

1 **Genomic analyses identify hundreds of variants associated with age at menarche and**
2 **support a role for puberty timing in cancer risk**

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338 Abstract

339 The timing of puberty is a highly polygenic childhood trait that is epidemiologically associated
340 with various adult diseases. Using 1000-Genome imputed genotype data in up to ~370,000
341 women, we identify 389 independent signals ($P < 5 \times 10^{-8}$) for age at menarche, a notable
342 milestone in female pubertal development. In Icelandic data from deCODE, these signals
343 explain ~7.4% of the population variance in age at menarche, corresponding to ~25% of the
344 estimated heritability. We implicate ~250 genes via coding variation or associated
345 expression, demonstrating significant enrichment in neural tissues. Rare variants near
346 imprinted genes MKRN3 and DLK1 were identified, exhibiting large effects only when
347 paternally inherited. Mendelian randomization analyses indicate causal inverse associations,
348 independent of BMI, between puberty timing and risks for breast and endometrial cancers in
349 women, and prostate cancer in men. In aggregate, our findings reveal new complexity in the
350 genetic regulation of puberty timing and support causal links with cancer susceptibility.

351 Introduction

352 Puberty is the developmental stage of transition from childhood to physical and sexual
353 maturity and its timing varies markedly between individuals¹. This variation reflects the
354 influence of genetic, nutritional and other environmental factors and is associated with the
355 subsequent risks for several diseases in adult life². Our previous large-scale genomic
356 studies identified 113 independent regions associated with age at menarche (AAM), a well-
357 recalled milestone of puberty in females^{3,4}. The vast majority of those signals have
358 concordant effects on the age at voice breaking (genome-wide genetic correlation between
359 traits $r_g = 0.74$), a corresponding milestone in males⁵. Those genetic findings implicated a
360 diverse range of mechanisms involved in the regulation of puberty timing, identified
361 significant enrichment of AAM-associated variants in/near genes disrupted in rare disorders
362 of puberty, and highlighted shared aetiological factors between puberty timing and metabolic
363 disease outcomes^{2,3}.

364 However, those previous studies were based on genome-wide association data that were
365 imputed to the relatively sparse HapMap2 reference panel or they used gene-centric arrays.
366 Consequently, the reported genetic signals explained only a small fraction of the population
367 variance, suggesting that several hundreds or thousands of signals are involved^{3,4}. Here, we
368 report an enlarged genomic analysis for AAM in a nearly 2-fold higher sample of women
369 than previously³, and using more densely imputed genomic data. Our findings increase by
370 more than 3-fold the number of independently associated signals and indicate likely causal
371 effects of puberty timing on risks of various sex steroid sensitive cancers in men and women.

372 Results

373 Genome-wide array data, imputed to the 1000-Genome reference panel, were available in
374 up to 329,345 women of European ancestry. These comprised 40 studies from the
375 ReproGen consortium (N=179,117), in addition to the 23andMe, Inc. (N=76,831) and UK
376 Biobank studies (N=73,397) (**Table S1**). The distribution of genome-wide test statistics
377 demonstrated significant inflation ($\lambda_{GC} = 1.75$), however LD score regression
378 analyses confirmed that this inflation was solely due to polygenicity rather than population
379 structure (LD score intercept = 1.00, s.e 0.02). In total, 37,925 variants were associated with
380 AAM at $P < 5 \times 10^{-8}$, which were resolved to 389 statistically-independent signals (**Figure S1**,

381 **Table S2).** Per-allele effect sizes ranged from ~1 week to 5 months, 16 index variants were
382 classed as low-frequency (minor allele frequency <5%; minimum observed 0.5%), and 26
383 were insertion/deletion polymorphisms. Signals were distributed evenly across all 23
384 chromosomes with respect to chromosome size (**Figure S2**). Of the previously reported 106
385 autosomal, 5 exome-array and 2 X-chromosome signals for AAM, all remained associated at
386 genome-wide significance, except for two common loci (reported as *SCRIB/PARP10*
387 [$P=5 \times 10^{-4}$] and *FUT8* [$P=5.4 \times 10^{-7}$]) and one rare variant not captured by the 1000G
388 reference panel (p.W275X, *TACR3*).

389 Independent replication in the deCODE study (N=39,543 women) showed that 367 (94.3%)
390 of the 389 signals had directionally-concordant effects (187 at $P < 0.05$) and 368 retained
391 genome-wide significance in a combined meta-analysis (**Table S3**). In aggregate, the top
392 389 index SNPs explained 7.4% of the trait variance in deCODE and 7.2% in UK Biobank
393 (the latter estimate used weights derived from a meta-analysis excluding UK Biobank).
394 These estimates are double that explained by the previously reported 106 signals³ (3.7% in
395 deCODE) and are equivalent to one quarter of the total chip-captured heritability
396 ($h^2_{\text{SNP}}=32\%$, $se=1\%$) for AAM, estimated in UK Biobank.

397 Consistent with our previous reports, we found a strongly shared genetic architecture
398 between AAM in women and age at voice breaking in men (considered as a continuous trait
399 in 55,871 men in 23andMe, Inc.) (genetic correlation (r_g)=0.75 $P=1.2 \times 10^{-79}$). Of the 389 AAM
400 signals, 327 demonstrated directionally-consistent trends or associations with age at voice
401 breaking in men (binomial $P=1.4 \times 10^{-44}$), and 18 signals reached a conservative multiple test-
402 corrected significance threshold ($P < 1 \times 10^{-4}$; i.e. 0.05 / 389) (**Table S4**). Similarly, in UK
403 Biobank where age at voice breaking was recorded using only 3 categories, 277 and 297 of
404 the 377 autosomal loci demonstrated directionally-consistent trends or associations with
405 “relatively early voice breaking” (N=2,678 cases, N=55,763 controls, binomial $P=2.4 \times 10^{-20}$)
406 and “relatively late voice breaking” (N=3,566 cases, $P=1.9 \times 10^{-30}$), respectively (**Table S5**).

407 **Implicated genes and tissues**

408 We used a number of analytical techniques to implicate genes in the regulation of AAM.
409 These included: mapping of non-synonymous SNPs, gene expression QTLs and integration
410 of Hi-C chromatin interaction data. Eight of the 389 lead variants were non-synonymous, and
411 a further 24 genes were implicated by highly correlated non-synonymous variants ($r^2 > 0.8$)
412 (**Table S6**). These include genes disrupted in rare disorders of puberty: aromatase
413 (*CYP19A1*, #307), gonadotropin-releasing hormone (*GNRH1*, #178), kisspeptin (*KISS1*,
414 signal #31); and the stop-gained variant in fucosyltransferase 2 (*FUT2*, #357) that confers
415 blood group secretor status.

416 Two approaches were used to interrogate publicly available gene expression datasets, both
417 of which use one or more SNPs (not restricted to lead SNPs) to infer patterns of gene
418 expression based on imputation reference panels (see **methods**). Firstly, to maximise power
419 we analysed data from the largest available eQTL dataset for any tissue (whole blood,
420 N=5,311)⁶, under the assumption that some causal genes and regulatory mechanisms might
421 be ubiquitously expressed or functionally involved in blood tissues. Systematic eQTL
422 integration using the Summary Mendelian Randomization approach⁷ prioritised 113
423 transcripts, for 60 of which there was evidence for causal or pleiotropic effects, rather than
424 coincidental overlap of signal (as indicated by HEIDI heterogeneity test $P > 0.009$) (**Table S7**).

425 Secondly, we used LD score regression applied to specifically expressed genes (LDSC-
426 SEG)⁸ to identify AAM-relevant tissues and cell types that are enriched for AAM heritability.
427 Five of the 46 GTEx tissues were positively enriched for AAM-associated variants (**Figure**
428 **1**). Notably, all of these were central nervous system tissues, including the pituitary and,
429 additionally, the hypothalamus was just below the significance threshold for enrichment
430 ($P=9.8\times 10^{-3}$), consistent with the key role of this central axis². Targeted assessment of these
431 six enriched brain tissues using MetaXcan identified 205 genes whose expression was
432 regulated by AAM-associated variants (**Table S8**). Of note, later AAM was associated with
433 higher transcript levels of *LIN28B* (#147) in the pituitary, *NCOA6* (Nuclear receptor
434 coactivator 6; #365) in the cerebellum, and *HSD17B12* (encoding Hydroxysteroid (17-Beta)
435 Dehydrogenase 12; #250) in various tissues.

436 To identify possible distal causal genes, we interrogated reported Hi-C data to assess if any
437 of the AAM loci are located in regions of chromatin looping⁹. 335 of the 389 loci were located
438 within a topologically associating domain (TAD) – a defined boundary region containing
439 chromatin contact points, each of which contained on average ~5 genes (**Table S9**). These
440 included 22 of the 31 gene desert regions (nearest protein-coding gene >300kb), where
441 TADs contained notable distal candidate genes such as *INHBA* (#158), *BDNF* (#248),
442 *JARID2* (#128) and several gamma-aminobutyric acid receptors (#91). We also observed
443 several regions where multiple independent AAM signals all reside within one TAD
444 containing the same single gene – *RORB* (signal #200 intronic, signal #199 ~200kb
445 downstream, #198 ~1.2Mb downstream), *THRB* (#67 intronic, #68 ~180kb upstream) and
446 *TACR3* (#96 5'UTR, #97 ~25kb upstream, #98 ~133kb upstream and #95 ~263Kb
447 downstream).

448 66 AAM signals were located in a specific contact point (between 5-25kb in size) within the
449 335 TADs, indicating a direct physical connection between these signals and a distal
450 genomic region, on average ~320kb away. This included the previously reported example of
451 the BMI-associated (and AAM-associated) *FTO* SNP and a distal *IRX3* promoter ~1Mb away
452 (signal #326)¹⁰. The longest chromatin interaction observed was ~38.6Mb, where two distinct
453 AAM signals located ~300kb apart (#206 and #207) were both in contact with the same
454 distal genomic region ~38.6Mb away that contains only one gene: prostaglandin E synthase
455 2 (*PTGES2*).

456 **Transcription factor binding enrichment**

457 To identify functional gene networks implicated in the regulation of AAM, we tested for
458 enriched co-occurrence of AAM associations and predicted regulators within 226 enhancer
459 modules combining DNaseI hypersensitive sites and chromatin states in 111 cell types and
460 tissues. In total, we tested 2,382 transcription factor-enhancer module combinations. Sixteen
461 transcription factor motifs were enriched for co-occurrence with AAM-associated variants
462 within enhancer regions at study level significance ($FDR<0.05$) (**Table S10**). Furthermore, 5
463 of the 16 motif-associated transcription factors also mapped within 1Mb of an index AAM-
464 associated SNP. These transcription factors included notable candidates; firstly, pituitary
465 homeobox 1 (*PITX1*), is located within 50kb of genome-wide significant SNPs (~500kb from
466 lead index #114). Secondly, *SMAD3*, a gene recently implicated in susceptibility to dizygous
467 twinning¹¹, is located within 600kb of an index SNP and its expression in several GTEx brain
468 tissues is genetically correlated with AAM. Thirdly, *RXRB* is located within ~500kb of a novel
469 index SNP (signal #133), and it represents the fifth (out of nine) retinoid-related receptor

470 gene implicated by genome-wide significant AAM variants. This set now includes all three
471 retinoid X receptor genes (*RXRA*, *RXRB* and *RXRG*), and retinoid-related receptor genes
472 are the nearest gene to the index SNP at three AAM loci (*RXRA*, *RORA* and *RORB*).

473 **Pathway analyses**

474 To identify other mechanisms that regulate pubertal timing, we tested all SNPs genome-wide
475 for enrichment of AAM associations with pre-defined biological pathway genes. Ten
476 pathways reached study-wide significance (FDR<0.05). Five pathways were related to
477 transcription factor binding, and the other pathways were: peptide hormone binding, PI3-
478 kinase binding, angiotensin stimulated signalling, neuron development and gamma-
479 aminobutyric acid (GABA) type B receptor signalling (**Table S11**).

480 All of our previously reported custom pathways (**Table S12**)³ remained significant in this
481 expanded dataset: nuclear hormone receptors ($P=2.4\times 10^{-3}$); Mendelian pubertal disorder
482 genes ($P=1.9\times 10^{-3}$); and JmjC-domain-containing lysine-specific demethylases ($P=1\times 10^{-4}$).
483 Notably, new genome-wide significant signals mapped to lysine-specific demethylase genes:
484 *JMJD1C* (signal #223), *PHF2* (#208), *KDM4B* (#347), *KDM6B* (#332), *JARID2* (#128), or to
485 Mendelian pubertal disorder genes: *CYP19A1* (#307), *FGF8* (#230), *GNRH1* (#178) *KAL1*
486 (#378), *KISS1* (#31), *NR5A1* (#215), and *NR0B1* (#379). The strongest AAM signal remains
487 at *LIN28B*^{3,12,13}, which encodes a key repressor of *let-7* miRNA biogenesis and cell
488 pluripotency¹⁴. Transgenic *Lin28a/b* mice demonstrate both altered pubertal growth and
489 glycaemic control¹⁵, suggesting that the *Lin28/let-7* axis could link puberty timing to type 2
490 diabetes susceptibility in humans. *let-7* miRNA targets are reportedly enriched for variants
491 associated with type 2 diabetes¹⁶. We tested the same set of computationally-predicted and
492 experimentally-derived mRNA/protein *let-7* miRNA targets¹⁶, and observed significant
493 enrichment of AAM-associated variants at miRNA targets that are down-regulated by *let-7b*
494 overexpression in primary human fibroblasts (**Table S12**, $P_{\min}=1\times 10^{-3}$).

495 **Imprinted genes and parent-of-origin effects**

496 We previously reported an excess of parent-of-origin specific associations for those AAM
497 variants that map near imprinted genes, as defined primarily from animal studies³. Recent
498 data from the GTEx consortium now allow a more systematic assessment of imprinted gene
499 enrichment using genes defined from human transcriptome-wide analyses¹⁷. Consistent with
500 our previous observations, imprinted genes were enriched for AAM-associated variants
501 (MAGENTA $P=4\times 10^{-3}$), with a concordant excess of parent-of-origin specific associations for
502 the 389 index AAM variants (**Figure S3**, **Table S3**).

503 Systematic assessment of the 389 AAM gene regions in the Icelandic deCODE study
504 revealed novel rare variants in two imprinted gene regions with robust parent-of-origin
505 specific associations with AAM. Firstly, we identified a rare 5' UTR variant rs530324840
506 (MAF=0.80% in Iceland) in *MKRN3* that is associated with AAM under the paternal
507 ($P=6.4\times 10^{-11}$, $\beta= -0.52$ years) but not the maternal model ($P=0.20$, $\beta=0.098$, $P_{\text{het}}=1.3\times 10^{-7}$)
508 (**Table 1 & S13**). rs530324840 is by far the most significant variant at the *MKRN3* locus and
509 is uncorrelated with our previously reported common variant rs12148769 at the same locus
510 ($r^2 < 0.001$ in deCODE)³ (**Figure S4**). We note that the rare 5' UTR variant rs184950120
511 detected in the current GWAS meta-analysis also shows paternal-specific association in

512 deCODE and, despite their near location (235bp from rs530324840), is uncorrelated to
513 rs530324840 ($r^2 < 0.0001$ in deCODE).

514 The second novel robust parent-of-origin specific signal is indicated by a rare intergenic
515 variant at the *DLK1* locus (rs138827001; MAF=0.36% in Iceland) that associates with AAM
516 under the paternal model ($P=4.7 \times 10^{-10}$, $\beta = -0.70$ years) but not the maternal model ($P=0.88$,
517 $\beta = -0.018$ years, $P_{\text{het}}=1.4 \times 10^{-4}$) (**Table 1, Figure S5**). rs138827001 is uncorrelated with the
518 two previously reported common variants rs10144321 and rs7141210 at the *DLK1* locus (r^2
519 < 0.01 in Iceland) that both also showed paternal allele-specific associations³. At this locus,
520 we observed a further common variant rs61992671 (MAF=48.5% in Iceland) 4.4kb upstream
521 of the Maternally Expressed 9 (*MEG9*) gene (~300kb from *DLK1*) that was associated with
522 AAM under the maternal model ($P=6.0 \times 10^{-8}$, $\beta = -0.077$ years) but not the paternal model
523 ($P=0.27$, $\beta = 0.015$ years, $P_{\text{het}}=1.9 \times 10^{-5}$). rs61992671 was uncorrelated ($r^2 < 0.05$) with the two
524 common signals identified in the meta-analysis (rs10144321 and rs7141210) and replicated
525 with a consistent magnitude of effect in the our GWAS meta-analysis (additive model,
526 $P=5.1 \times 10^{-6}$).

527 **Disproportionate genetic effects on early or late puberty timing**

528 Family-based studies in twins have suggested age-related differences in the impacts of
529 genetic and environmental factors on AAM¹⁸. To test for asymmetry in the genetic effects on
530 puberty timing, we defined two groups of women in the UK Biobank study based on
531 approximated quintiles for AAM – “early” (8-11 years inclusive, N=14,922) and “late” (15-19,
532 N=12,290). Each group was compared to the same median quintile AAM reference group
533 (age 13, N=17,717). Estimated genome-wide heritability was higher for early AAM
534 ($h^2_{\text{SNP}}=28.8\%$; s.e 2.3%) than late AAM ($h^2_{\text{SNP}}=21.5\%$; s.e. 2.5%, $P_{\text{diff}}=0.03$). Accordingly,
535 217/377 (57.7%) autosomal index SNPs had larger effect estimates on early than late AAM
536 (binomial $P=0.004$ vs. 50% expected), and the aggregated effect of the 377 SNPs also
537 differed between strata ($P=2.3 \times 10^{-4}$) (**Figure 2, Table S14**). These differences remained
538 when matching the early and late AAM strata for sample size and phenotype ranges (**Table**
539 **S15**).

540 In contrast, we observed the opposite pattern of disproportion in the genetic effects on male
541 voice breaking in UK Biobank (“relatively early” N=2678, “relatively late” N=3566). Genome-
542 wide heritability estimates tended to be higher for relatively late voice breaking (7.8%, s.e
543 1.2%) than for relatively early (6.9%, s.e 1.3%), and 227/377 (60.2%) index SNPs had larger
544 effect estimates on relatively late than relatively early voice breaking (binomial $P=4.3 \times 10^{-5}$).

545 **BMI-independent effects of puberty timing on cancer risks**

546 Traditional (non-genetic) epidemiological studies have reported complex associations
547 between puberty timing, body mass index (BMI) and adult cancer risks. For example, large
548 studies using historical growth records identified lower adolescent BMI and earlier puberty
549 timing (estimated by the age at peak adolescent growth) as predictors of higher breast
550 cancer risk in women^{19,20}. Conversely, BMI is positively associated with breast cancer risk in
551 postmenopausal women²¹. Furthermore, the strong inter-relationship between puberty timing
552 and BMI limits the ability to consider their distinct influences on disease risks in traditional
553 observational studies. Consistent with our previous report⁵, we observed a strong inverse
554 genetic correlation between AAM and BMI ($rg = -0.35$, $P=1.6 \times 10^{-72}$). 39 AAM loci overlapped

555 with reported loci for adult BMI²², yet even those AAM signals with weak individual
556 associations with adult BMI still contributed to BMI when considered in aggregate: the 237
557 AAM variants without a nominal individual association with adult BMI (all $P > 0.05$) were
558 collectively associated with adult BMI ($P = 4.2 \times 10^{-9}$) (**Figure S6**). This finding precludes an
559 absolute distinction between BMI-related and BMI-unrelated AAM variants.

560 In Mendelian randomisation analyses, we therefore included adjustment for genetically-
561 predicted BMI (as predicted by the 375 autosomal AAM variants) in order to assess the likely
562 direct (i.e. BMI-independent) effects of AAM on the risks for various sex steroid-sensitive
563 cancers (see **methods**). In these BMI-adjusted models, increasing AAM was associated with
564 lower risk for breast cancer (OR=0.935 per year, 95% confidence interval: 0.894-0.977;
565 $P = 2.6 \times 10^{-3}$), and in particular with oestrogen receptor (ER)-positive but not ER-negative
566 breast cancer (P -heterogeneity = 0.02) (**Figure 3, Table S16**). Similarly, increasing AAM
567 adjusted for genetically-predicted BMI was associated with lower risks for: ovarian cancer
568 (OR=0.930, 0.880-0.982; $P = 9.3 \times 10^{-3}$), in particular serous ovarian cancer (OR=0.917,
569 0.859-0.978; $P = 8.9 \times 10^{-3}$); and endometrial cancer (OR=0.781, 0.699-0.872; $P = 9.97 \times 10^{-6}$).
570 Assuming an equivalent per-year effect of the current AAM variants on age at voice
571 breaking, as we reported for the 106 previously identified AAM variants⁵, we could also infer
572 a protective effect of later puberty timing, independent of BMI, on lower risk for prostate
573 cancer in men (OR=0.925, 0.876-0.976; $P = 4.4 \times 10^{-3}$).

574 These findings were supported by sensitivity tests using sub-groups of AAM signals stratified
575 by their individual associations with adult BMI. The 'BMI-unrelated' variant score (comprising
576 314 variants) supported a direct effect of AAM timing on breast cancer risk in women
577 (OR=0.946, 0.904-0.988; $P = 1.3 \times 10^{-2}$). In contrast, a score using only the 61 BMI-related
578 AAM variants gave a significant result in the opposite direction (OR=1.15, 1.06-1.25;
579 $P = 4.3 \times 10^{-4}$) (**Table S16**), consistent with the recently reported inverse association between
580 genetically-predicted BMI and breast cancer risk^{23,24}. Further sensitivity tests (heterogeneity
581 and MR-Egger tests) using the 'BMI-unrelated' variant score suggested that additional sub-
582 pathways might link AAM to risk of ovarian cancer (MR-Egger Intercept $P = 0.036$), but
583 reassuringly these tests indicated no further pleiotropy (i.e. beyond the effects of BMI) in our
584 analyses of breast, endometrial and prostate cancers (for all: I-square < 23% and MR-Egger
585 Intercept $P > 0.1$) (**Table S16, Figure S7**).

586 Discussion

587 In a substantially enlarged genomic analysis using densely imputed genomic data, we have
588 identified 389 independent, genome-wide significant signals for AAM. In aggregate, these
589 signals explain ~7.4% of the population variance in AAM, corresponding to ~25% of the
590 estimated heritability. While assigning possible causal genes to associated loci is an ongoing
591 challenge for GWAS findings, we adopted a number of recently described methods to
592 implicate the underlying genes and tissues. 33 genes were implicated by non-synonymous
593 variants and >200 genes were implicated by transcriptome-wide association in the five
594 neural tissues enriched for AAM-associated gene activation. Transcriptome-wide association
595 analyses also enabled the estimation of direction of gene expression in relation to AAM,
596 notably indicating the likely delaying effect of *LIN28B* gene expression on AAM, which is
597 consistent with inhibitory effects of this gene on developmental timing in animal and cell
598 models^{14,15}.

599 Our findings add to the growing evidence for a significant role of imprinted genes in the
600 regulation of puberty timing³. In a recent family study, rare coding mutations (two frameshift,
601 one stop-gained and one missense) in *MKRN3* were shown to cause central precocious
602 puberty when paternally inherited²⁵. Taken together, three distinct types of variants at
603 *MKRN3* appear to influence puberty timing when paternally inherited: (i) multiple rare loss-of-
604 function mutations with large effects²⁵ (ii) a common intergenic variant (rs530324840) with
605 small effect, and (iii) two 5' UTR variants (rs184950120 and rs12148769) with intermediate
606 allele frequencies (1 in 95 Icelandic women) and effects (~0.5 years per allele). Similarly, we
607 found allelic heterogeneity at the imprinted *DLK1* locus where, as at *MKRN3*, a low
608 frequency paternally-inherited allele conferred a substantial decrease in the age of puberty
609 timing. At the same locus, maternal allele-specific association with an unrelated variant near
610 to the maternally-expressed gene *MEG9* is consistent with multiple imprinting control centres
611 at this imprinted gene cluster²⁶.

612 The strong collective influence of the identified loci on AAM allowed informative stratification
613 of AAM-associated variants in causal analyses to distinguish between BMI-related and BMI-
614 unrelated pathways linking puberty timing to risk of sex steroid sensitive cancers. These
615 findings were supported in BMI-adjusted models and, except for ovarian cancer, by
616 additional tests for pleiotropy, and indicate causal influences of both lower adolescent BMI
617 and earlier AAM on later cancer risks. The association between BMI and breast cancer risk
618 is complex; directionally-opposing associations have been reported with adolescent and
619 adult BMI, and with differing associations with pre- and post-menopausal breast
620 cancer^{19,20,21}. Recent Mendelian randomisation studies report a consistent protective effect
621 of higher BMI on pre- and post-menopausal breast cancer^{23,24}. Some studies have reported
622 on the association between later puberty timing and lower risk of prostate cancer in men, but
623 such data on puberty timing in men is scarcely recorded²⁷. The influences of earlier puberty
624 timing, independent of BMI, on higher risks of breast, ovarian and endometrial cancers in
625 women, and prostate cancer in men, could be mediated by a longer duration of exposure to
626 sex steroids. Alternatively, mechanisms that confer earlier puberty timing might also promote
627 higher levels of hypothalamic-pituitary-gonadal axis activity, as exemplified by a variant in
628 *FSHB* that confers earlier AAM, higher circulating follicle stimulating hormone concentrations
629 in women, and higher susceptibility to dizygous twinning¹¹.

630 We identified disproportionate effects of AAM variants on early or late puberty timing in a
631 sex-discordant pattern. In females, variant effect estimates and heritability were higher for
632 early versus late puberty timing, but the opposite was seen in males. These findings are
633 concordant with clinical observations of sex-dependent penetrance of abnormal early and
634 late puberty timing, even when accounting for presentation bias. Girls are more susceptible
635 than boys to start puberty at abnormally young ages²⁸, whereas boys are more susceptible
636 than girls to have delayed onset of puberty²⁹. These findings suggest some, yet to be
637 unidentified, sex-specific gene-environment interactions. Future studies should
638 systematically explore the potential influence of AAM-associated variants on rare disorders
639 of puberty. In summary, our findings suggest unprecedented genetic complexity in the
640 regulation of puberty timing and support new causal links with susceptibility to sex steroid-
641 sensitive cancers in women and men.

642 Online Methods

643 GWAS meta-analysis for age at menarche in women

644 Each individual study tested SNPs using a two tailed additive linear regression model for
645 association with age at menarche (AAM), including age at study visit and other study specific
646 covariates. Insertion/deletion polymorphisms were coded as “I” and “D” for data storage
647 efficiency and to allow harmonisation across all studies. Genetic variants and individuals
648 were filtered on the basis of study specific quality control metrics. Association statistics for
649 each SNP were then uploaded by study analysts for central processing. Study level results
650 files were assessed following standardised quality control pipeline³⁰, and results for each
651 SNP were meta-analysed across studies using an inverse variance weighted model using
652 METAL³¹ in a two stage process. Firstly, results from ReproGen consortium studies (**Table**
653 **S1**) were combined and then filtered so that only those SNPs which appeared in over half of
654 these studies were taken forward. Secondly, aggregated ReproGen consortium results were
655 combined with data from the UK Biobank^{32,33} and 23andMe, Inc. studies⁵. Variants were only
656 included in the final results file if they had results from at least two of these three sources,
657 and a combined minor allele frequency (MAF) > 0.1%. We assessed potential inflation of test
658 statistics due to sample relatedness and population stratification using LD score
659 regression³⁴. Here, an intercept value not significantly different from 1 indicates no such
660 inflation, with a value over 1 indicating inflation.

661 A final list of index variants was first defined using a distance based metric, by which any
662 SNPs passing the two tailed threshold of significance ($P < 5 \times 10^{-8}$) within 1Mb of another
663 significant SNP were considered to be located in the same locus. This list of signals was
664 then further augmented using approximate conditional analysis in GCTA, using an LD
665 reference panel from the UK Biobank study. Only secondary signals that were uncorrelated
666 ($r^2 < 0.05$) were included in the final list.

667 Replication and parent-of-origin testing

668 Replication of identified hits was performed in an independent sample of 39,486 women of
669 European ancestry from the deCODE study, Iceland. Main effects and parent-of-origin
670 association testing was performed using the same methodology as previously reported^{3,4}.
671 The fraction of variance explained by a variant associating under the additive model was
672 calculated using the formula $2 f (1-f) \beta_a^2$, where f denotes the minor allele frequency of the
673 variant and β_a is the additive effect. For variants associating under the recessive model, the
674 formula $f_h (1-f_h) \beta_r^2$ was used, where f_h denotes the homozygous frequency of the variant
675 and β_r denotes the recessive effect. For variants associating under parent-of-origin models,
676 fraction of variance explained was computed using the formulas $f (1-f) \beta_m^2$ for the maternal
677 model and $f (1-f) \beta_p^2$ for the paternal model, where f denotes the minor allele frequency of
678 the variant, β_m denotes the effect under the maternal model and β_p denotes the effect under
679 the paternal model. Variance explained across multiple SNPs was calculated by summing
680 the individual variances for all uncorrelated variants. We also estimate variance explained for
681 top hits in UK Biobank using a combined allele score of all 377 autosomal genetic variants.
682 Each individual variant was weighted using effect estimates derived from a meta-analysis
683 excluding UK Biobank.

684

685 **Age at voice breaking in men**

686 Data on male voice breaking were available from two sources. Firstly, the 23andMe, Inc.
687 study recorded recalled age at voice breaking in a sample of 55,871 men, as previously
688 described⁵. This was recorded as a quantitative trait into pre-defined 2-year age bins by
689 online questionnaire in response to the question “How old were you when your voice began
690 to crack/deepen?”⁵. Individual SNP effect estimates from the two year age bins were
691 rescaled to 1 year estimates for both voice breaking and AAM as reported previously.

692 Age at voice breaking was also recalled in the UK Biobank study, as previously described³³.
693 This was recorded as a categorical trait: “younger than average”, “about average age”, “older
694 than average”, “do not know” or “prefer not to answer” in response to the question “When did
695 your voice break”. In separate models, the earlier or later voice breaking groups were
696 compared to the average group (used as the reference group).

697 **Disproportionate effects on early or late puberty timing**

698 Disproportionate effects on early or late puberty timing of AAM-associated SNPs were tested
699 for AAM in UK Biobank. The distribution of AAM was divided into approximate quintiles, as
700 previously reported³³. Odds ratios for being in the youngest quintile (range 8-11) or the
701 oldest (range 15-19) were compared to the middle quintile (age 13) as the reference, for
702 each AAM-associated SNP and also for a combined weighted AAM-increasing allele score,
703 with weights derived from a meta-analysis of all other studies except for UK Biobank.
704 Sensitivity tests were performed by dividing UK Biobank individuals into broad strata based
705 on birth year (before or after 1950) and geographic location (attendance at a study
706 assessment centre in the North or South of the UK, as indicated by a line joining Mersey-
707 Humber).

708 **Genetic correlation and genome-wide variance analysis**

709 Genome-wide genetic correlations with adult BMI²² and voice breaking⁵ were estimated
710 using LD score regression implemented in LDSC³⁴. The total trait variance of all genotyped
711 SNPs was calculated using Restricted Estimate Maximum Likelihood (REML) implemented
712 in BOLT³⁵. This was estimated using the same UK Biobank study sample in the discovery
713 analysis, excluding any related individuals. The proportion of heritability explained by index
714 SNPs was estimated by dividing the variance explained by the index SNPs, by the total
715 variance explained by all genotyped SNPs genome-wide.

716 **Mendelian randomisation analyses**

717 Individual genotype data on cancer outcomes were available from the Breast Cancer
718 Association Consortium (BCAC) and Endometrial Cancer Association Consortium (ECAC).
719 In addition, summary level results for ovary and prostate cancer were made available from
720 the Ovarian Cancer Association Consortium (OCAC) and the Prostate Cancer Association
721 Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL)
722 consortium, respectively. Total analysed numbers were: 47,800 breast cancer cases and
723 40,302 controls, 4401 endometrial cancer cases and 28,758 controls, 18,175 ovarian cancer
724 cases and 26,134 controls, and 20,219 prostate cancer cases and 20,440 controls (from the
725 PRACTICAL iCOGS dataset).

726 We performed Mendelian randomisation analyses to assess the likely causal effects of
727 puberty timing on the risks for various sex steroid-sensitive cancers. Hence, AAM was
728 predicted by a weighted genetic risk score of all 375 autosomal AAM-associated SNPs, and
729 genetically-predicted AAM was tested for association with each cancer in a logistic
730 regression model. The individual SNP genotype dosages comprising this score were
731 imputed using the 1000 Genomes reference panel (minimum imputation $r^2=0.43$, median
732 0.95). To avoid potential confounding by effects of the AAM genetic risk score on BMI, we
733 performed BMI-adjusted analyses by including in models as a covariate the same AAM
734 genetic risk score, but weighting each SNP for its effect on BMI (rather than on AAM) in the
735 same study sample. Hence, we estimated the effect of genetically-predicted AAM controlling
736 for genetically-predicted BMI by the same SNPs. BMI weighting was based on the
737 association between each SNP and adult BMI in this sample (childhood BMI measurements
738 were not available but there is reportedly high genetic correlation between adult and
739 childhood obesity ($rg=0.73$)³⁶. We did not adjust for measured BMI because such
740 measurements in prevalent cancer cases are likely to introduce bias. As sensitivity tests,
741 three further genetic score associations were performed for each cancer outcome: firstly,
742 AAM predicted by the 314 AAM-associated SNPs that *were not* also individually associated
743 with BMI in the BCAC iCOGs sample (at a nominal level of $p<0.05$); secondly, AAM
744 predicted by the 61 AAM-associated SNPs that *were* also associated with BMI in this sample
745 (i.e $P<0.05$); finally, AAM predicted by all 375 autosomal AAM-associated SNPs (unadjusted
746 for BMI). To further consider pleiotropy, we tested for presence of heterogeneity between
747 AAM-associated SNPs and analysed MR-Egger regression models³⁷.

748 **Pathway analyses**

749 Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA) was used to
750 explore pathway-based associations in the full GWAS dataset. MAGENTA implements a
751 gene set enrichment analysis (GSEA) based approach, as previously described³⁸. Briefly,
752 each gene in the genome is mapped to a single index SNP with the lowest P-value within a
753 110 kb upstream, 40 kb downstream window. This P-value, representing a gene score, is
754 then corrected for confounding factors such as gene size, SNP density and LD-related
755 properties in a regression model. Genes within the HLA-region were excluded from analysis
756 due to difficulties in accounting for gene density and LD patterns. Each mapped gene in the
757 genome is then ranked by its adjusted gene score. At a given significance threshold (95th
758 and 75th percentiles of all gene scores), the observed number of gene scores in a given
759 pathway, with a ranked score above the specified threshold percentile, is calculated. This
760 observed statistic is then compared to 1,000,000 randomly permuted pathways of identical
761 size. This generates an empirical GSEA P-value for each pathway. Significance was
762 determined when an individual pathway reached a false discovery rate (FDR) <0.05 in either
763 analysis. In total, 3216 pathways from Gene Ontology, PANTHER, KEGG and Ingenuity
764 were tested for enrichment of multiple modest associations with AAM. MAGENTA software
765 was also used for enrichment testing of custom gene sets.

766 **Gene expression data integration**

767 In order to identify which tissues and cell types were most relevant to genes involved in
768 pubertal development, we used an applied LD score regression³⁹ to specifically expressed
769 genes ("LDSC-SEG")⁸. For each tissue, we ranked genes by a t-statistic for differential
770 expression, using sex and age as covariates, and excluding all samples in related tissues.

771 For example, we compared expression in hippocampus samples to expression in all non-
772 brain samples. We then took the top 10% of genes by this ranking, formed a genome
773 annotation including these genes (exons and introns) plus 100kb on either side, and used
774 stratified LD score regression to estimate the contribution of this annotation to per-SNP AAM
775 heritability, adjusting for all categories in the baseline model³⁹. We computed significance
776 using a block jackknife over SNPs, and corrected for 46 hypotheses tested at $P=0.05$.

777 To identify specific eQTL linked genes, we utilised two complementary approaches to
778 systematically integrate publicly available gene expression data with our genome-wide
779 dataset:

780 Summary Mendelian Randomization (SMR) uses summary-level gene expression data to
781 map potentially functional genes to trait-associated SNPs⁷. We ran this approach against the
782 publicly available whole-blood eQTL dataset published by Westra et al.⁶, giving association
783 statistics for 5,950 transcripts. A conservative significance threshold was set at $P<8.4\times 10^{-6}$,
784 in addition to a heterogeneity in dependent instruments (HEIDI) test statistic $P>0.009$ for any
785 variants which surpass the main threshold.

786 MetaXcan, a meta-analysis extension of the PrediXcan method⁴⁰, was used to infer the
787 association between genetically predicted gene expression (GPGE) and AAM. PrediXcan is
788 a novel gene-based data aggregation and integration method which incorporates information
789 from gene-expression data and GWAS data to translate evidence of association with a
790 phenotype from the SNP-level to the gene. Briefly, PrediXcan first imputes gene-expression
791 at an individual level using prediction models trained on measured transcriptome datasets
792 with genome-wide SNP data and then regresses the imputed transcriptome levels with
793 phenotype of interest. MetaXcan extends its application to allow inference of the direction
794 and magnitude of GPGE-phenotype associations with only summary GWAS statistics, which
795 is advantageous when SNP-phenotype associations result from a meta-analysis setting and
796 also when individual level data are not available. As input we utilized GWAS meta-analysis
797 summary statistics for AAM, LD matrix from the 1000 Genomes project, and as weights,
798 gene-expression regression coefficients for SNPs from models trained with transcriptome
799 data (V6p) from the GTEx Project⁴¹. GTEx is a large-scale collaborative effort where DNA
800 and RNA from multiple tissues were sequenced from almost 1,000 deceased individuals of
801 European, African, and Asian ancestries. MetaXcan analyses were targeted to those tissue
802 types with prior evidence of association with AAM (based on the GTEx enrichment analyses
803 described above). The threshold for statistical significance was estimated using the
804 Bonferroni method for multiple testing correction across all tested tissues ($P<2.57\times 10^{-6}$).

805 **Motif enrichment testing**

806 We identified transcription factors whose binding could be disrupted by AAM associated
807 variants in enhancer regions by combining predicted enhancer regions across 111 human
808 cell types and tissues with predicted motif instances of 651 transcription factor families as
809 previously described⁴².

810 Briefly, we defined enhancer regions by first applying ChromHMM⁴³, training a 15-state
811 model for each reference epigenome on 5 histone modifications: H3K4me1, H3K4me3,
812 H3K36me3, H3K9me3, and H3K27me3. We then produced a higher confidence set of
813 predicted enhancer regions in each reference epigenome by intersecting DNaseI

814 hypersensitive sites (taking the union over 53 reference epigenomes for which DNase-Seq
815 was performed) with enhancer-like chromatin states predicted in that reference
816 epigenomes⁴². We defined 226 disjoint enhancer modules with distinct patterns of activity by
817 hierarchically clustering the high confidence regions according to their patterns of activity
818 (presence/absence) across the 111 reference epigenomes.

819 We predicted motif instances by first building a database of position weight matrices (PWMs)
820 combining known motifs from Transfac and Jaspar with de novo discovered motifs in 427
821 ChIP-Seq experiments for 123 transcription factors from ENCODE⁴⁴. We predicted active
822 regulators in each enhancer module by computing the enrichment of true PWM matches in
823 the set of regions assigned to that module against the background of shuffled PWM
824 matches. We only considered PWMs with conservation score at least 0.3, and used log2-fold
825 enrichment > 1.5 as the significance cutoff.

826 We used the full set of AAM association summary statistics, excluding the 23andMe
827 component, to identify a heuristic p-value threshold⁴². Briefly, we pruned a set of 8,094,080
828 variants to 432,550 independent loci (pairwise $r^2 < 0.1$). We scored each locus as the
829 proportion of variants in the locus overlapping a predicted enhancer region, ranked loci by
830 the best p-value in the locus, and then plotted enrichment curves comparing the cumulative
831 score every 100 loci against the expected score for that total number of loci under the null
832 where the score increases uniformly to the genome-wide value. We defined the right-most
833 elbow point (inflection point) among all the enrichment curves as the heuristic p-value cutoff.

834 For each combination of enhancer module and predicted regulator, we constructed a 2x2
835 contingency table counting enhancer regions in that module partitioned by presence of that
836 motif and orthogonally by presence of an AAM association (based on the heuristic p-value
837 cutoff described above). We restricted the set of regions to the domain on which motifs were
838 discovered (excluding coding regions, 3' UTRs, transposons, and repetitive regions) and
839 additionally to the subset of regions which harbor an imputed SNP for the disease. We
840 computed one-sided p-values using Fisher's exact test.

841 **Hi-C integration**

842 Significant Hi-C interactions and contact domains were obtained from Rao et al. (GSE63525)
843 for 6 ENCODE cell lines: K562, GM12878, HeLa-S3, IMR90, NHEK, and HUVEC. Their
844 Juicer pipeline assigns statistical significance to each Hi-C interaction at resolutions ranging
845 from 5kb-25kb, depending on coverage, at a 10% False Discovery Rate (FDR). Contact
846 domains are genomic regions enriched for regulatory interactions and are more conserved
847 across cell types than are specific interactions. They are conceptually similar to
848 Topologically Associating Domains (TADs, Dixon et al. 2012) but with improved resolution
849 (185kb median length vs. 880kb). We used the intersect command of bedtools to produce a
850 list of significantly interacting Hi-C fragments containing one or more of our identified SNPs
851 in either fragment from any of the six cell lines. For each SNP-containing fragment, genes
852 present in the corresponding interacting fragment were identified as potential regulatory
853 targets. As a second approach, we also scored genes based on the number of ENCODE cell
854 types in which they were in the same contact domain as a SNP.

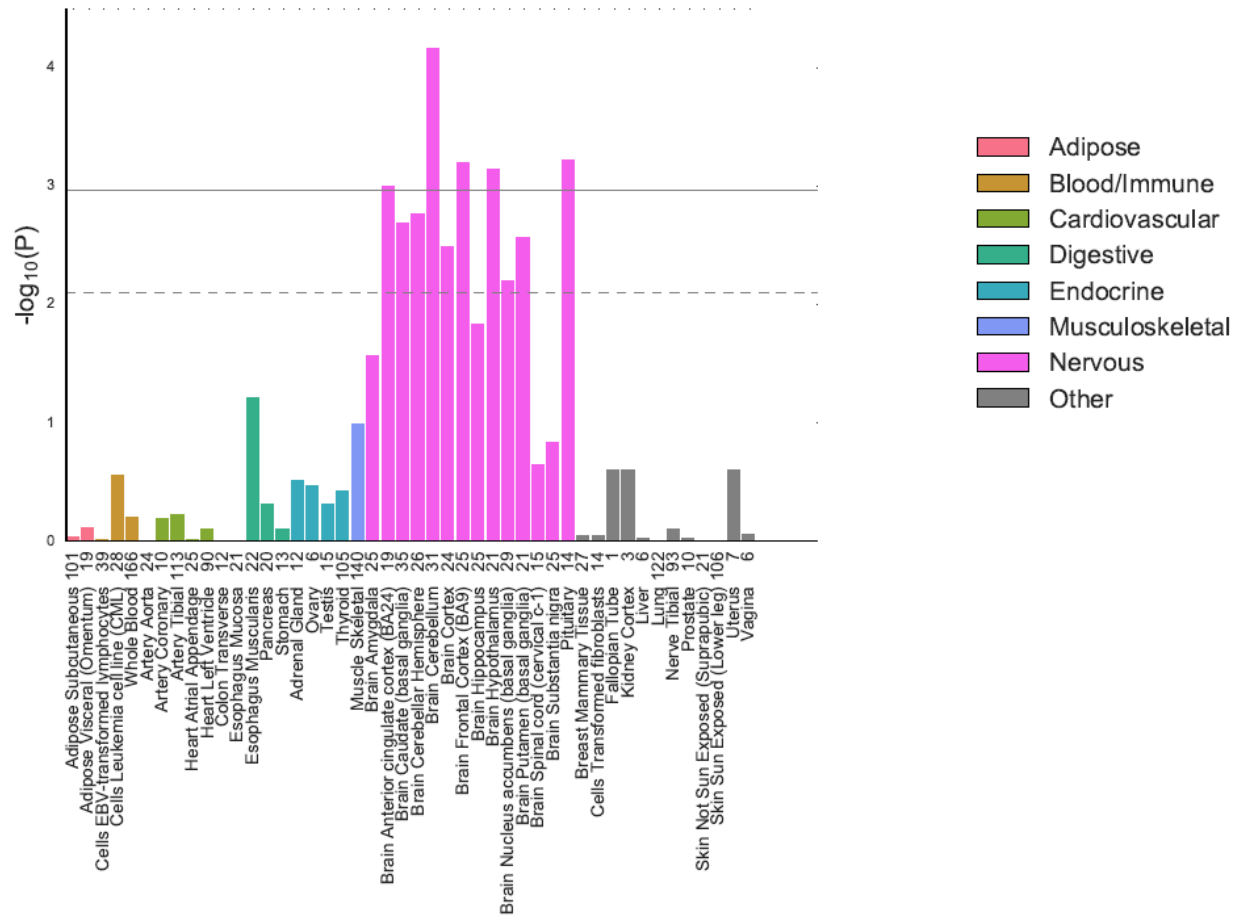


Figure 1. GTEx tissue enrichment using LD score regression. Numbers on the X-axis show sample number for each tissue. Dotted line represents significance at FDR < 5%, solid horizontal line represents Bonferroni-corrected significance for number of tissues tested.

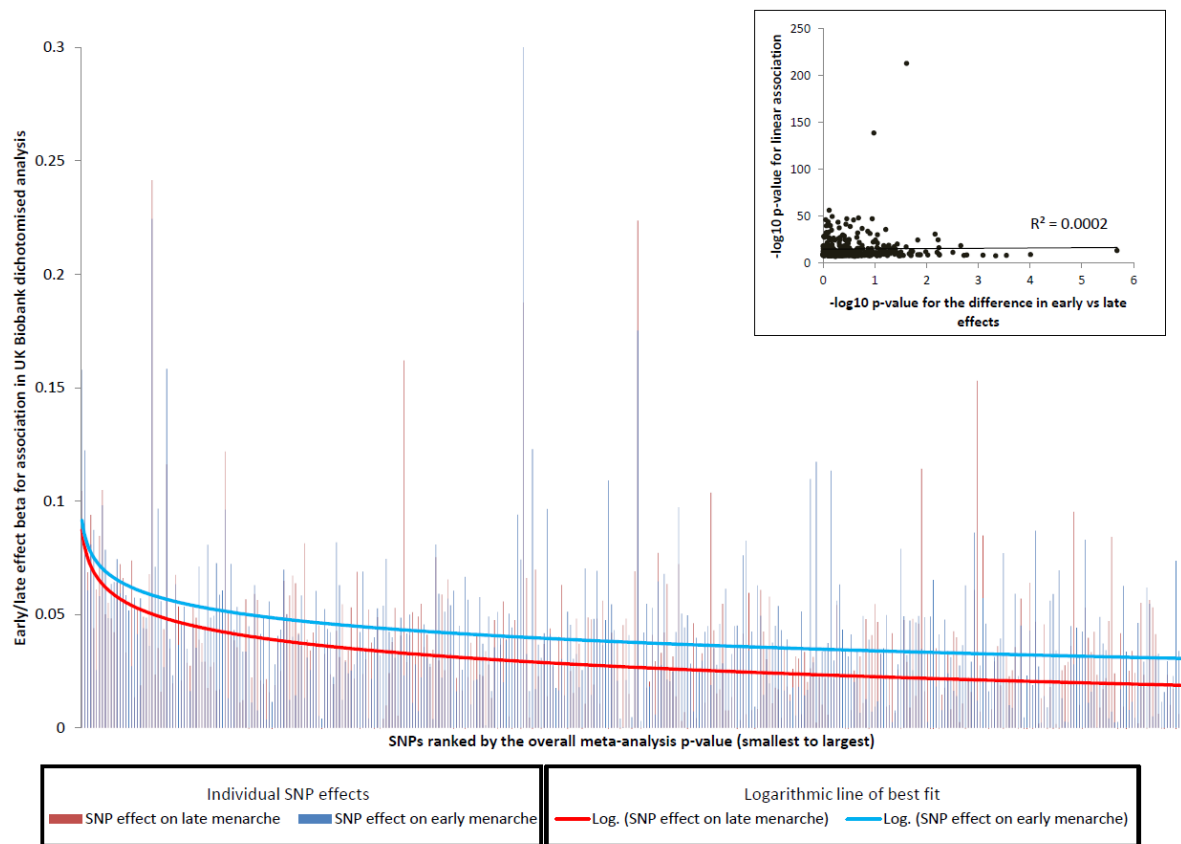


Figure 2. Stronger effects of age at menarche-associated signals on early menarche (blue) than late menarche (red) in women. The 377 index menarche-associated SNPs are ordered from smallest to largest p-value for their continuous associations with age at menarche. The Y-axis indicates the log-odds ratio for each SNP on early menarche (blue; ages 8–11 years inclusive) or late menarche (red; 15–19 years inclusive). The reference group are women with menarche at 13 years. **Insert** shows the $-\log_{10}$ p-values for the heterogeneity (based on Cochran’s Q) between the early and late menarche associations plotted against the $-\log_{10}$ p-value for the continuous age at menarche association.

Associations between genetic scores and a range of cancers

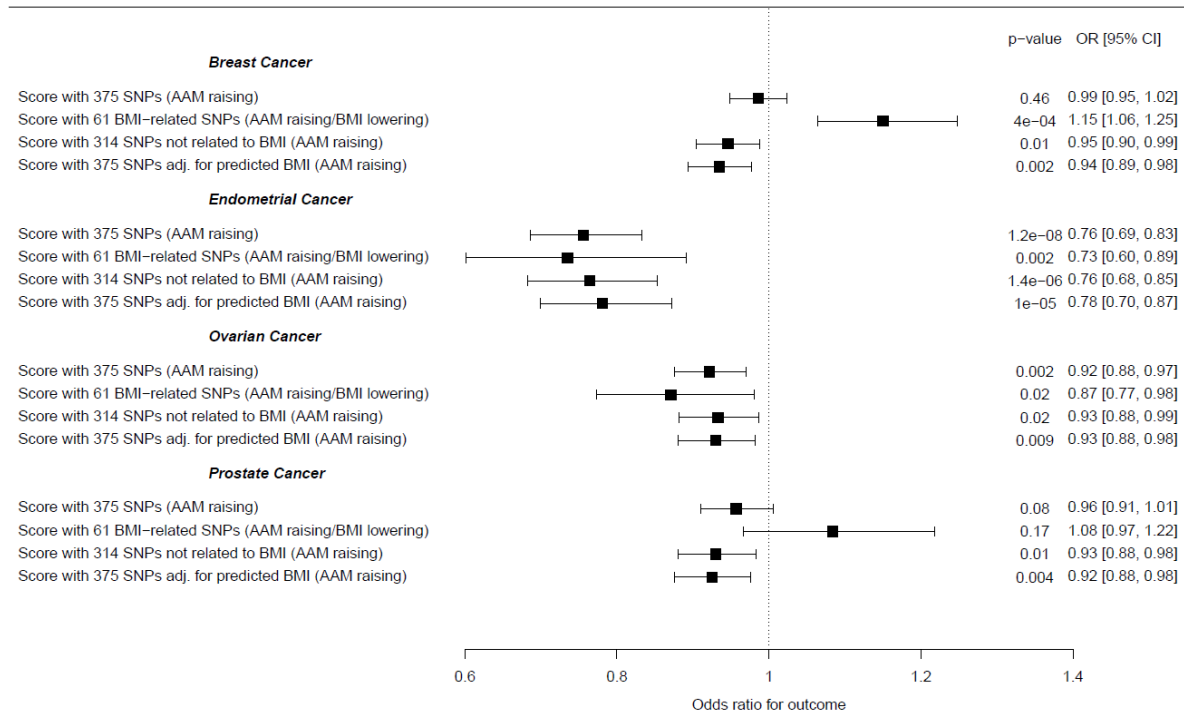


Figure 3. Effects and 95% confidence intervals of genetically-predicted age at menarche (AAM) on risks for various sex steroid-sensitive cancers, adjusted for the effects of the same AAM variants on BMI. AAM was predicted by all 375 autosomal AAM-associated SNPs, and models were adjusted for the genetic effects of the same AAM variants on BMI. Three further genetic score associations are shown as sensitivity analyses for each outcome: firstly, AAM predicted by the 314 AAM-associated SNPs that *were not* also associated with BMI in the BCAC iCOGs sample (at a nominal level of $p < 0.05$); secondly, AAM predicted by the 61 AAM-associated SNPs that *were* also associated with BMI in this sample; finally, AAM predicted by all 375 autosomal AAM-associated SNPs (unadjusted for BMI).

Table 1: Parent-of-origin specific associations between sequence variants at *MKRN3*, *DLK1* and *MEG9* with age at menarche in Iceland (N=39,543).

Marker	Position (hg38)	Allele		Freq. A1 (%)	Region	Additive		Maternal		Paternal		$P_{\text{mat vs. pat}}^2$
		A1	A2			P	β^1	P	β^1	P	β^1	
rs530324840 ³	15:23,565,461	A	C	0.80	<i>MKRN3</i>	4.4×10^{-4}	-0.206	2.0×10^{-1}	0.098	6.4×10^{-11}	-0.523	1.3×10^{-7}
rs184950120 ³	15:23,565,696	T	C	0.26	<i>MKRN3</i>	1.0×10^{-2}	-0.265	9.8×10^{-1}	0.003	1.5×10^{-4}	-0.502	4.9×10^{-2}
rs12148769 ³	15:23,906,947	A	G	10.1	<i>MKRN3</i>	5.8×10^{-6}	-0.078	3.4×10^{-1}	-0.022	9.2×10^{-8}	-0.120	2.3×10^{-3}
rs138827001 ⁴	14:100,771,634	T	C	0.36	<i>DLK1</i>	6.8×10^{-6}	-0.387	8.8×10^{-1}	-0.018	4.7×10^{-10}	-0.704	1.4×10^{-4}
rs10144321 ⁴	14:100,416,068	G	A	23.0	<i>DLK1</i>	5.6×10^{-6}	-0.056	4.0×10^{-1}	-0.014	1.9×10^{-7}	-0.084	9.7×10^{-3}
rs7141210 ⁴	14:100,716,133	T	C	38.2	<i>DLK1</i>	4.5×10^{-2}	0.021	1.5×10^{-1}	-0.021	2.3×10^{-5}	0.059	4.0×10^{-4}
rs61992671 ⁵	14:101,065,517	A	G	48.5	<i>MEG9</i>	4.7×10^{-3}	-0.029	6.0×10^{-8}	-0.077	2.7×10^{-1}	0.015	1.9×10^{-5}

1. β indicates the effect of allele A1 in years per allele.

2. P -value for heterogeneity between paternal and maternal allele associations.

3. rs530324840 is a novel variant identified by the parent-of-origin specific analysis. rs184950120 is the rare variant identified by the meta-analysis. rs12148769 is the previously reported intergenic common signal (Ref. 3).

4. rs138827001 is a novel variant identified by the parent-of-origin specific analysis. rs10144321 and rs7141210 are previously reported common variants (Ref. 3).

5. rs61992671 is a suggestive novel parent-of-origin specific association signal.

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Competing financial interests

The authors declare no competing financial interests

Data availability statement

GWAS meta-analysis summary statistics from the ReproGen consortium are available to download from the ReproGen website (www.reprogen.org).

Author Contributions

All authors reviewed the original and revised manuscripts. Statistical analysis: F.R.D, D.J.T, H.H, D.I.C, H.F, P.S, K.S.R, S.W, A.Sa, E.Alb, E.Alt, M.A, C.M.B, T.Bo, A.Ca, E.D, A.G, C.He, J.J.H, R.K, I.K, P.L, K.L.L, M.M, B.M, G.M, S.E.M, I.M.N, R.N, T.N, L.P, N.Per, E.P, L.M.R, K.E.S, A.Se, A.V.S, L.S, A.T, J.R.B.P. Sample collection, genotyping and phenotyping: I.L.A, S.Ba, M.W.B, J.B, S.Be, M.B, E.B, S.E.B, M.K.B, J.S.B, H.Bra, H.Bre, L.B, T.Br, J.E.B, H.C, E.C, S.C, G.C, T.C, F.J.C, D.L.C, A.Co, L.C, K.C, G.D, E.J.C.N.d, R.d, I.DeV, J.D, P.D, I.D-S, A.M.D, J.G.E, P.A.F, L.F-R, L.Fe, D.F, L.Fr, M.G, I.G, G.G.G, H.G, D.F.G, P.G, P.H, E.H, U.H, T.B.H, C.A.H, G.H, M.J.H, J.L.H, F.H, D.Hu, A.I, H.I, M.J, P.K.J, D.K, Z.K, G.L, D.L, C.L, L.J.L, J.S.E.L, S.Le, J.Li, P.A.L, S.Li, Y.L, J.Lu, R.M, A.Ma, H.M, M.I.M, C.Mei, T.M, C.Men, A.Me, K.M, L.M, R.L.M, G.W.M, A.M.M, M.A.N, P.N, H.N, D.R.N, A.J.O, T.A.O, S.P, A.Pa, N.Ped, A.Pe, J.P, P.D.P.P, A.Po, P.R, I.Ra, S.M.R, A.R, F.R.R, I.Ru, R.R, D.R, C.F.S, M.K.S, R.A.S, M.Sh, R.S, M.C.S, U.S, M.Sta, M.Ste, K.Str, T.Ta, E.T, N.J.T, M.T, T.Tr, J.P.T, A.G.U, D.R.V, V.V, U.V, P.V, Q.W, E.W, K.W, G.W, R.W, B.H.RW, J.Z, M.Zo, M.Zy. Individual study principal investigators: B.Z.A, D.I.B, M.C, F.C, T.E, N.F, C.G, V.G, C.Ha, P.K, D.A.L, P.K.EM, N.G.M, D.O.M, E.A.N, O.P, D.P, A.L.P, P.M.R, H.S, T.D.S, D.S, D.T, S.U, J.A.V, H.V, N.J.W, J.F.W, A.B.S, U.T, K.P, D.F.E, J.Y.T, J.C, D.Hi, A.Mu, J.M.M, K.Ste, K.K.O, J.R.B.P. Working group: F.R.D, D.J.T, H.H, D.I.C, H.F, P.S, K.S.R, S.W, A.Sa, A.B.S, U.T, K.P, D.F.E, J.Y.T, J.C, D.Hi, A.Mu, J.M.M, K.Ste, K.K.O, J.R.B.P.