Supplemental Material to DW Belsky et al. "Polygenic Risk and Asthma's Development and Course in the First 4 Decades of Life"

Supplemental Table 1. Single nucleotide polymorphisms (SNPs) used to construct the genetic risk score for asthma. SNPs were selected based on association with asthma at $p<5x10^{-8}$ in a recent meta-analysis.[1] The full set of eligible SNPs was then pruned using an R^2 threshold of 0.60 to derive the SNP set for the GRS. This process yielded a set of 17 SNPs. Two SNPs near the gene *HLA-DQ* could not be assayed due to the complex repetitive structure of the proximal sequence. Specifically, rs9273349 and rs17843604 are located 8 and 21bp upstream from repeat regions, precluding their incorporation into the BeadPlex array. Thus the final GRS included 15 SNPs. In 3 cases, the lead SNP from GWAS could not be genotyped and a proxy SNP was chosen in its place. All proxy SNPs were in LD with GWAS SNPs at $R^2>0.95$. Thus, the proxy SNPs captured nearly identical information to the GWAS SNPs.

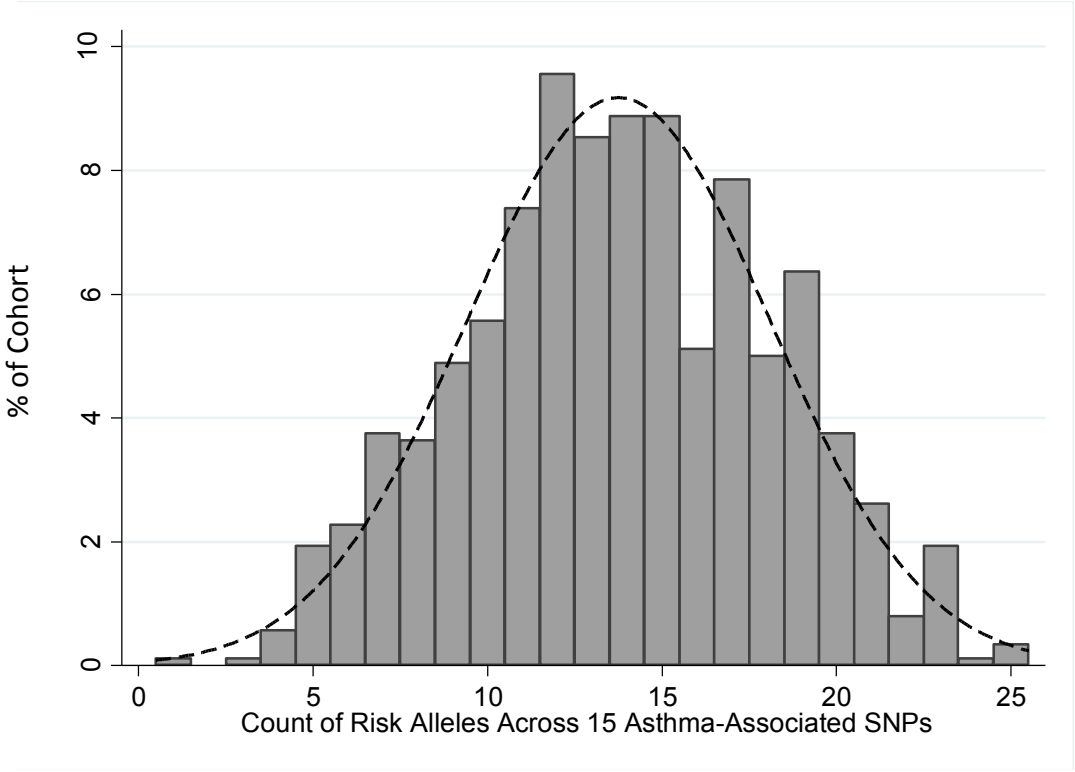
CHR	Gene	GRS SNP	Effect Allele Frequency	GWAS SNP	R2 with GWAS SNP
2	*ILa1RL1, IL18R1, IL18RAP*	rs10206753	62%	rs3771166	1.00
		rs13431828	87%	rs13431828	
5	*IL13*	rs1295686	18%	rs1295686	
	RAD50	rs2897443	16%	rs6871536	1.00
9	*IL33*	rs1342326	17%	rs1342326	
		rs3939286	25%	rs3939286	
15	*SMAD3*	rs744910	51%	rs744910	
17	*ZNF1A3, ZPB2, GSDMB*	rs907092	52%	rs2305480	0.97
	STARD3, PERLD, ERBB2	rs12150298	33%	rs12150298	
	ZPB2	rs12150079	65%	rs12150079	
	ORMDL3, GSDMA	rs3894194	45%	rs3894194	
	GSDMA	rs3902025	55%	rs3902025	
		rs3859192	46%	rs3859192	
	MED24	rs9916158	62%	rs9916158	
22	IL2RB	rs2284033	55%	rs2284033	

Supplemental Table 2. Effect-sizes for genetic risk scores that selectively omit SNPs one by one. Effect-sizes are presented for analysis of the life-course-persistent asthma phenotype. The effect-size in the first box is the change in an individual's risk for life-course-persistent asthma associated with a one standard deviation increase in their genetic risk score. The effect-size for the full genetic risk score is presented in the top row. Subsequent rows present effects-sizes for genetic risk scores that omit each SNP in turn. Rows are labeled with the omitted SNP. SNPs on Chromosome 17 are listed separately because they constitute the largest block of SNPs in the score. Effect-sizes estimated after removing SNPs from the Chromosome 17 set were similar to effect-sizes estimated after removing SNPs from other regions. Percentile-based 95% confidence intervals were estimated from 1000 bootstrap repetitions of the model. The second box shows the log odds effect size for individual SNPs in the genetic risk score.

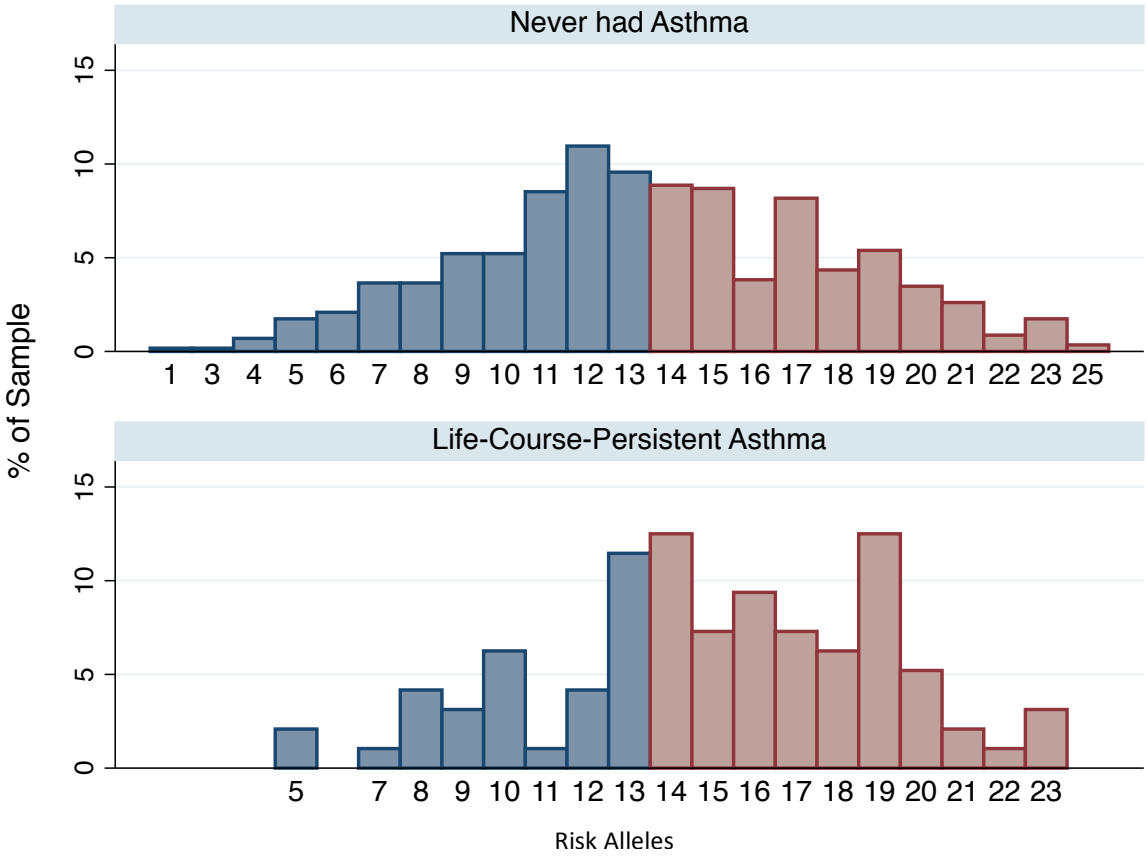
	Per-Allele Percentage Point Change in Risk	95% CI
Full Genetic Risk Score	3.44	[1.48-5.47]
Genetic Risk Scores Omitting Selected SNPs		
Chromosome 17 SNPs		
rs907092	3.34	[1.38-5.36]
rs12150298	3.48	[1.44-5.49]
rs12150079	3.55	[1.62-5.53]
rs3894194	3.36	[1.43-5.37]
rs3902025	3.21	[1.28-5.24]
rs3859192	3.39	[1.44-5.41]
rs9916158	3.56	[1.65-5.63]
SNPs from Other Chromosomes		
rs10206753	3.33	[1.31-5.38]
rs1295686	3.44	[1.48-5.50]
rs2897443	3.09	[1.14-5.17]
rs1342326	3.37	[1.31-5.53]
rs3939286	3.43	[1.36-5.57]
rs744910	3.87	[1.78-5.95]
rs2284033	3.36	[1.41-5.36]
rs13431828	3.35	[1.36-5.37]

Association with Life-Course-Persistent Asthma		
rs Number	**Log Odds Ratio**	**SE**
rs10206753	0.176	0.163
rs13431828	0.252	0.246
rs1295686	0.051	0.198
rs2897443	0.541	0.185
rs1342326	0.159	0.190
rs3939286	0.068	0.172
rs744910	-0.337	0.160
rs907092	0.435	0.156
rs12150298	0.209	0.163
rs12150079	0.262	0.166
rs3894194	0.407	0.155
rs3902025	0.565	0.161
rs3859192	0.372	0.154
rs9916158	0.223	0.159
rs2284033	0.161	0.164

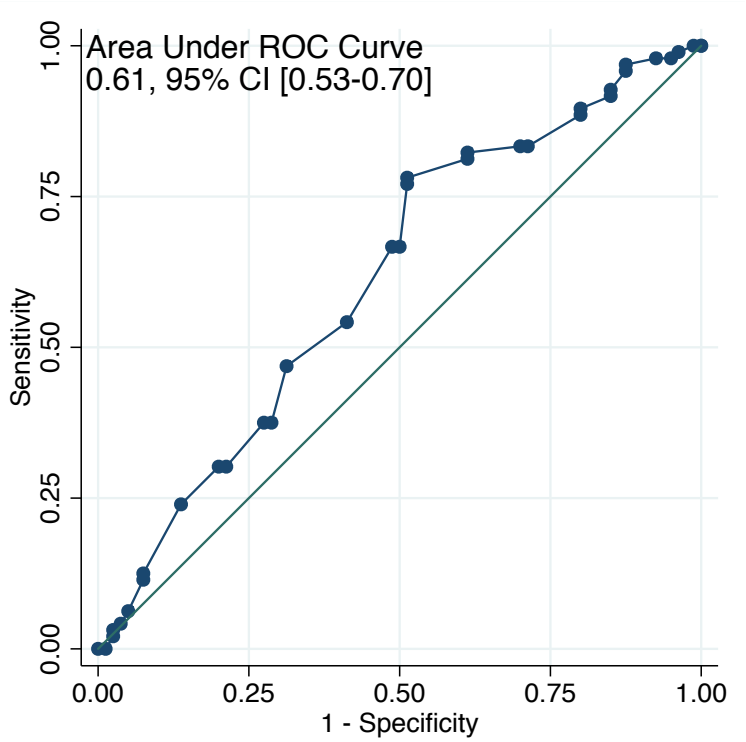
Supplemental Figure 1. Distribution of the asthma genetic risk score in the Dunedin cohort. The figure graphs the proportion of cohort members by the number of risk alleles carried. Because each SNP in the genetic risk score could contribute 0, 1, or 2 risk alleles, the genetic risk score had theoretical minimum/maximum values of 0 and 30. In the Dunedin cohort, the observed minimum and maximum risk allele counts were 1 and 25, with mean=13.74 and standard deviation=4.36 (inter-quartile range 11-17).



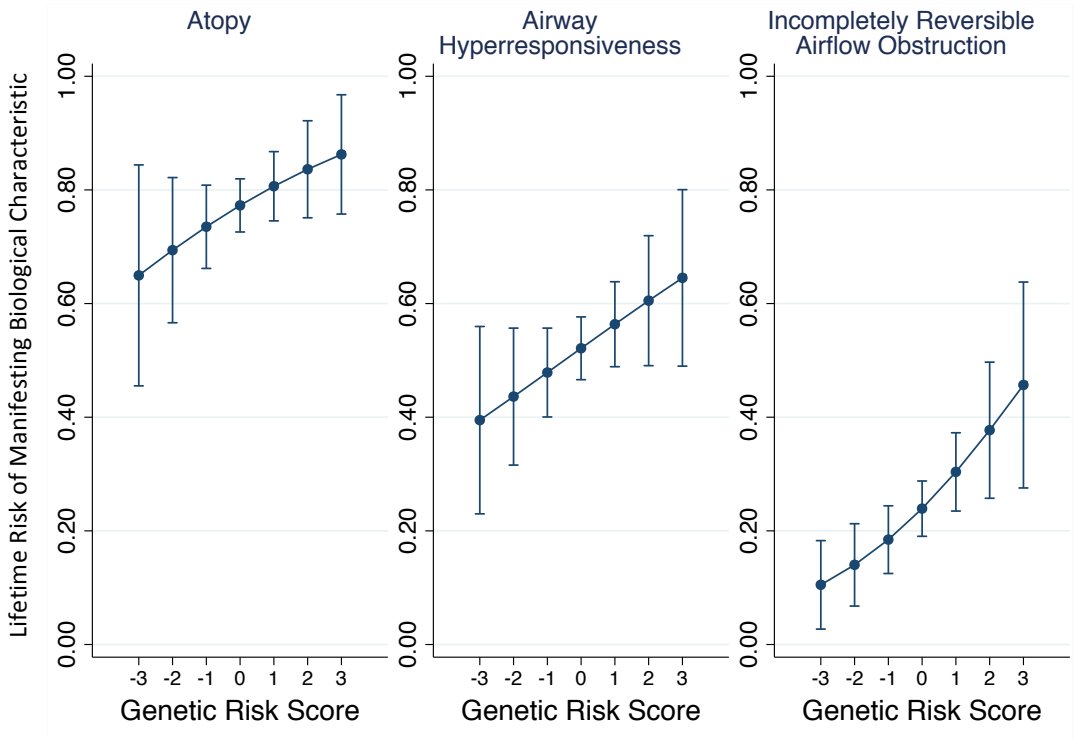
Supplemental Figure 2. Distributions of Genetic Risk in Cohort Members who Never Developed Asthma and Cohort Members with Life-Course-Persistent Asthma. The x-axis of the figure plots the count of risk alleles carried. The y-axis plots the proportion of the sample. Blue bars are for risk allele counts below the cohort mean. Red bars are for risk allele counts above the cohort mean. The figure shows that genetic risk distribution is shifted to the right in the life-course-persistent asthma group.



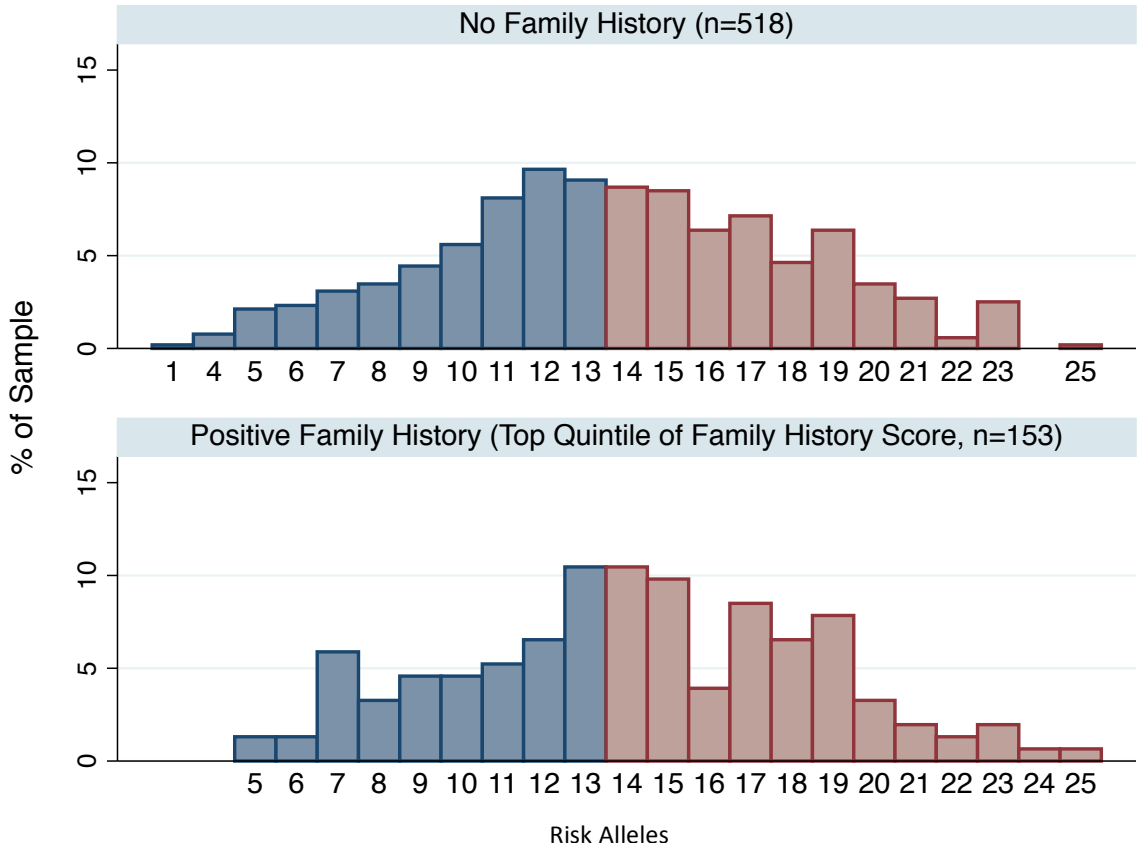
Supplemental Figure 3. Sensitivity and Specificity of Genetic Prediction of Life-Course-Persistent Asthma Among Cases Who Onset by Age 13 Years. The figure presents the receiver operating characteristic (ROC) curve generated by the genetic risk score for life-course-persistent asthma among childhood-onset asthma cases. The figure plots each value of the genetic risk score against its sensitivity (true positive rate) and 1-specificity (false positive rate) for prediction of life-course-persistence. The straight line depicts the result of random prediction of life-course-persistent case status. The departure from that line is quantified as the Area Under the Curve (AUC), which can be interpreted as the probability that a randomly sampled life-course-persistent case will have a higher genetic risk score than a randomly sampled non-life-course-persistent case.



Supplemental Figure 4. Genetic Associations with Risk of Manifesting Atopy, Airway Hyperresponsiveness, and Incompletely Reversible Airway Obstruction in Asthma. The figure graphs genetic associations with lifetime (though age 38 years) risk for atopy, airway hyperresponsiveness, and incompletely reversible airflow obstruction among asthma cases (n=305). Asthma cases at higher genetic risk were more likely to manifest atopy (assessed at ages 13, 21, and 32 years; RR=1.07 [1.01-1.14]), airway hyperresponsiveness (assessed at ages 9, 11, 13, 15, 18, 21, 26, 32, and 38 years; RR=1.16 [1.03-1.32]), and incompletely reversible airflow obstruction (assessed at ages 18, 26, 32, and 38 years; RR=1.28 [1.04-1.57]). Error bars reflect 95% confidence intervals for point estimates.



Supplemental Figure 5. Distribution of Genetic Risk in Cohort Members with No Family History of Asthma and Cohort Members with a Positive Family History for Asthma. The x-axis of the figure plots the count of risk alleles carried. The y-axis plots the proportion of the sample. Blue bars are for risk allele counts below the cohort mean. Red bars are for risk allele counts above the cohort mean. The figure shows that genetic risk distribution is similar in cohort members with no family history of asthma and those with a positive family history—for graphical purposes, positive family history was defined using the 80th percentile of the family history risk score distribution.



References

1. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med 2010;363:1211-21.