.9	-99.8	107.6
ARIC	12.0	16.6	-20.5	44.6
B58C-T1DGC	26.5	32.2	-36.7	89.7
B58C-WTCCC	-27.6	38.7	-103.4	48.2
COLAUS	17.5	23.2	-28.1	63.1
DECODE	33.1	8.5	16.4	49.8
DNBC	13.1	24.5	-34.8	61.1
EGCUT	60.7	38.7	-15.2	136.6
EPIC	-23.7	40.1	-102.2	54.8
ERF	62.3	50.2	-36.0	160.6
FHS	20.9	18.4	-15.2	57.0
GENMETS	78.0	46.2	-12.5	168.5
HBCS	49.7	37.9	-24.7	124.0
INCHIANTI	-85.2	47.7	-178.7	8.2
INDIANA	17.5	27.0	-35.4	70.5
INGI-VB	-43.3	37.6	-116.9	30.4
KORA F3	-14.1	39.9	-92.2	64.1
KORA S4	8.2	36.1	-62.6	79.1
KORCULA	55.8	51.7	-45.4	157.1
NFBC	-25.5	19.3	-63.3	12.3
NHS-BRCA	51.3	21.6	9.0	93.6
NHS-T2D	-3.0	18.7	-39.8	33.7
NTR	49.0	34.0	-17.7	115.7
ORCADES	93.1	63.7	-31.7	217.9
QIMR	-	-	-	-
RAINE	-29.3	32.5	-93.0	34.4
RS1	29.2	21.2	-12.3	70.7
RS2	16.1	35.1	-52.7	84.8
RS3	14.6	35.1	-54.1	83.3
SAGE	3.9	32.0	-58.7	66.6
SARDINIA	20.5	31.4	-41.1	82.0
SPLIT	-45.4	67.1	-176.9	86.1
TWINSUK1	7.7	18.6	-28.7	44.1
TWINSUK2	19.6	46.8	-72.2	111.4

TWINSUK3	47.7	37.9	-26.7	122.1
VIS	-111.7	54.9	-219.4	-4.0
WGHS	3.7	7.3	-10.7	18.0
***MAP2K5* (rs2241423-A)**				
AGES	38.9	19.3	1.1	76.7
AMISH	-31.0	44.8	-118.8	56.8
ARIC	19.5	13.6	-7.2	46.1
B58C-T1DGC	-6.4	26.2	-57.7	45.0
B58C-WTCCC	46.8	34.4	-20.6	114.2
COLAUS	22.0	18.5	-14.3	58.4
DECODE	19.7	6.4	7.1	32.2
DNBC	-14.2	19.4	-52.2	23.7
EGCUT	15.1	35.9	-55.3	85.5
EPIC	1.9	32.6	-62.1	65.8
ERF	16.6	32.0	-46.2	79.4
FHS	36.4	15.8	5.5	67.3
GENMETS	27.4	46.6	-64.0	118.7
HBCS	8.6	30.6	-51.4	68.7
INCHIANTI	72.3	35.7	2.2	142.3
INDIANA	-0.7	22.3	-44.4	42.9
INGI-VB	-16.5	30.6	-76.4	43.4
KORA F3	-71.7	31.9	-134.3	-9.2
KORA S4	-15.7	29.9	-74.3	42.9
KORCULA	-40.6	44.8	-128.3	47.2
NFBC	-17.1	17.4	-51.2	17.1
NHS-BRCA	-7.3	18.2	-43.0	28.4
NHS-T2D	19.7	15.5	-10.6	50.0
NTR	22.0	26.4	-29.7	73.8
ORCADES	24.3	50.7	-75.1	123.8
QIMR	17.5	16.1	-14.0	49.0
RAINE	82.0	28.5	26.1	137.9
RS1	19.7	17.9	-15.4	54.8
RS2	31.4	29.6	-26.6	89.4
RS3	-5.8	29.2	-63.1	51.4
SAGE	-7.4	26.0	-58.4	43.6
SARDINIA	-12.1	28.1	-67.2	43.1
SPLIT	-8.3	56.1	-118.2	101.6
TWINSUK1	10.2	13.6	-16.5	37.0
TWINSUK2	73.4	37.2	0.5	146.3

TWINSUK3	-38.7	30.5	-98.4	21.0
VIS	27.9	44.2	-58.8	114.6
WGHS	11.7	5.8	0.2	23.1
		***TNNI3K* (rs1514175-A)**		
AGES	3.9	15.8	-27.2	34.9
AMISH	16.9	31.6	-45.1	78.8
ARIC	-20.1	11.6	-42.8	2.5
B58C-T1DGC	-11.8	21.8	-54.5	30.9
B58C-WTCCC	-25.8	27.4	-79.5	28.0
COLAUS	-30.1	15.9	-61.3	1.2
DECODE	-4.0	5.2	-14.3	6.2
DNBC	-16.8	16.4	-49.0	15.4
EGCUT	-18.8	27.4	-72.5	35.0
EPIC	-21.7	27.0	-74.6	31.3
ERF	-0.9	27.2	-54.2	52.5
FHS	-13.1	13.2	-39.1	12.8
GENMETS	-107.1	32.7	-171.2	-42.9
HBCS	-48.1	24.1	-95.4	-0.8
INCHIANTI	18.1	30.6	-41.9	78.1
INDIANA	-27.0	19.4	-65.0	10.9
INGI-VB	-31.8	27.0	-84.7	21.0
KORA F3	-86.9	26.4	-138.7	-35.2
KORA S4	47.1	26.4	-4.7	98.9
KORCULA	9.8	39.6	-67.8	87.4
NFBC	-11.3	13.1	-36.9	14.4
NHS-BRCA	-19.7	15.3	-49.8	10.3
NHS-T2D	-20.7	12.9	-46.1	4.6
NTR	0.7	22.7	-43.8	45.1
ORCADES	-17.6	39.0	-94.0	58.8
QIMR	-5.8	13.1	-31.6	19.9
RAINE	-49.1	23.6	-95.3	-2.8
RS1	-9.5	15.3	-39.6	20.6
RS2	26.3	25.2	-23.1	75.7
RS3	-72.0	24.8	-120.6	-23.3
SAGE	-51.2	23.2	-96.7	-5.8
SARDINIA	-	-	-	-
SPLIT	4.2	51.0	-95.8	104.2
TWINSUK1	-4.8	8.5	-21.4	11.7
TWINSUK2	1.3	32.4	-62.3	64.8

TWINSUK3	3.4	25.5	-46.6	53.4
VIS	-24.1	39.7	-102.0	53.8
WGHS	-11.7	5.1	-21.7	-1.7
		***RBJ* (rs713586-T)**		
AGES	-4.8	15.7	-35.5	25.9
AMISH	50.3	36.5	-21.3	121.8
ARIC	12.5	11.7	-10.3	35.4
B58C-T1DGC	-16.6	21.5	-58.7	25.5
B58C-WTCCC	50.5	29.0	-6.4	107.3
COLAUS	1.9	16.6	-30.7	34.5
DECODE	6.2	5.3	-4.1	16.6
DNBC	23.0	16.4	-9.2	55.2
EGCUT	40.9	28.5	-15.0	96.8
EPIC	-4.2	30.1	-63.2	54.8
ERF	-51.5	26.8	-104.1	1.0
FHS	23.0	13.5	-3.3	49.4
GENMETS	28.0	32.5	-35.6	91.7
HBCS	1.7	24.4	-46.1	49.5
INCHIANTI	16.1	30.4	-43.4	75.6
INDIANA	34.3	19.0	-2.9	71.6
INGI-VB	8.2	26.9	-44.5	61.0
KORA F3	13.5	28.9	-43.1	70.1
KORA S4	-24.2	25.9	-74.9	26.5
KORCULA	-25.6	39.5	-103.1	51.9
NFBC	1.3	13.4	-25.1	27.6
NHS-BRCA	33.4	15.0	3.9	62.9
NHS-T2D	14.5	12.9	-10.9	39.9
NTR	1.3	22.2	-42.3	44.9
ORCADES	15.6	40.5	-63.8	95.0
QIMR	10.2	12.8	-14.8	35.3
RAINE	20.7	22.7	-23.7	65.2
RS1	2.9	15.0	-26.4	32.3
RS2	37.3	24.8	-11.4	85.9
RS3	30.7	24.5	-17.3	78.6
SAGE	-17.5	22.2	-61.1	26.1
SARDINIA	24.5	23.0	-20.6	69.6
SPLIT	40.1	45.7	-49.5	129.6
TWINSUK1	17.9	7.3	3.7	32.2
TWINSUK2	6.3	30.9	-54.3	66.9

TWINSUK3	-0.9	25.5	-50.9	49.1
VIS	-3.8	39.6	-81.4	73.7
WGHS	14.6	5.1	4.6	24.6
		***FANCL* (rs887912-T)**		
AGES	14.3	17.6	-20.2	48.8
AMISH	7.8	31.6	-54.1	69.8
ARIC	-7.4	12.6	-32.1	17.3
B58C-T1DGC	-38.1	25.1	-87.4	11.1
B58C-WTCCC	6.6	30.9	-53.9	67.2
COLAUS	-0.8	17.5	-35.1	33.5
DECODE	-16.9	5.9	-28.5	-5.3
DNBC	1.1	17.9	-34.0	36.2
EGCUT	-14.6	31.8	-77.0	47.8
EPIC	-41.2	30.9	-101.7	19.4
ERF	-0.4	31.0	-61.2	60.4
FHS	-28.5	14.2	-56.4	-0.7
GENMETS	10.8	37.5	-62.8	84.3
HBCS	-31.8	26.3	-83.4	19.8
INCHIANTI	-0.5	34.4	-67.8	66.9
INDIANA	-7.3	20.8	-48.1	33.5
INGI-VB	23.4	29.0	-33.5	80.3
KORA F3	-57.2	31.1	-118.2	3.7
KORA S4	16.2	27.7	-38.1	70.5
KORCULA	-46.6	41.8	-128.5	35.4
NFBC	-12.9	14.5	-41.4	15.6
NHS-BRCA	17.1	16.6	-15.6	49.7
NHS-T2D	-10.5	14.3	-38.5	17.4
NTR	-7.4	24.0	-54.5	39.6
ORCADES	56.2	40.1	-22.4	134.9
QIMR	-15.7	13.9	-42.9	11.5
RAINE	-4.7	25.5	-54.6	45.3
RS1	-19.7	16.4	-51.9	12.5
RS2	15.0	28.1	-40.1	70.1
RS3	-14.2	25.9	-65.1	36.6
SAGE	-43.5	24.9	-92.3	5.3
SARDINIA	-18.6	23.7	-65.2	27.9
SPLIT	-56.1	56.1	-166.1	53.8
TWINSUK1	-3.5	11.5	-25.9	19.0
TWINSUK2	-11.3	35.5	-81.0	58.3

TWINSUK3	-27.5	28.8	-83.9	28.9
VIS	-56.0	45.3	-144.8	32.8
WGHS	-10.2	5.8	-21.7	1.2
		***STK33* (rs10769908-T)**		
AGES	-0.4	15.6	-31.0	30.2
AMISH	-9.1	33.1	-74.1	55.8
ARIC	11.5	11.4	-11.0	33.9
B58C-T1DGC	1.6	21.8	-41.2	44.4
B58C-WTCCC	8.6	28.7	-47.7	64.8
COLAUS	9.1	15.8	-21.9	40.0
DECODE	9.2	5.3	-1.1	19.5
DNBC	15.7	16.4	-16.5	47.9
EGCUT	-13.0	26.9	-65.7	39.8
EPIC	-19.7	29.3	-77.2	37.8
ERF	-15.9	26.5	-67.9	36.0
FHS	20.1	13.3	-6.0	46.3
GENMETS	-15.9	31.8	-78.2	46.3
HBCS	19.3	24.1	-28.0	66.6
INCHIANTI	22.4	31.0	-38.3	83.0
INDIANA	-2.6	19.0	-39.8	34.7
INGI-VB	21.6	26.8	-30.9	74.1
KORA F3	36.4	26.8	-16.0	88.9
KORA S4	-9.5	25.4	-59.3	40.2
KORCULA	54.8	37.6	-19.0	128.6
NFBC	3.6	12.7	-21.4	28.5
NHS-BRCA	28.9	15.0	-0.5	58.3
NHS-T2D	6.7	12.9	-18.5	32.0
NTR	-19.5	22.6	-63.8	24.9
ORCADES	-34.1	40.3	-113.1	44.9
QIMR	-	-	-	-
RAINE	52.2	23.6	6.0	98.3
RS1	15.0	15.3	-15.1	45.0
RS2	6.9	25.2	-42.5	56.3
RS3	8.8	24.5	-39.2	56.7
SAGE	18.4	22.5	-25.6	62.5
SARDINIA	-	-	-	-
SPLIT	-28.4	47.8	-122.0	65.3
TWINSUK1	3.1	7.9	-12.4	18.6
TWINSUK2	14.7	32.0	-48.1	77.5

TWINSUK3	2.6	24.6	-45.6	50.8
VIS	43.6	37.7	-30.2	117.5
WGHS	12.8	5.1	2.8	22.8

[a]For study abbreviations see Web Table 1.

Web Table 7. SNP-Associations with Age at Menarche Using Family Wise Error Rate or False Discovery Rate to Adjust for Multiple Testing, Ranked From Lowest to Highest Nominal *P* Values[a]

SNP ID	Nominal *P* value	Bonferroni *P* value	Holm *P* value	FDR	pFDR
rs9939609	**$4.2X10^{-12}$**	**$3.9X10^{-10}$**	**$3.9X10^{-10}$**	**$2.9X10^{-10}$**	**$1.3X10^{-10}$**
rs1558902	**$6.2X10^{-12}$**	**$5.8X10^{-10}$**	**$5.8X10^{-10}$**	**$2.9X10^{-10}$**	**$1.3X10^{-10}$**
rs8050136	**$9.5X10^{-12}$**	**$9.1X10^{-10}$**	**$8.9X10^{-10}$**	**$3.0X10^{-10}$**	**$1.3X10^{-10}$**
rs1121980	**$2.6X10^{-11}$**	**$2.5X10^{-9}$**	**$2.4X10^{-9}$**	**$6.1X10^{-10}$**	**$2.7X10^{-10}$**
rs543874	**$6.7X10^{-10}$**	**$6.4x10^{-8}$**	**$6.1x10^{-8}$**	**$1.3x10^{-8}$**	**$5.6X10^{-9}$**
rs2867125	**$1.6X10^{-9}$**	**$1.5X10^{-7}$**	**$1.5X10^{-7}$**	**$2.6x10^{-8}$**	**$1.1x10^{-8}$**
rs7561317	**$8.5X10^{-9}$**	**$8.1X10^{-7}$**	**$7.6X10^{-7}$**	**$1.2X10^{-7}$**	**5.0x10-^{8}**
rs6548238	**$2.1X10^{-8}$**	**$2.0X10^{-6}$**	**$1.8X10^{-6}$**	**$2.4X10^{-7}$**	**$1.1X10^{-7}$**
rs2568958	**$3.3X10^{-8}$**	**$3.2X10^{-6}$**	**$2.9X10^{-6}$**	**$3.3X10^{-7}$**	**$1.4X10^{-7}$**
rs2815752	**$3.5X10^{-8}$**	**$3.3X10^{-6}$**	**$3.0X10^{-6}$**	**$3.3X10^{-7}$**	**$1.4X10^{-7}$**
rs10913469	**$8.5x10^{-8}$**	**$8.0X10^{-6}$**	**$7.2X10^{-6}$**	**$7.3X10^{-7}$**	**$3.2X10^{-7}$**
rs10938397	**$1.7X10^{-7}$**	**$1.6X10^{-5}$**	**$1.4X10^{-5}$**	**$1.3X10^{-6}$**	**$5.8X10^{-7}$**
rs1514175	**$4.0X10^{-7}$**	**$3.8X10^{-5}$**	**$3.3X10^{-5}$**	**$2.9X10^{-6}$**	**$1.3X10^{-6}$**
rs713586	**$8.4X10^{-7}$**	**$7.9X10^{-5}$**	**$6.9X10^{-5}$**	**$5.7X10^{-6}$**	**$2.5X10^{-6}$**
rs7138803	**$2.2X10^{-6}$**	**$2.1X10^{-4}$**	**$1.8X10^{-4}$**	**$1.4X10^{-5}$**	**$6.1X10^{-6}$**
rs10767664	**$3.6X10^{-6}$**	**$3.4X10^{-4}$**	**$2.9X10^{-4}$**	**$2.1X10^{-5}$**	**$9.2X10^{-6}$**
rs925946	**$5.9X10^{-6}$**	**$5.6X10^{-4}$**	**$4.6X10^{-4}$**	**$3.2X10^{-5}$**	**$1.4X10^{-5}$**
rs2241423	**$6.1X10^{-6}$**	**$5.8X10^{-4}$**	**$4.8X10^{-4}$**	**$3.2X10^{-5}$**	**$1.4X10^{-5}$**
rs29941	**$9.3X10^{-6}$**	**$8.8X10^{-4}$**	**$7.1X10^{-4}$**	**$4.6X10^{-5}$**	**$2.0X10^{-5}$**
rs7481311	**$1.3X10^{-5}$**	**$1.2X10^{-3}$**	**$9.8X10^{-4}$**	**$6.1X10^{-5}$**	**$2.7X10^{-5}$**
rs6265	**$1.7X10^{-5}$**	**$1.6X10^{-3}$**	**$1.3X10^{-3}$**	**$7.6X10^{-5}$**	**$3.3X10^{-5}$**
rs4923461	**$2.4X10^{-5}$**	**$2.2X10^{-3}$**	**$1.7X10^{-3}$**	**$1.0X10^{-4}$**	**$4.4X10^{-5}$**
rs987237	**$3.3X10^{-5}$**	**$3.1X10^{-3}$**	**$2.4X10^{-3}$**	**$1.3X10^{-4}$**	**$5.8X10^{-5}$**
rs887912	**$3.8X10^{-5}$**	**$3.6X10^{-3}$**	**$2.7X10^{-3}$**	**$1.5X10^{-4}$**	**$6.5X10^{-5}$**
rs4929949	**$4.1X10^{-5}$**	**$3.9X10^{-3}$**	**$2.9X10^{-3}$**	**$1.6X10^{-4}$**	**$6.8X10^{-5}$**
rs9816226	**$7.0X10^{-5}$**	**$6.6X10^{-3}$**	**$4.9X10^{-3}$**	**$2.5X10^{-4}$**	**$1.1X10^{-4}$**

rs10769908	**$7.8X10^{-5}$**	**$7.4X10^{-3}$**	**$5.4X10^{-3}$**	**$2.8X10^{-4}$**	**$1.2X10^{-4}$**
rs11084753	**$1.0X10^{-4}$**	**$9.6X10^{-3}$**	**$6.8X10^{-3}$**	**$3.4X10^{-4}$**	**$1.5X10^{-4}$**
rs12444979	**$2.6X10^{-4}$**	**$2.5X10^{-2}$**	**$1.7X10^{-2}$**	**$8.5X10^{-4}$**	**$3.7X10^{-4}$**
rs3810291	**$1.6X10^{-3}$**	0.16	0.11	**$5.2X10^{-3}$**	**$2.3X10^{-3}$**
rs6429082	**$3.1X10^{-3}$**	0.30	0.20	**$9.6X10^{-3}$**	**$4.2X10^{-3}$**
rs7647305	**$3.3X10^{-3}$**	0.31	0.21	**$9.7X10^{-3}$**	**$4.2X10^{-3}$**
rs7826222	**$5.2X10^{-3}$**	0.50	0.33	**$1.5X10^{-2}$**	**$6.5X10^{-3}$**
rs11847697	**$6.3X10^{-3}$**	0.60	0.39	**$1.8X10^{-2}$**	**$7.7X10^{-3}$**
rs4771122	**$1.2X10^{-2}$**	1.0	0.75	**$3.4X10^{-2}$**	**$1.5X10^{-2}$**
rs824931	**$2.0X10^{-2}$**	1.0	1.0	$5.2X10^{-2}$	**$2.3X10^{-2}$**
rs1024889	**$2.0X10^{-2}$**	1.0	1.0	$5.2X10^{-2}$	**$2.3X10^{-2}$**
rs6499640	**$2.9X10^{-2}$**	1.0	1.0	$7.2X10^{-2}$	**$3.1X10^{-2}$**
rs3803915	**$3.3X10^{-2}$**	1.0	1.0	$8.0X10^{-2}$	**$3.5X10^{-2}$**
rs1458095	**$3.8X10^{-2}$**	1.0	1.0	$9.0X10^{-2}$	**$3.9X10^{-2}$**
rs13107325	**$4.0X10^{-2}$**	1.0	1.0	$9.2X10^{-2}$	**$4.0X10^{-2}$**
rs10146997	**$4.2X10^{-2}$**	1.0	1.0	$9.4X10^{-2}$	**$4.1X10^{-2}$**
rs206936	**$4.3X10^{-2}$**	1.0	1.0	$9.5X10^{-2}$	**$4.1X10^{-2}$**
rs10150332	**$4.7X10^{-2}$**	1.0	1.0	0.10	**$4.5X10^{-2}$**
rs12324805	$5.3X10^{-2}$	1.0	1.0	0.11	**$4.9X10^{-2}$**
rs571312	$6.4X10^{-2}$	1.0	1.0	0.13	$5.7X10^{-2}$
rs4701252	$6.8X10^{-2}$	1.0	1.0	0.14	$6.0X10^{-2}$
rs1106683	$7.7X10^{-2}$	1.0	1.0	0.15	$6.7X10^{-2}$
rs10838738	$7.9X10^{-2}$	1.0	1.0	0.15	$6.7X10^{-2}$
rs17782313	$8.3X10^{-2}$	1.0	1.0	0.16	$6.8X10^{-2}$
rs3817334	$8.4X10^{-2}$	1.0	1.0	0.16	$6.8X10^{-2}$
rs1106684	$9.0X10^{-2}$	1.0	1.0	0.16	$7.2X10^{-2}$
rs6861681	0.12	1.0	1.0	0.21	$9.1X10^{-2}$
rs718314	0.14	1.0	1.0	0.24	0.10
rs7081678	0.14	1.0	1.0	0.24	0.10
rs1555543	0.16	1.0	1.0	0.27	0.12

rs2287019	0.22	1.0	1.0	0.37	0.16
rs2145270	0.27	1.0	1.0	0.44	0.19
rs1927702	0.30	1.0	1.0	0.49	0.21
rs1333026	0.32	1.0	1.0	0.49	0.21
rs7359397	0.32	1.0	1.0	0.49	0.21
rs2275215	0.32	1.0	1.0	0.49	0.21
rs7932813	0.34	1.0	1.0	0.52	0.22
rs6795735	0.36	1.0	1.0	0.53	0.23
rs10783050	0.36	1.0	1.0	0.53	0.23
rs2890652	0.38	1.0	1.0	0.53	0.23
rs1875517	0.38	1.0	1.0	0.53	0.23
rs2112347	0.39	1.0	1.0	0.53	0.23
rs7498665	0.39	1.0	1.0	0.53	0.23
rs4836133	0.40	1.0	1.0	0.54	0.24
rs6905288	0.48	1.0	1.0	0.64	0.28
rs1443512	0.50	1.0	1.0	0.66	0.29
rs1878047	0.51	1.0	1.0	0.66	0.29
rs1555967	0.53	1.0	1.0	0.69	0.30
rs13078807	0.56	1.0	1.0	0.70	0.31
rs1294421	0.58	1.0	1.0	0.72	0.31
rs2605100	0.59	1.0	1.0	0.72	0.31
rs10458787	0.59	1.0	1.0	0.72	0.31
rs4846567	0.63	1.0	1.0	0.74	0.32
rs9491696	0.63	1.0	1.0	0.74	0.32
rs489693	0.63	1.0	1.0	0.74	0.32
rs2383393	0.67	1.0	1.0	0.77	0.34
rs12970134	0.69	1.0	1.0	0.79	0.34
rs1055144	0.72	1.0	1.0	0.82	0.36
rs4823006	0.78	1.0	1.0	0.87	0.38
rs10968576	0.81	1.0	1.0	0.89	0.38

rs3934834	0.81	1.0	1.0	0.89	0.38
rs12517906	0.84	1.0	1.0	0.90	0.39
rs1011731	0.85	1.0	1.0	0.90	0.39
rs6784615	0.86	1.0	1.0	0.91	0.39
rs2076529	0.88	1.0	1.0	0.92	0.40
rs10195252	0.92	1.0	1.0	0.95	0.41
rs1152846	0.96	1.0	1.0	0.98	0.42
rs984222	0.97	1.0	1.0	0.98	0.43
rs4471028	1.0	1.0	1.0	1.0	0.43

Abbreviations: FDR, False discovery rate; pFDR, Positive false discovery rate

[a]*P* values are shown to two significant digits and those in bold represent SNP-associations below the 5% threshold for either (family wise) type 1 error rate or false discovery rate.

Web Table 8. Number of SNPs Associated with Age at Menarche at Various Thresholds Using Either Family Wise Error Rate or False Discovery Rate Methodologies

Threshold	Bonferroni	Holm	FDR	pFDR
0.01	28	28	32	34
0.05	29	29	35	45
0.10	29	29	43	53
0.15	29	30	47	56
0.20	30	30	52	58
0.25	30	32	55	70

Abbreviations: FDR, False discovery rate; pFDR, Positive false discovery rate

Web Table 9. Genes Within 300kb From the 32 Confirmed BMI SNPs that are Associated Suggestively (in Bold), and Significantly (in Red) With Age at Menarche Loci

Term type	Term name	Genes in significantly enriched pathways nearby loci implicated in BMI
Panther, BP	Protein phosphorylation	*COL4A3BP, DMPK*, ***FLJ40125***, ***MAP2K5***, *PACSIN1*, ***PRKD1***, ***STK33***, ***TNNI3K***
Panther	PDGF signalling	*SPDEF*
Panther, MF	Homeobox TF	***IRX3***, *MEIS3*, *SIX5*
Panther, MF	Translation Elongation Factor	*TUFM*
GO, BP	Neurogenesis	***NRXN3***, ***RACGAP1***
GO, BP	Neuron differentiation	***NRXN3***
GO, BP	Generation of neurons	***NRXN3***, ***RACGAP1***
GO, BP	Regulation of cellular metabolic process	***AKTIP***, *ERCC1*, *FOSB*, ***GRLF1***, *HMGA1*, ***IGF2BP2***, ***MTIF3***, ***SMARCD1***, *SPI1*, *SPN*, ***TFAP2B***
GO, MF	Hormone receptor binding	*HMGA1*
GO, MF	Nuclear hormone receptor binding	*HMGA1*

Web Table 10. gProfiler Results for Enrichment in Biologic Pathways of the Gene Nearest (n=16) to Waist Circumference and BMI SNPs Implicated[a] in Age at Menarche, Using a *P* value Cutoff of 0.01[b]

Term type	Term name	# Genes under this term	*P* value[c]	Genes implicated
Gene Ontology, BP	tube development	401	2.98X10-3	*BDNF, ETV5, TFAP2B*
Gene Ontology, BP	eye morphogenesis	115	3.22X10-3	*BDNF, TFAP2B*
Gene Ontology, BP	regulation of organ morphogenesis	123	3.67X10-3	*BDNF, ETV5*
Gene Ontology, BP	regulation of neuron apoptosis	148	5.27X10-3	*BDNF, TFAP2B*
Gene Ontology, BP	macromolecule modification	2386	5.46X10-3	*FANCL, FTO, MAP2K5, MSRA, ADCY3, STK33*
Gene Ontology, BP	neuron apoptosis	162	6.28X10-3	*BDNF, TFAP2B*
Gene Ontology, BP	neuron death	166	6.58X10-3	*BDNF, TFAP2B*
Gene Ontology, BP	regulation of cell proliferation	1099	7.46X10-3	*BDNF, FTO, MAP2K5, TFAP2B*
Gene Ontology, BP	negative regulation of apoptosis	580	8.34X10-3	*BDNF, FAIM2, TFAP2B*
Gene Ontology, BP	negative regulation of programmed cell death	586	8.58X10-3	*BDNF, FAIM2, TFAP2B*
Gene Ontology, BP	negative regulation of cell death	604	9.32X10-3	*BDNF, FAIM2, TFAP2B*
Gene Ontology, CC	nucleus	5916	3.49X10-3	*ETV5, FANCL, FTO, GPRC5B, MAP2K5, MSRA, ADCY3, STK33, TFAP2B, TMEM18*
Gene Ontology, CC	postsynaptic membrane	174	7.21X10-3	*FAIM2, LIN7C*
Gene Ontology, CC	synaptic membrane	199	9.33X10-3	*FAIM2, LIN7C*
KEGG	Gap junction	97	2.31X10-3	*MAP2K5, ADCY3*
KEGG	Neurotrophin signaling pathway	126	3.85X10-3	*BDNF, MAP2K5*
REACTOME	TRKA signalling from the plasma membrane	99	2.40X10-3	*MAP2K5, ADCY3*
REACTOME	Signalling by NGF	167	6.66X10-3	*MAP2K5, ADCY3*

[a]Below a Bonferroni correction for 95 tests (*P*<0.0005).
[b]Using the following input parameters: *P* value cutoff=0.01, significance threshold=Bonferroni, statistical domain size=all annotated genes.

[c]No results were considered to be significant after Bonferonni correction, as gProfiler did not out put any in bold.

Web Table 11. gProfiler Results for Enrichment in Biologic Pathways of the Gene Nearest (n=23) to Waist Circumference and BMI SNPs Implicated[a] and Suggestively[b] Associated with Age at Menarche, Using a *P* value Cutoff of 0.001[c]

Term type	Term name	# Genes under this term	*P* value[d]	Genes implicated
Gene Ontology, BP	circulatory system development	686	6.70X10-4	*MAP2K5, TFAP2B, NRXN3, PRKD1, PAX3*
Gene Ontology, BP	cardiovascular system development	686	6.70X10-4	*MAP2K5, TFAP2B, NRXN3, PRKD1, PAX3*
Gene Ontology, BP	tube development	401	7.87X10-4	*BDNF, ETV5, TFAP2B, PAX3*
Gene Ontology, BP	regulation of cell proliferation	1099	8.24X10-4	*BDNF, FTO, MAP2K5, TFAP2B, PRKD1, PAX3*
Gene Ontology, CC	nucleus	5916	7.89X10-4	*ETV5, FANCL, FTO, GPRC5B, MAP2K5, MSRA, ADCY3, STK33, TFAP2B, TMEM18, PRKD1, DOT1L, PAX3, TBCE*

[a]Below a Bonferroni correction for 95 tests (*P*<0.0005).
[b]Suggestive associations were defined as *P*<0.05 with inverse effects on BMI and age at menarche.
[c]Using the following input parameters: *P* value cutoff=0.001, significance threshold=Bonferroni, statistical domain size=all annotated genes.
[d]No results were considered to be significant after Bonferonni correction, as gProfiler did not out put any in bold.

Web Table 12. gProfiler Results for Enrichment in Biologic Pathways of the Gene Nearest (n=18) to BMI SNPs Not Suggestively[a] Associated with Age at Menarche, Using a *P* value Cutoff of 0.01[b]

Term type	Term name	# Genes under this term	*P* value[c]	Genes implicated
Gene Ontology, BP	regulation of cell migration	325	2.34X10-3	*BMP2, LAMA2, PODXL*
Gene Ontology, BP	regulation of cell motility	340	2.66X10-3	*BMP2, LAMA2, PODXL*
Gene Ontology, BP	regulation of cellular component movement	364	3.22X10-3	*BMP2, LAMA2, PODXL*
Gene Ontology, BP	regulation of locomotion	369	3.35X10-3	*BMP2, LAMA2, PODXL*
Gene Ontology, BP	positive regulation of multicellular organismal process	442	5.55X10-3	*BMP2, MC4R, PROK2*
Gene Ontology, BP	biological adhesion	923	6.30X10-3	*LAMA2, LPP, PCDH9, PODXL*
Gene Ontology, BP	cell adhesion	923	6.30X10-3	*LAMA2, LPP, PCDH9, PODXL*
Gene Ontology, BP	rhythmic process	191	1.09X10-2	*BMP2, PROK2*

[a]Suggestive associations were defined as *P*<0.05 with inverse effects on BMI and age at menarche.
[b]Using the following input parameters: *P* value cutoff=0.01, significance threshold=Bonferroni, statistical domain size=all annotated genes.
[c]No results were considered to be significant after Bonferonni correction, as gProfiler did not out put any in bold.

Web Table 13. gProfiler Results for Enrichment in Biologic Pathways of the Gene Nearest (n=20) to Waist Circumference and Waist-Hip Ratio SNPs Not Suggestively[a] Associated with Age at Menarche, Using a *P* value Cutoff of 0.01[b]

Term type	Term name	# Genes under this term	*P* value[c]	Genes implicated
Gene Ontology, BP	regulation of bone resorption	24	2.23X10-4	*MC4R, VEGFA*
Gene Ontology, BP	regulation of bone remodeling	25	2.42X10-4	*MC4R, VEGFA*
Gene Ontology, BP	regulation of tissue remodeling	37	5.33X10-4	*MC4R, VEGFA*
Gene Ontology, BP	bone resorption	39	5.93X10-4	*MC4R, VEGFA*
Gene Ontology, BP	bone remodeling	50	9.74X10-4	*MC4R, VEGFA*
Gene Ontology, BP	embryonic organ development	287	2.25X10-3	*RSPO3, TBX15, VEGFA*
Gene Ontology, BP	secretion by cell	648	2.66X10-3	*ITPR2, MC4R, NISCH, VEGFA*
Gene Ontology, BP	tissue homeostasis	96	3.53X10-3	*MC4R, VEGFA*
Gene Ontology, BP	negative regulation of cellular component movement	97	3.61X10-3	*NISCH, PKHD1*
Gene Ontology, BP	tissue remodeling	102	3.98X10-3	*MC4R, VEGFA*
Gene Ontology, BP	secretion	735	4.19X10-3	*ITPR2, MC4R, NISCH, VEGFA*
Gene Ontology, BP	regulation of cellular component movement	364	4.39X10-3	*NISCH, PKHD1, VEGFA*
Gene Ontology, BP	multicellular organismal homeostasis	140	7.36X10-3	*DNM3, PKHD1*
Gene Ontology, BP	chordate embryonic development	450	7.90X10-3	*RSPO3, TBX15, VEGFA*
Gene Ontology, BP	embryo development ending in birth or egg hatching	457	8.24X10-3	*RSPO3, TBX15, VEGFA*
Gene Ontology, BP	cell projection assembly	156	9.07X10-3	*DNM3, PKHD1*
Gene Ontology, BP	insulin secretion	158	9.29X10-3	*ITPR2, MC4R*
Gene Ontology, BP	canonical Wnt receptor signaling pathway	159	9.40X10-3	*KREMEN1, RSPO3*
Gene Ontology, BP	kidney development	164	9.98X10-3	*PKHD1, VEGFA*
Gene Ontology, BP	renal system development	170	1.07X10-2	*PKHD1, VEGFA*

Gene Ontology, BP	morphogenesis of a branching epithelium	171	1.08X10-2	*RSPO3, VEGFA*
Gene Ontology, MF	phosphatidylinositol binding	138	7.16X10-3	*ITPR2, NISCH*
Gene Ontology, MF	heparin binding	144	7.77X10-3	*RSPO3, VEGFA*

[a]Suggestive associations were defined as *P*<0.05 with inverse effects on BMI and age at menarche.
[b]Using the following input parameters: *P* value cutoff=0.01, significance threshold=Bonferroni, statistical domain size=all annotated genes.
[c]No results were considered to be significant after Bonferonni correction, as gProfiler did not out put any in bold.