Supplementary data of

Sex-specific autosomal genetic effects across 26 human complex traits

Wan-Yu Lin [1,2]*, Chang-Chuan Chan [2,3], Yu-Li Liu [4], Albert C. Yang [5,6,7], Shih-Jen Tsai [5,7,8], Po-Hsiu Kuo [1,2]*

[1] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[2] Department of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan
[3] Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei, Taiwan
[4] Center for Neuropsychiatric Research, National Health Research Institutes, Zhunan, Taiwan
[5] Division of Psychiatry, National Yang-Ming University, Taipei, Taiwan
[6] Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA
[7] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
[8] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

* Corresponding authors: Po-Hsiu Kuo, Ph.D. and Wan-Yu Lin, Ph.D.

Po-Hsiu Kuo, Ph.D. (ORCID iD: 0000-0003-0365-3587)
Room 521, No. 17, Xu-Zhou Road, Taipei 100, Taiwan
Phone: +886-2-33668015; Fax: +886-2-23511955; E-mail: phkuo@ntu.edu.tw

Wan-Yu Lin, Ph.D. (ORCID iD: 0000-0002-3385-4702)
Room 501, No. 17, Xu-Zhou Road, Taipei 100, Taiwan
Phone/Fax: +886-2-33668106; E-mail: linwy@ntu.edu.tw

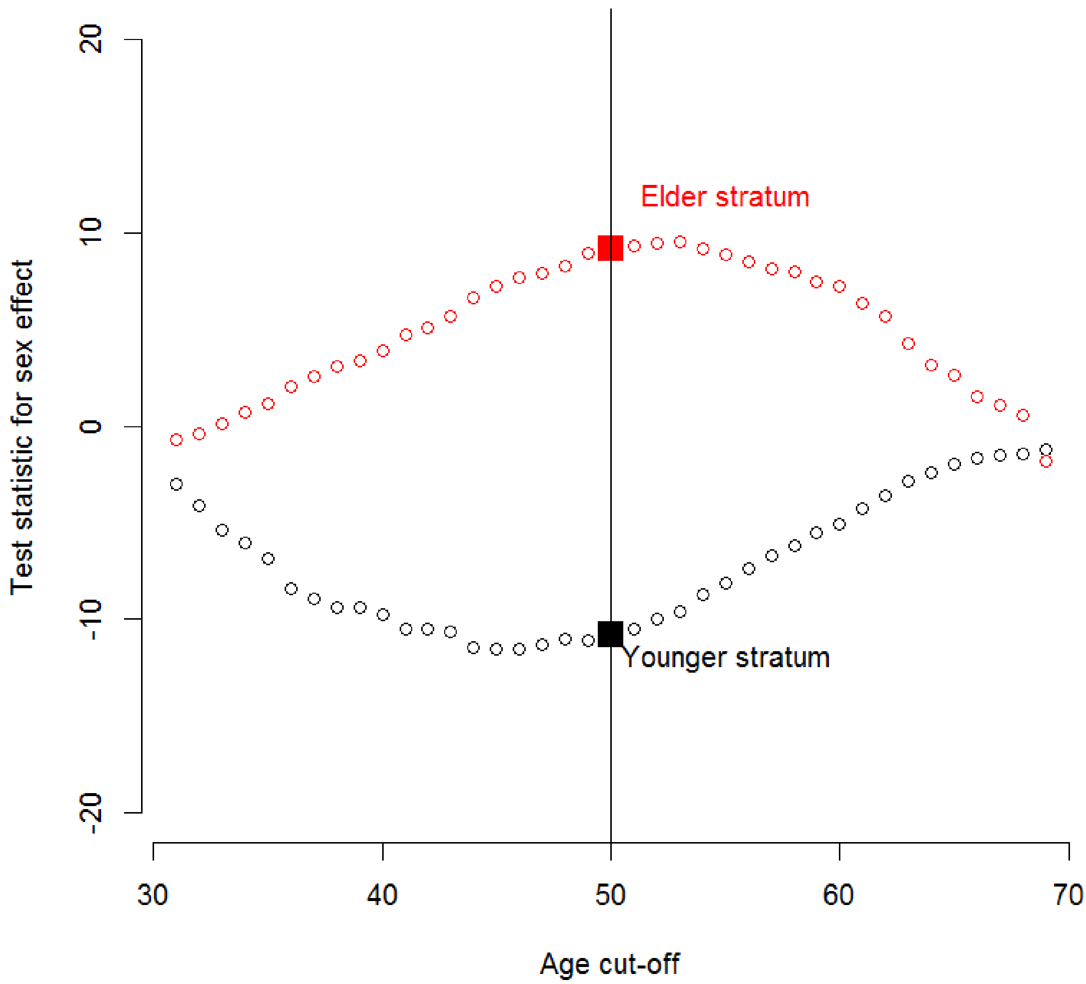

Fig. S1 Sex effects on low-density lipoprotein cholesterol (LDL-C) in the younger stratum vs. elder stratum

Analyses were stratified according to the age cut-off of 31, 32, …, 68, and 69 (the *x*-axis). Given an age cut-off, we regressed LDL-C according to the following model, for the younger stratum and the elder stratum, respectively.

$$Y = \beta_0 + \beta_F Female + \boldsymbol{\beta_C Covariates} + \varepsilon, \tag{1}$$

where *Y* is LDL-C, *Female* is coded as 1 for females and 0 for males, and ε is the random error term. Covariates included age (in years), BMI, drinking status (yes vs. no), smoking status (yes vs. no), performing regular exercise (yes vs. no), educational attainment (a value from 1 to 7), and the first 10 ancestry principal components.

The *y*-axis in this figure is $t_F = \hat{\beta}_F / s.e.(\hat{\beta}_F)$, where $s.e.(\hat{\beta}_F)$ is the standard error of $\hat{\beta}_F$. Completely different sex effects on LDL-C were shown in subjects aged ≤ 50 (black square) vs. > 50 (red square). Given an age cut-off of 50, women have lower mean LDL-C than men in the younger stratum ($t_F = -10.84$), but the situation is reversed in the elder stratum ($t_F = 9.15$).

[Supplementary Proof]

Let Y be the phenotype, G be the genotype, S be sex (S=1 for females and S=0 for males), and ε be the error term. Consider the model incorporating G×S, we have

$$Y = \gamma_0 + \gamma_G G + \gamma_S S + \gamma_{INT} G \times S + \varepsilon,$$

$$Var(Y|S = s) = Var(\gamma_0 + \gamma_G G + \gamma_S S + \gamma_{INT} G \times S + \varepsilon | S = s)$$

$$= 0 + Var(\gamma_G G) + 0 + Var(\gamma_{INT} G \times S | S = s) + 2Cov(\gamma_G G, \gamma_{INT} G \times S | S = s) + Var(\varepsilon)$$

$$= \gamma_G^2 Var(G) + \gamma_{INT}^2 s^2 Var(G) + 2\gamma_G \gamma_{INT} s Var(G) + Var(\varepsilon)$$

$$= (\gamma_G + \gamma_{INT} s)^2 Var(G) + Var(\varepsilon)$$

We obtain $Var(Y|S = s) = (\gamma_G + \gamma_{INT} s)^2 Var(G) + Var(\varepsilon)$.

For males, $Var(Y|S = s = 0) = \gamma_G^2 Var(G) + Var(\varepsilon)$.

For females, $Var(Y|S = s = 1) = (\gamma_G + \gamma_{INT})^2 Var(G) + Var(\varepsilon)$.

If $\gamma_{INT} = 0$ (in the absence of G×S), $Var(Y|S = s = 0) = Var(Y|S = s = 1)$, representing equal phenotypic variability for men and women.

If $\gamma_{INT} \neq 0$ (in the presence of G×S), $Var(Y|S = s = 0) \neq Var(Y|S = s = 1)$, representing unequal phenotypic variability for men and women. Therefore, unequal phenotypic variability for the two sexes is a direct consequence of the presence of G×S.

Table S1	Younger stratum (age ≤ 50 y)			Elder stratum (age > 50 y)		
Human complex traits (traits were first normalized within sex)	Number of SNPs used to construct the PS	PS effect in females relative to males	P_{INT}	Number of SNPs used to construct the PS	PS effect in females relative to males	P_{INT}
6 cardiovascular-related traits						
Diastolic blood pressure (mmHg)	3709	0.016	1	71	-0.039	0.77
Systolic blood pressure (mmHg)	19	0.025	1	3679	-0.035	0.04
Triglycerides (mg/dL)	3816	0.031	0.06	180	0.018	1
Total cholesterol (mg/dL)	78	-0.040	0.57	14512	-0.010	1
LDL cholesterol (mg/dL)	7483	0.015	1	85	-0.023	1
HDL cholesterol (mg/dL)	3779	0.024	0.36	110	-0.014	1
2 diabetes-related traits						
Fasting glucose (mg/dL)	1533	0.032	0.22	392	-0.050	0.08
HbA1c (%)	7443	0.025	0.12	3693	-0.023	0.54
3 kidney-related traits						
Creatinine (mg/dL)	46	0.020	1	387	0.027	1
Uric acid (mg/dL)	7552	0.013	1	3644	-0.021	0.90
Blood urea nitrogen (mg/dL)	83	0.036	0.88	14505	-0.012	1
2 liver-related traits						
Total bilirubin (mg/dL)	168	0.025	1	3684	-0.022	1
Albumin (g/dL)	90	0.049	0.16	50	-0.039	0.81
6 anthropometric traits						
Height (cm)	511	-0.029	0.89	15143	0.015	0.85
Body mass index (kg/m^2)	18	0.030	1	69	0.028	1
Body fat (%)	3654	**-0.083**	**1.3E-30**	740	**-0.115**	**1.4E-33**
Waist circumference (cm)	3811	**0.073**	**2.09E-22**	1522	**0.079**	**9.65E-16**
Hip circumference (cm)	7506	0.020	0.03	3718	0.016	0.40

Table S1	Younger stratum (age $\leq$ 50 y)			Elder stratum (age > 50 y)		
Human complex traits (traits were first normalized within sex)	Number of SNPs used to construct the PS	PS effect in females relative to males	P_{INT}	Number of SNPs used to construct the PS	PS effect in females relative to males	P_{INT}
Waist-to-hip ratio	3760	**0.092**	**4.43E-18**	88	**0.083**	**0.0002**
5 blood-related traits						
Red blood cells (million/uL)	22	0.023	1	14652	-0.018	0.42
White blood cells (1000/uL)	192	0.022	1	7483	-0.011	1
Platelet (1000/uL)	854	-0.030	0.75	67	-0.040	0.82
Hemoglobin (g/dL)	756	0.040	0.20	80	0.042	0.59
Hematocrit (%)	892	0.022	1	1580	0.029	0.51
2 other traits						
Educational attainment (degree)	46	0.021	1	15024	-0.022	0.06
Bone stiffness index	3851	0.025	0.39	408	-0.063	0.0093

Table S1. Interaction between PS (polygenic score) and sex on each complex trait (significant results with $P_{INT} < {0.05}/{104} = 0.00048$ are highlighted), where the traits were first normalized within sex

Table S2	Younger stratum (age $\leq$ 50 y)				Elder stratum (age > 50 y)			
Human complex traits	Number of SNPs used to construct the PS	R_A^2	R_B^2	R_5^2	Number of SNPs used to construct the PS	R_A^2	R_B^2	R_5^2
6 cardiovascular-related traits								
Diastolic blood pressure (mmHg)	15	0.2884	0.3057	0.3057	3764	0.1436	0.7528	0.7529
Systolic blood pressure (mmHg)	15	0.2696	0.2896	0.2902	399	0.1378	0.4227	0.4233
Triglycerides (mg/dL)	3842	0.3030	0.7874	0.7877	810	0.1362	0.5462	0.5464
Total cholesterol (mg/dL)	415	0.0577	0.3666	0.3673	397	0.0591	0.3631	0.3633
LDL cholesterol (mg/dL)	423	0.0933	0.3994	0.4004	7193	0.0235	0.8143	0.8144
HDL cholesterol (mg/dL)	765	0.2872	0.5780	0.5807	411	0.2414	0.5074	0.5103
2 diabetes-related traits								
Fasting glucose (mg/dL)	14131	0.1317	0.8614	0.8617	752	0.0634	0.5020	0.5062
HbA1c (%)	7234	0.1127	0.8191	0.8197	348	0.0616	0.3656	0.3708
3 kidney-related traits								
Creatinine (mg/dL)	1566	0.5488	0.7377	0.7380	1503	0.4491	0.7021	0.7022
Uric acid (mg/dL)	1575	0.4720	0.7188	0.7221	3649	0.2630	0.7785	0.7803
Blood urea nitrogen (mg/dL)	742	0.1110	0.4602	0.4607	72	0.0574	0.1582	0.1584
2 liver-related traits								
Total bilirubin (mg/dL)	1496	0.1063	0.5975	0.5977	3669	0.0912	0.7528	0.7534
Albumin (g/dL)	3901	0.1631	0.7234	0.7236	51	0.0342	0.1222	0.1225
6 anthropometric traits								
Height (cm)	7653	0.5739	0.8532	0.8535	1548	0.5609	0.7537	0.7541
Body mass index (kg/m^2)	48	0.1002	0.1605	0.1608	765	0.0626	0.4822	0.4834
Body fat (%)	14546	0.8502	0.9350	0.9359	14606	0.8704	0.9427	0.9433

Table S2	Younger stratum (age ≤ 50 y)				Elder stratum (age > 50 y)			
Human complex traits	Number of SNPs used to construct the PS	R_A^2	R_B^2	R_5^2	Number of SNPs used to construct the PS	R_A^2	R_B^2	R_5^2
Waist circumference (cm)	416	0.7998	0.8580	0.8595	770	0.6875	0.8288	0.8325
Hip circumference (cm)	87	0.7444	0.7709	0.7711	1556	0.6558	0.8614	0.8623
Waist-to-hip ratio	780	0.4763	0.6828	0.6883	722	0.3201	**0.6145**	**0.6258**
5 blood-related traits								
Red blood cells (million/uL)	1533	0.3671	0.6664	0.6671	1532	0.2121	0.6568	0.6586
White blood cells (1000/uL)	3763	0.1159	0.7270	0.7271	3874	0.1066	0.7573	0.7577
Platelet (1000/uL)	1646	0.1069	0.5924	0.5952	3889	0.0773	0.7366	0.7371
Hemoglobin (g/dL)	1498	0.5005	0.7036	0.7054	837	0.3649	0.6233	0.6254
Hematocrit (%)	1605	0.4311	0.6882	0.6888	876	0.2884	0.5958	0.5977
2 other traits								
Educational attainment (degree)	375	0.1543	0.3906	0.3907	392	0.1494	0.4283	0.4298
Bone stiffness index	831	0.0624	0.4755	0.4762	385	0.1506	0.4144	0.4181

Table S2. R-squares of model A (R_A^2), model B (R_B^2), and model 5 (R_5^2)

Model A (no polygenic score):

$$Y = \phi_0 + \phi_F Female + \boldsymbol{\phi_C Covariates} + \boldsymbol{\phi_{FC}} Female \times \boldsymbol{Covariates} + \varepsilon.$$

Model B (including polygenic score, but no interaction between sex and polygenic score):

$$Y = \phi_0 + \phi_{PS_t} PS_t + \phi_F Female + \boldsymbol{\phi_C Covariates} + \boldsymbol{\phi_{PSC}} PS_t \times \boldsymbol{Covariates} + \boldsymbol{\phi_{FC}} Female \times \boldsymbol{Covariates} + \varepsilon.$$

$(R_B^2 - R_A^2)$ is the improvement of incorporating PS-related terms, i.e., PS_t and $PS_t \times \boldsymbol{Covariates}$. $(R_B^2 - R_A^2)$ will increase with a larger number of SNPs used in the PS.

Model 5 (including interaction between sex and polygenic score, this is model 5 in the manuscript):

$$Y = \phi_0 + \phi_{PS_t} PS_t + \phi_F Female + \phi_{INT_t} PS_t \times Female + \boldsymbol{\phi_C Covariates} + \boldsymbol{\phi_{PSC}} PS_t \times \boldsymbol{Covariates} + \boldsymbol{\phi_{FC}} Female \times \boldsymbol{Covariates} + \varepsilon.$$

As described in the manuscript, the most significant evidence of G×S was detected in waist-to-hip ratio ($P_{INT} = 3.2 \times 10^{-55}$) for the elder stratum.

As highlighted, the improvement of incorporating G×S ($R_5^2 - R_B^2$) is $62.58\,\% - 61.45\,\% = 1.13\,\%$.