

Supplementary Material. GENOME-WIDE ASSOCIATION STUDY AND POLYGENIC RISK SCORES OF SERUM DHEAS LEVELS IN A CHILEAN CHILDREN COHORT

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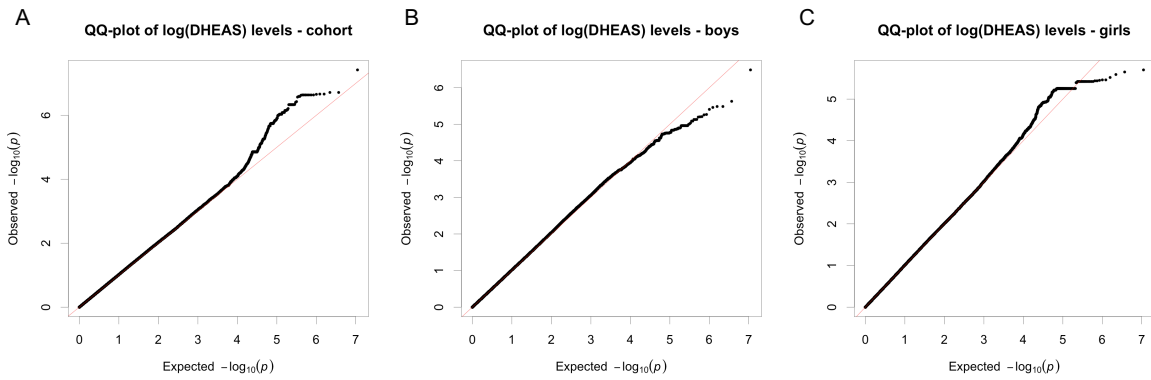
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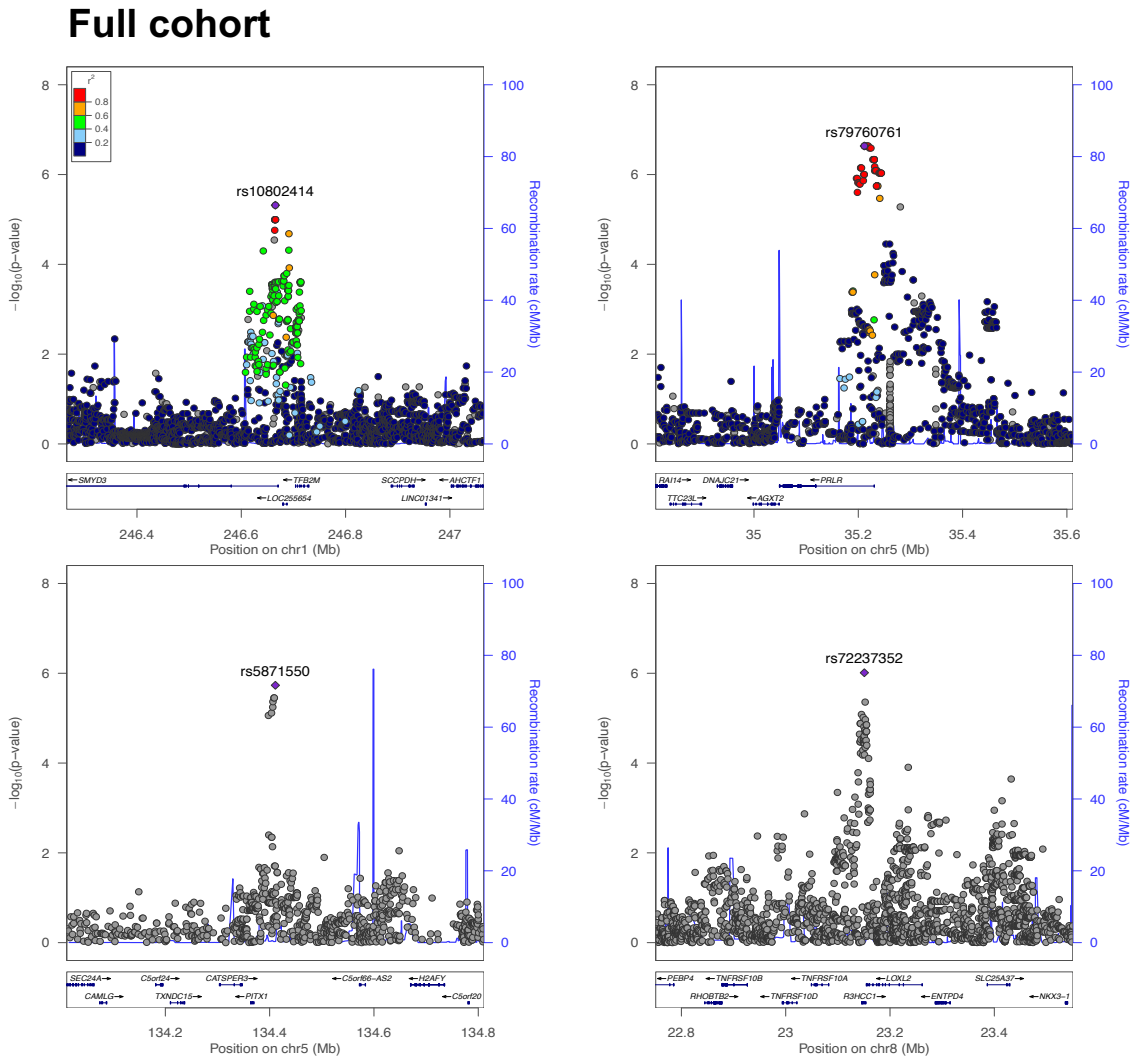
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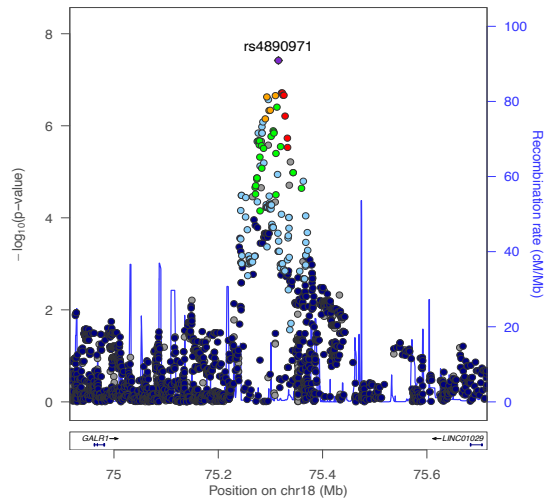
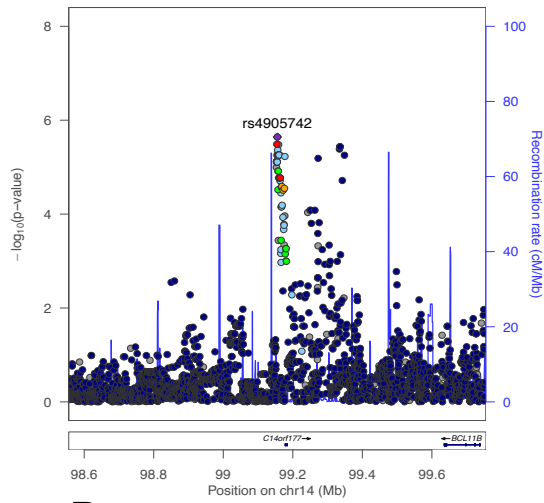
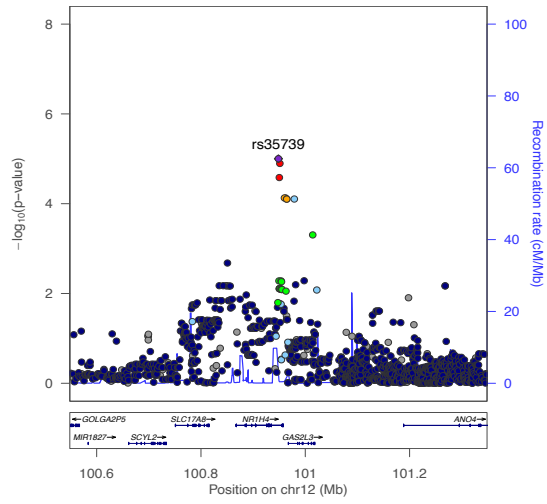
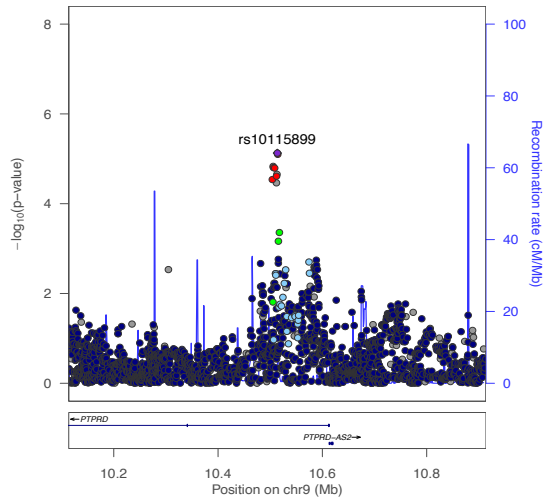
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Supplementary Figure 1. QQ plot of GWAS of log-DHEAS. **A)** full GOCS cohort, **B)** only boys, and **C)** only girls. The genomic inflation factor for each GWAS was $\lambda = 1.022$, $\lambda = 1.013$ and $\lambda = 1$, respectively.

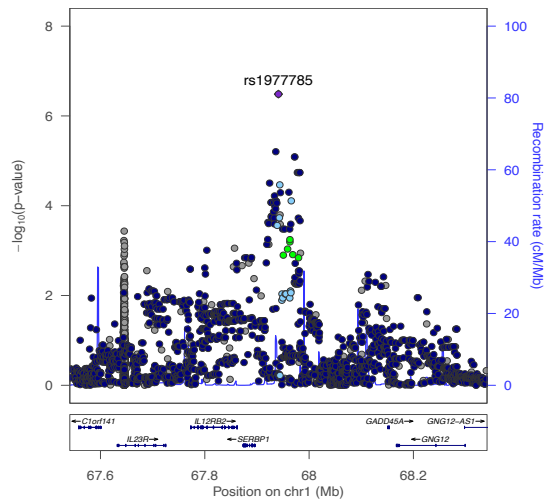
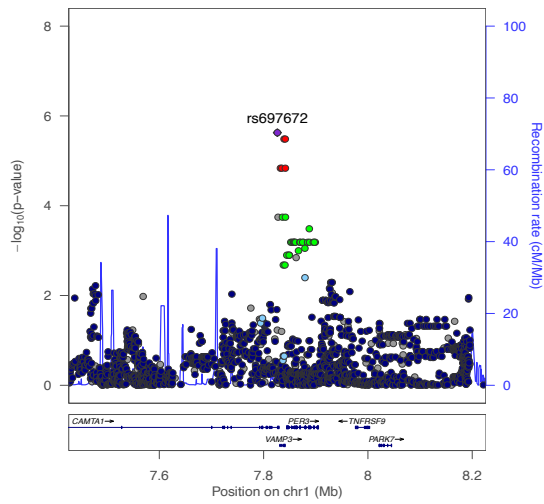


Supplementary Figure 2. Locus zoom of the top regions in the GWAS with log-DHEAS. A genomic region of ± 400 Kb from the top variants of the GWAS is shown, including the main variant (purple diamond) of the region for the full cohort, boys, or girls. The closest genes and genomic coordinates for GRCh37 assembly at bottom. The color scale shows the linkage disequilibrium (LD) values (r^2) relative to the main variant of the region and varies between absent LD (blue) and total LD (red) for Native American population (AMR). In gray, regions without LD information for the main variant. Images were prepared using LocusZoom (www.locuszoom.org).



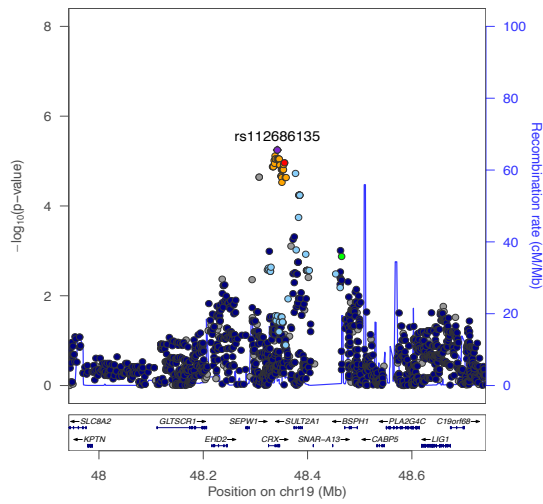
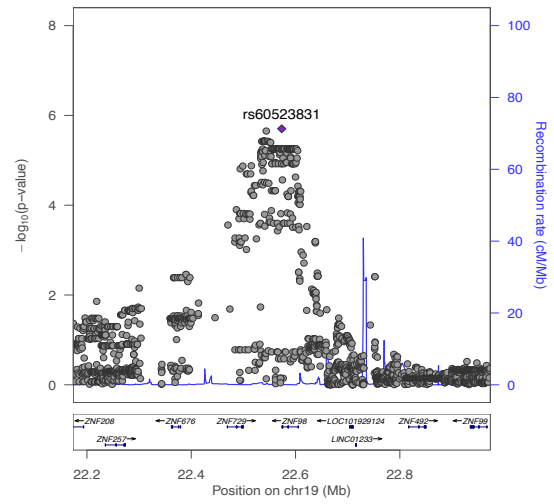
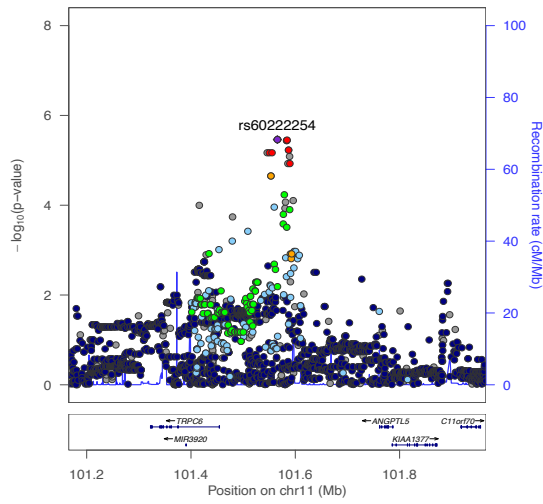
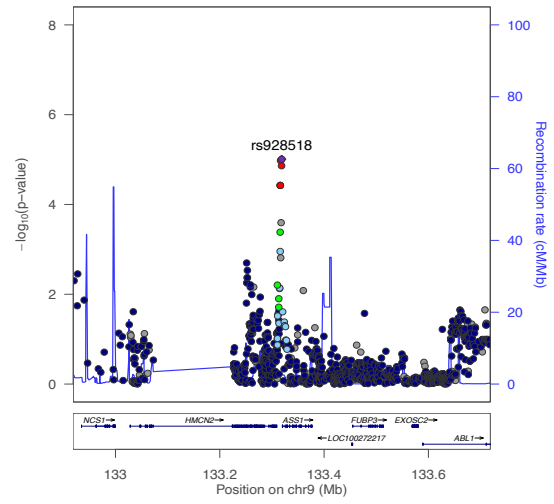
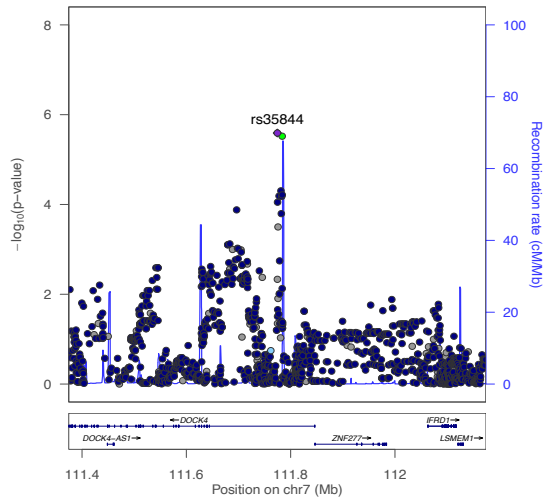


Boys



Supplementary Figure 2 continued.

Girls



Supplementary Figure 2 continued.

Supplementary Table 1. Genomic regions selected for targeted association with log-transformed DHEAS concentration. We considered DHEAS metabolism-related genes.

Gene	Gene Name	Chromosome	Analysis Start (bp)	Analysis Stop (bp)	N° of Variants
<i>HSD3B2</i>	Hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2	1	119947554	119975662	64
<i>HSD11B1</i>	Hydroxysteroid 11-beta dehydrogenase 1	1	209849525	209918295	125
<i>POR</i>	Cytochrome p450 oxidoreductase	7	75534420	75626173	241
<i>CYP11B1</i>	Cytochrome P450 family 11 subfamily B member 1	8	143943773	143971236	127
<i>HSD17B5</i>	Hydroxysteroid (17-beta) dehydrogenase 5 (now AKR1C3)	10	5080958	5159878	475
<i>PAPSS2</i>	3'-phosphoadenosine 5'-phosphosulfate synthase 2	10	89409476	89517462	390
<i>CYP17A1</i>	Cytochrome P450 family 17 subfamily A member 1	10	104580288	104607290	65
<i>IGF1</i>	Insulin-like growth factor 1	12	102779645	102885563	174
<i>IGF1R</i>	Insulin-like growth factor 1 receptor	15	99182272	99517759	802
<i>HSD11B2</i>	Hydroxysteroid 11-beta dehydrogenase 2	16	67455036	67481456	41
<i>HSD17B2</i>	Hydroxysteroid 17-beta dehydrogenase 2	16	82058842	82142139	206
<i>MC2R</i>	Melanocortin 2 receptor	18	13872043	13925535	216
<i>CYB5A</i>	Cytochrome b5 type A	18	71910527	71969251	292
<i>SULT2A1</i>	Sulfotransferase family 2A member 1	19	48363723	48399654	166

Supplementary Table 2. Top significant variants in the targeted association analysis with log-DHEAS. All FDR-BH significant variants were in *SULT2A1* gene and only in girls.

Position	Variant	Ref	Alt*	MAF GOCS	Full cohort (N=788)			Girls (N=390)			Boys (n=398)		
					Beta	95% CI	P	Beta	95% CI	P**	Beta	95% CI	P
48365523	rs296396	C	T	0.073	-0.043	-0.090;0.005	0.081	-0.140	-0.207;-0.073	4.85x10-5	0.034	-0.033;0.102	0.315
48365568	rs62128827	C	T	0.073	-0.043	-0.090;0.005	0.081	-0.140	-0.207;-0.073	4.85x10-5	0.034	-0.033;0.102	0.315
48366505	rs296393	C	T	0.073	-0.043	-0.090;0.005	0.081	-0.140	-0.207;-0.073	4.85x10-5	0.034	-0.033;0.102	0.315
48369314	rs296387	T	C	0.081	-0.044	-0.091;0.002	0.063	-0.125	-0.189;-0.061	0.00016	0.023	-0.043;0.090	0.496
48369432	rs296386	C	T	0.079	-0.041	-0.088;0.006	0.086	-0.126	-0.190;-0.061	0.00016	0.030	-0.037;0.097	0.379
48369844	rs296385	C	G	0.075	-0.039	-0.087;0.008	0.107	-0.130	-0.198;-0.063	0.00018	0.030	-0.037;0.097	0.379
48370400	rs296384	T	G	0.073	-0.039	-0.087;0.010	0.118	-0.137	-0.206;-0.068	0.00012	0.034	-0.033;0.102	0.315
48370888	rs296383	G	A	0.075	-0.039	-0.087;0.008	0.107	-0.130	-0.198;-0.063	0.00018	0.030	-0.037;0.097	0.379
48371853	rs296369	C	T	0.081	-0.044	-0.090;0.003	0.066	-0.134	-0.198;-0.069	5.68x10-5	0.030	-0.035;0.096	0.364
48376941	rs296363	G	C	0.116	-0.055	-0.094;-0.017	0.005	-0.115	-0.168;-0.063	1.89x10-5	0.003	-0.054;0.059	0.918
48382753	rs2547237	T	C	0.088	-0.045	-0.089;-0.001	0.044	-0.117	-0.177;-0.056	0.00018	0.017	-0.046;0.080	0.592
48383197	rs58296429	T	TA	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48383906	rs2547234	C	T	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48384385	rs9304669	C	T	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48384626	rs10425963	A	G	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48384635	rs10425975	A	G	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48384648	rs10425629	T	C	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48384749	rs10426201	A	G	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48385057	rs2547231	A	C	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592
48385627	rs2637115	C	T	0.087	-0.048	-0.093;-0.004	0.033	-0.127	-0.189;-0.066	5.76x10-5	0.017	-0.046;0.080	0.592

*Alt: effect/minor allele. **FDR-BH adjusted p-values <0.0013. MAF: minor allele frequency.

Supplementary Table 3. Selected variants included in the calculation of adult-DHEAS polygenic risk score.

Chr	Variant	Effect allele	Other allele	EAF	Beta (log[μ mol/L])	P-value	Proposed candidate gene	Author GWAS
2	rs77533229	A	G	0.02	-0.149	5.72×10^{-5}	THADA	Pott
6	rs36139342	AC	A	0.19	-0.087	7.52×10^{-12}	MCM9	Pott
7	rs117978821*	C	T	0.03	-0.321	1×10^{-26}	CYP3A4	Pott/Zhai
7	rs740160	T	C	0.05	0.150	1.5×10^{-16}	ARPC1A	Zhai
7	rs17277546	A	G	0.05	-0.110	4.5×10^{-11}	TRIM4;CYP3A43	Zhai
10	rs2185570	C	T	0.13	-0.060	2.29×10^{-8}	CYP2C9	Zhai
10	rs2497306	C	A	0.49	-0.040	4.64×10^{-9}	HHEX	Zhai
13	rs615567	T	A	0.39	-0.078	1.95×10^{-14}	FGF9	Pott
15	rs28620926	G	A	0.37	0.069	2.23×10^{-11}	BMF	Pott/Zhai
16	rs57159061 [#]	C	T	0.08	0.118	1.90×10^{-8}	CMIP	Pott/Prims
19	rs296360	C	T	0.17	-0.092	3.53×10^{-12}	SULT2A1	Pott/Zhai

*rs117978821 replaces rs574637649 which is not genotyped in the GOCS cohort. [#]Represents the same locus as rs2911280 at 16q13 reported in Prims et al 2016. EAF: effect allele frequency.

Supplementary Table 4. Association of age at pubarche with child-DHEAS polygenic risk score in different models.

	Beta	R ²	P-value
Full cohort			
Model 1 (child-DHEAS PRS)	-0.314	0.003	0.136
Model 2 (child-DHEAS PRS + BMI-SDS)	-0.322	0.014	0.007 (0.124)
Model 3 (child-DHEAS PRS + BMI-SDS + sex)	-0.313	0.192	<0.001 (0.098)
Girls only			
Model 1 (child-DHEAS PRS)	-0.396	0.011	0.060
Model 2 (child-DHEAS PRS + BMI-SDS)	-0.411	0.032	0.005 (0.049)
Boys only			
Model 1 (child-DHEAS PRS)	-0.218	0.001	0.481
Model 2 (child-DHEAS PRS + BMI-SDS)	-0.221	0.024	0.010 (0.469)

Dependent variable: *age at pubarche (years)*. Beta: effect size for age at pubarche (years). Children-DHEAS polygenic risk score (PRS) included the genetic variants associated with log-DHEAS serum concentrations in the full cohort (Table 2). P values are shown for the model and for the variable children-DHEAS PRS in each model (in parenthesis).