Vitiligo age-of-onset and PRS Association

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Introduction

In this study, we aim to investigate the association between a vitiligo Polygenic Risk Score (PRS) excluding MHC Class II region SNPs and the age-of-onset. Our hypothesis posits a correlation wherein a higher PRS (excluding MHC Class II) is linked to an earlier age-of-onset, indicating a potential association with elevated genetic risk.

Moreover, we extend our hypothesis to carriers of the extreme risk/early age of onset MHC Class II haplotype. In this subgroup, we anticipate that the impact of a high PRS without MHC Class II may be diminished due to the substantial genetic risk conferred by the haplotype (haplotype OR=8.1). We believe there may be an interaction effect, suggesting that the slope of the regression line for age-of-onset ~ PRS is smaller in individuals carrying the high-risk haplotype compared to non-carriers.

Results

Categorizing age-of-onset into Early- and Late- Onset Groups

I no longer have the AOO classifications that we created previously, so I have re-fit the finite mixture model to categorize GWAS123 cases as either early onset or late onset. I have used the same methods here.

In the eAOO paper it says, "After subgroup assignment and control matching, the combined early-onset subgroup contained 704 cases and 9,031 controls and the combined late-onset subgroup contained 1,467 cases and 19,156 controls."

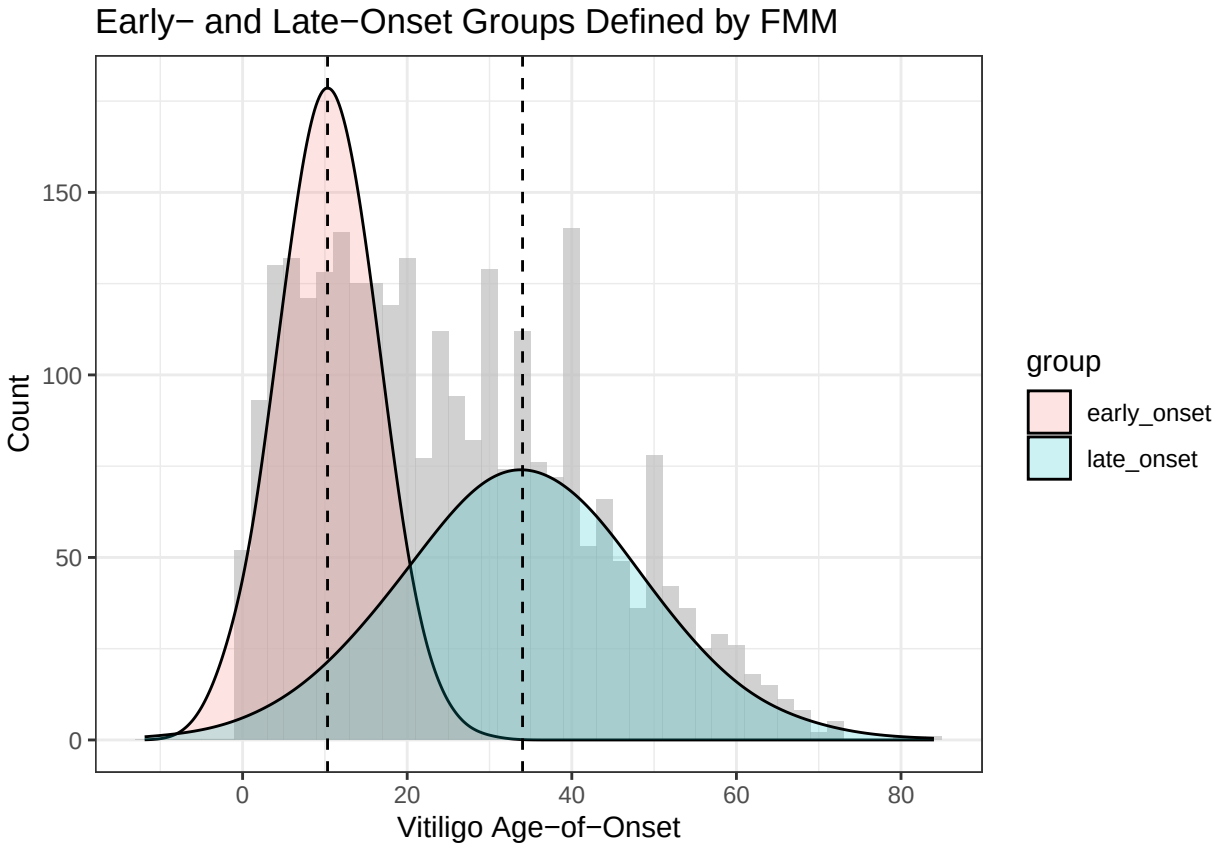
number of iterations= 100

Table 1: Early and Late Onset Subgroup Descriptive Statistics (continued below)

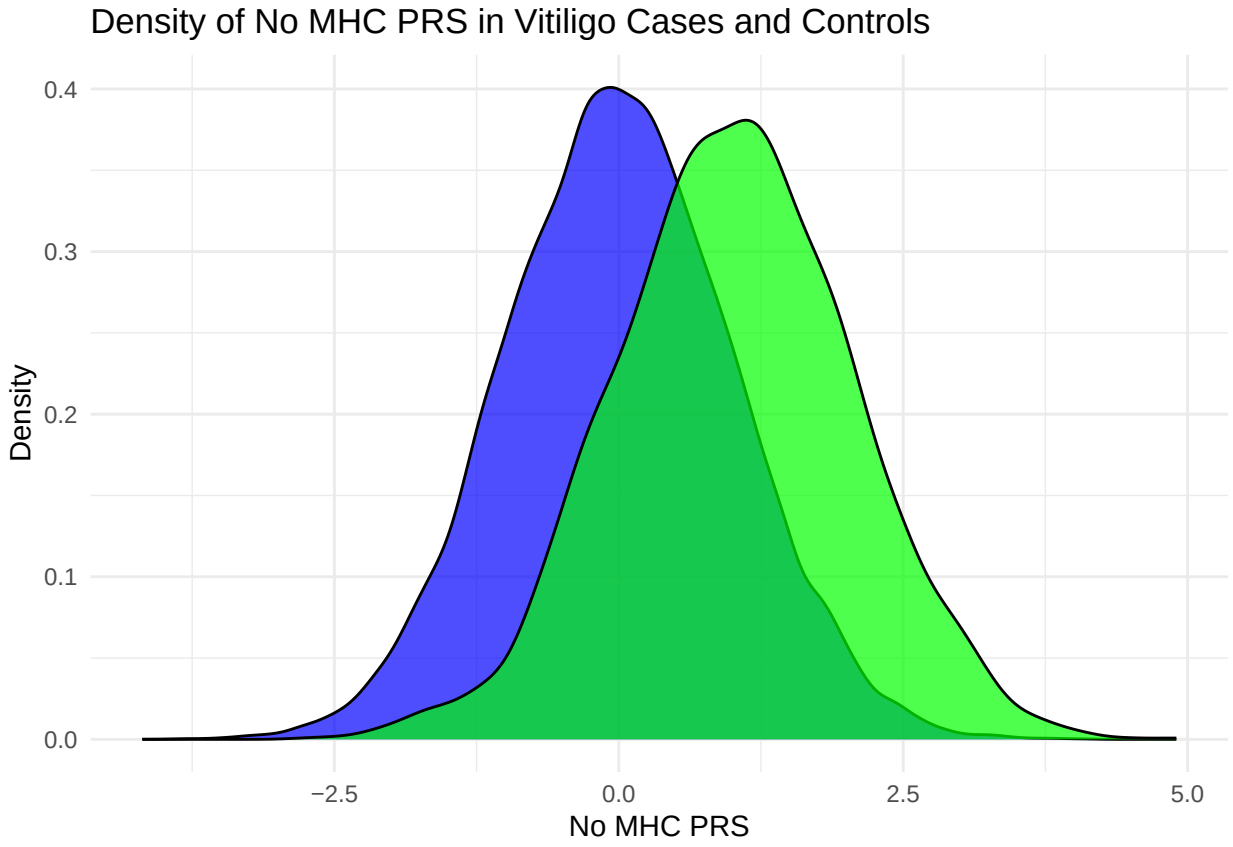
Age of Onset Category	n	FMM Mean	Actual Mean	FMM SD	Actual SD
early_onset	719	10.32	6.68	5.86	3.39
late_onset	1430	34.02	39.07	14.4	11.4
NA	617	NA	17.19	NA	2.82

Actual Minimum	Actual Maximum
0	12
23	84
12.5	22

As shown in the table above, you can see that we achieve similar sample sizes for early and late onset (719 early here vs. 704 in our earlier analysis and 1,431 late here vs. 1,467 in our earlier analysis).The FMM-estimated distribution means are also identical, at 10.3 here versus 10.3 for GWAS123 + Rep in our earlier analysis and 34.0 here versus 34.0 for GWAS123 + Rep in our earlier analysis.


Early− and Late−Onset Groups Defined by FMM
Count
150
100
50
0
0
20
40
60
80
Vitiligo Age−of−Onset
group
early_onset
late_onset

PRS distributions



Associations with Vitiligo Risk (Case-Control)

To verify that the associations look in line with previous estimates, we check the association of the PRS and the MHC Class II high-risk SNPs with overall vitiligo risk (i.e. in all cases and controls in GWAS123):

Phenotype	PRS or SNP	pval	OR	lower_ci	upper_ci
vitiligo	CONFIRMED	0.00e+00	2.71	2.6	2.82
vitiligo	eA00_rs145954018	1.59e-49	2.36	2.1	2.64
vitiligo	eAOO_hap_carrier	2.12e-49	2.43	2.16	2.74
vitiligo	generic_rs9271597	1.10e-97	1.84	1.74	1.95
vitiligo	mhc_class2_only	3.75e-110	1.46	1.42	1.51
vitiligo	no_mhc_classII	0.00e+00	2.59	2.48	2.7
late_onset_vitiligo	CONFIRMED	3.61e-230	2.46	2.33	2.6
late_onset_vitiligo	eA00_rs145954018	8.65e-08	1.61	1.35	1.92
late_onset_vitiligo	eAOO_hap_carrier	2.13e-07	1.62	1.35	1.94
late_onset_vitiligo	generic_rs9271597	8.27e-32	1.59	1.47	1.72
late_onset_vitiligo	mhc_class2_only	7.66e-28	1.3	1.24	1.37
late_onset_vitiligo	no_mhc_classII	2.25e-222	2.51	2.37	2.66
early_onset_vitiligo	CONFIRMED	4.93e-192	3.06	2.84	3.3
early_onset_vitiligo	eA00_rs145954018	2.38e-75	4.7	3.99	5.55
early_onset_vitiligo	eAOO_hap_carrier	4.30e-75	5.14	4.32	6.13
early_onset_vitiligo	generic_rs9271597	4.00e-51	2.31	2.08	2.58
early_onset_vitiligo	mhc_class2_only	4.99e-92	1.82	1.72	1.93
early_onset_vitiligo	no_mhc_classII	1.61e-127	2.55	2.36	2.75

These results look generally as I would expect, with the CONFIRMED risk score having the highest performance with respect to OR per standard deviation of PRS. The P-values = 0 mean that the P-value is lower than the numerical precision in R, which I believe is something like P < 1e-300.

Note that the scaling is different for SNPs and for PRS, so the estimates are not directly comparable (for PRS, the OR is per standard deviation of PRS, whereas for SNPs, it is per SNP risk allele).

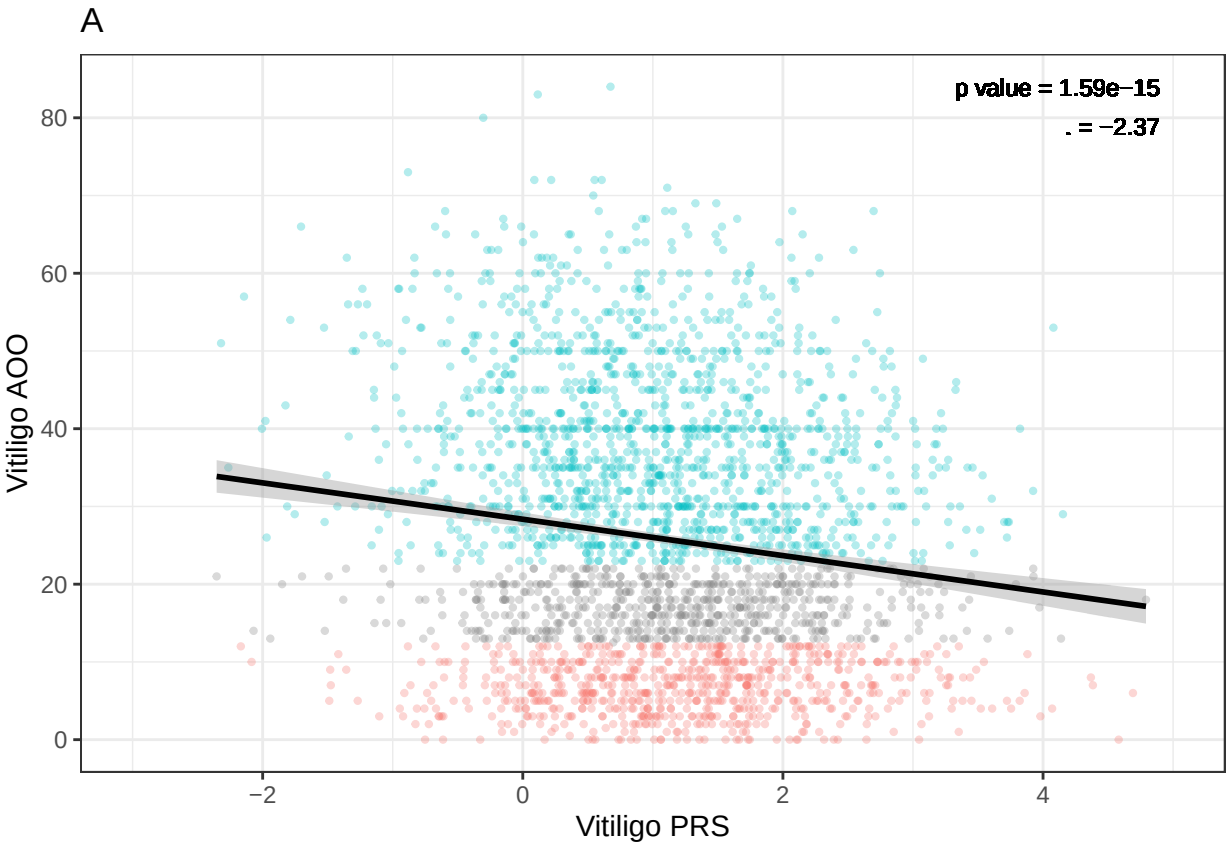
Associations with Vitiligo Age-of-Onset (Case Only)

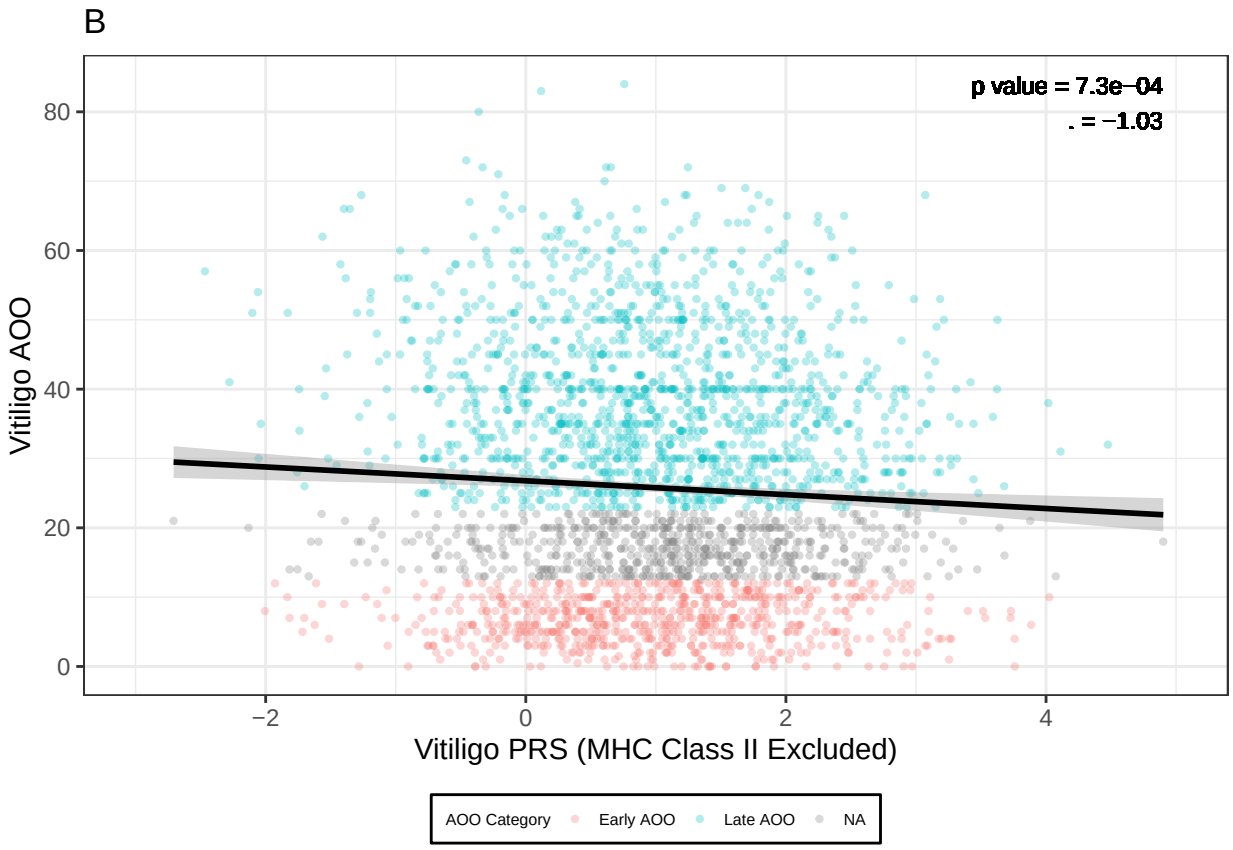
I also checked the association with vitiligo age-of-onset risk (i.e. cases with non-missing age-of-onset in GWAS123):

PRS or SNP	pval	estimate	lower_ci	upper_ci	n_obs	adj_r_sq
no_mhc_classII_prs	7.30e-04	-1.03	-1.63	-0.43	2766	0.00701
mhc_class2_only_prs	4.01e-22	-2.58	-3.1	-2.07	2766	0.0362
CONFIRMED_prs	1.59e-15	-2.37	-2.96	-1.79	2766	0.0257
eA00_rs145954018	1.05e-17	-7.28	-8.94	-5.63	2766	0.0292
generic_rs9271597	8.37e-11	-2.89	-3.76	-2.02	2766	0.0181
eAOO_hap_carrier	3.36e-18	-7.71	-9.43	-5.98	2765	0.03

The MHC Class II only PRS (P=4.01e-22) is more strongly associated with age-of-onset than the confirmed PRS (P=1.59e-15). Nevertheless, there is modest association between the non-MHC Class II PRS and lower vitiligo age-of-onset, as we hypothesized (P=7.30e-04).

Note that the scaling is different for SNPs and for PRS, so the estimates are not directly comparable (for PRS, the estimate is interpreted as years per standard deviation of PRS, whereas for SNPs, it is interpreted as years per copy of SNP risk allele).



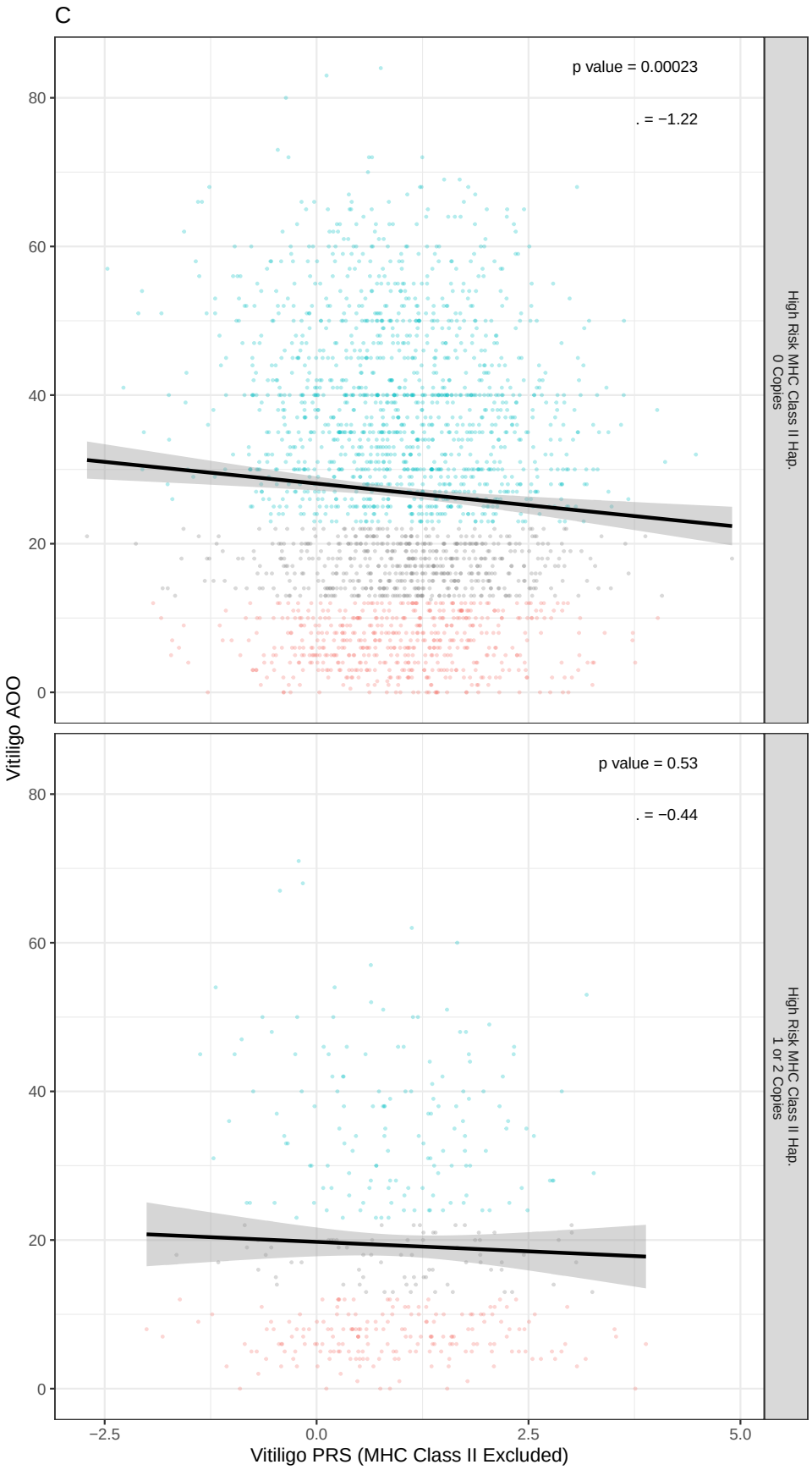

B
p value = 7.3e−04
. = −1.03
Vitiligo AOO
80
60
40
20
0
−2
0
2
4
Vitiligo PRS (MHC Class II Excluded)
AOO Category
Early AOO
Late AOO
NA

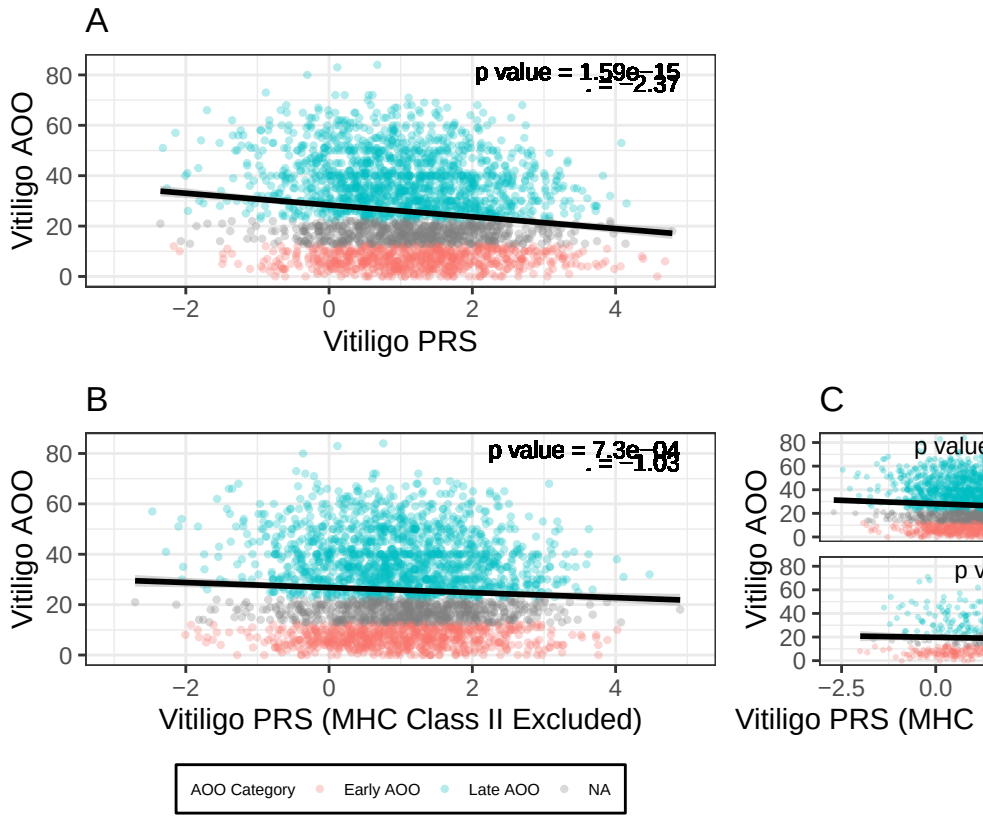
Stratified Association by High-Risk MHC Haplotype Carrier Status

Table 5: Stratified Association between PRS and Age-of-Onset in High Risk Haplotype Carrier Groups (continued below)

high_risk_MHC_haplotype_carrier	Phenotype	PRS	pval
1 or 2 Copies	VITageonset	no_mhc_classII	0.53
0 Copies	VITageonset	no_mhc_classII	0.00023

estimate	lower_ci	upper_ci	n_obs	adj_r_sq
-0.44	-1.82	0.94	408	0.0243
-1.22	-1.87	-0.57	2357	0.00827


C
p value = 0.00023
. = −1.22
High Risk MHC Class II Hap.
0 Copies
p value = 0.53
. = −0.44
High Risk MHC Class II Hap.
1 or 2 Copies
Vitiligo AOO
0
20
40
60
80
−2.5
0.0
2.5
5.0
Vitiligo PRS (MHC Class II Excluded)



Put all of the Figure 1 panels together. . .

AOO_category	high_risk_MHC_haplotype_carrier	n	sum	percent
early_onset	0 Copies	528	718	73.54
early_onset	1 or 2 Copies	190	718	26.46
late_onset	0 Copies	1285	1430	89.86
late_onset	1 or 2 Copies	145	1430	10.14

Stratified Association in Early and Late Onset Groups

Table 8: Stratified Association between PRS and Age-of-Onset in Early- and Late-Onset Groups (continued below)

AOO_category	Phenotype	PRS	pval	estimate	lower_ci
early_onset	VITageonset	no_mhc_classII	0.61	0.08	-0.22
late_onset	VITageonset	no_mhc_classII	0.2	-1.2	-3.04

upper_ci	n_obs	adj_r_sq
0.38	528	0.00867
0.64	145	0.044

Look at assocaition of PRS in MHC High Risk Haplotype Carriers

Table 10: Table continues below

Phenotype	PRS	term	pval
vitiligo	no_mhc_classII_prs_scaled	no_mhc_classII_prs_scaled	2.2e-42

estimate	std_error	OR	lower_ci	upper_ci
0.84	0.06	2.32	2.06	2.62

Compare non-MHC SNP effect estimates in early- and late-onset

Randomly downsample cases so that there are exactly 700 cases with early-onset and 700 cases with late-onset. Also randomly sample two sets of 700 cases each. Then, compute the association between each of the non-MHC lead GWAS variants and disease risk.

Table 12: Table continues below

estimate	estimate1	estimate2	statistic	p.value	parameter
0.06503	0.9677	0.9027	8.497	6.752e-15	182.3

conf.low	conf.high	method	alternative
0.04993	0.08012	Welch Two Sample t-test	two.sided

Table 14: Table continues below

estimate	statistic	p.value	parameter	conf.low	conf.high
0.9027	-15.81	7.742e-29	99	0.8905	0.9149

method	alternative
One Sample t-test	two.sided

Table 16: Table continues below

SNP	Locus	GWAS Reported Oveall OR
RS145954018	NA	NA
RS114448410	NA	NA
RS4268748	MC1R	1.374
RS2687812	SLA	1.212
RS2111485	IFIH1	1.34
RS12482904	UBASH3A	1.425
RS4308124	BCL2L11	1.17
RS35161626	UBE2E2	1.153
RS12771452	CASP7	1.2
RS10087240	PVT SNP	1.18
RS2247314	RNASET2-FGFR1OP-CCR6	1.258
RS1043101	CD44-SLC1A2	1.235
RS10986311	NEK6	1.158
RS6012953	PTPN1	1.163
RS71508903	ARID5B	1.182
RS9611565	ZC3H7B-TEF	1.283
RS72928038	BACH2	1.275
RS41342147	FARP2	1.255
RS60131261	HLA-A	1.532
RS34346645	FOXP1	1.248
RS11021232	Gene desert	1.381
RS78037977	FASLG	1.333
RS10200159	PPP4R3B	1.484
RS6059655	RALY-ASIP	1.583
RS706779	IL2RA	1.345
RS117744081	CPVL	1.949
RS1031034	PPP3CA	1.162
RS1126809	TYR	1.503
RS2476601	PTPN22	1.391
RS2017445	IKZF4	1.31
RS12421615	PLCB3-BAD-GPR137	1.152
RS231725	CTLA4	1.183
RS301807	RERE	1.224
RS16843742	PTPRC	1.226
RS13076312	LPP	1.318
RS2304206	IRF3-BCL2L12	1.221
RS229527	C1QTNF6	1.338
RS10774624	SH2B3	1.246
RS11079035	RAB5C	1.184
RS148136154	CD80	1.37
RS12203592	IRF4	1.193
RS35860234	TTBK2	1.158
RS78521699	SERPINB9	1.266
RS8192917	GZMB	1.23
RS4807000	TICAM1	1.19
RS1635168	OCA2-HERC2	1.426

SNP	Locus	GWAS Reported Oveall OR
RS6583331	NRROS	1.164
RS8083511	TNFRSF11A	1.237

Table 17: Table continues below

eAOO mean bootstrap OR	lAOO mean bootstrap OR
4.704	1.607
2.303	1.597
1.561	1.276
1.084	1.255
1.501	1.302
1.273	1.492
1.219	1.087
1.099	1.231
1.297	1.129
1.06	1.199
1.39	1.225
1.103	1.234
1.224	1.1
1.049	1.164
1.076	1.215
1.231	1.373
1.086	1.208
1.143	1.286
1.608	1.477
1.181	1.261
1.386	1.27
1.375	1.288
1.419	1.525
1.548	1.399
1.379	1.332
1.609	1.764
1.174	1.136
1.472	1.407
1.369	1.433
1.335	1.283
1.142	1.107
1.198	1.159
1.19	1.158
1.153	1.208
1.33	1.302
1.23	1.208
1.35	1.316
1.238	1.259
1.141	1.11
1.259	1.225
1.089	1.111
1.139	1.118
1.201	1.212
1.24	1.251
1.142	1.139

eAOO mean bootstrap OR	lAOO mean bootstrap OR
1.43	1.402
1.18	1.185
1.209	1.203

Table 18: Table continues below

Early AOO vs. Late AOO Effect Difference	Difference 95% CI Lower
1.067	1.033
0.3565	0.3392
0.2031	0.1814
-0.1434	-0.161
0.1445	0.126
-0.1558	-0.1766
0.1171	0.101
-0.1105	-0.1271
0.1373	0.1166
-0.1186	-0.1368
0.1313	0.1098
-0.1102	-0.129
0.1115	0.0921
-0.1039	-0.1234
-0.1091	-0.1307
-0.1196	-0.1437
-0.1058	-0.1295
-0.1226	-0.1524
0.07796	0.05816
-0.06833	-0.08618
0.08617	0.0634
0.06495	0.0375
-0.07294	-0.1051
0.09771	0.05301
0.03902	0.02115
-0.1036	-0.1525
0.04268	0.02195
0.03932	0.01901
-0.05057	-0.07696
0.03836	0.01834
0.0345	0.01573
0.03175	0.01239
0.0287	0.01068
-0.03714	-0.06115
0.02925	0.01009
0.02659	0.005174
0.02057	0.002087
-0.01905	-0.03742
0.0221	-0.001739
0.02097	-0.004074
-0.02254	-0.05194
0.01342	-0.006286
-0.01859	-0.05016
-0.01055	-0.03129

Early AOO vs. Late AOO Effect Difference	Difference 95% CI Lower
0.007041	-0.01113
0.01077	-0.02205
-0.004143	-0.022
0.001592	-0.02053

Table 19: Table continues below

Difference 95% CI Upper	Difference T Statistic	P-value
1.101	62.1	1.486e-113
0.3739	40.53	1.132e-94
0.2249	18.4	6.504e-44
-0.1258	-16.1	5.421e-36
0.1629	15.46	3.447e-35
-0.1351	-14.82	2.002e-32
0.1332	14.34	4.936e-31
-0.09391	-13.12	1.761e-28
0.1579	13.11	3.692e-28
-0.1004	-12.88	1.576e-27
0.1529	12.03	6.802e-25
-0.0913	-11.53	2.303e-23
0.1308	11.36	8.051e-23
-0.08428	-10.48	3.874e-20
-0.08747	-9.965	1.006e-18
-0.0955	-9.806	3.315e-18
-0.08199	-8.776	1.278e-15
-0.09292	-8.141	5.641e-14
0.09777	7.771	6.629e-13
-0.05048	-7.552	1.885e-12
0.1089	7.471	4.064e-12
0.09241	4.672	6.238e-06
-0.04081	-4.478	1.316e-05
0.1424	4.313	2.647e-05
0.05689	4.31	2.767e-05
-0.05462	-4.176	4.683e-05
0.06341	4.062	7.207e-05
0.05962	3.821	0.0001825
-0.02418	-3.782	0.0002138
0.05838	3.784	0.0002185
0.05327	3.624	0.0003688
0.05112	3.237	0.001456
0.04672	3.142	0.001959
-0.01312	-3.054	0.002645
0.04841	3.012	0.002963
0.048	2.45	0.01524
0.03905	2.196	0.02936
-0.0006772	-2.045	0.04221
0.04595	1.83	0.069
0.04601	1.652	0.1002
0.006858	-1.514	0.132
0.03312	1.344	0.1807
0.01298	-1.162	0.2468

Difference 95% CI Upper	Difference T Statistic	P-value
0.01019	-1.003	0.317
0.02521	0.7644	0.4456
0.04358	0.6475	0.5182
0.01372	-0.4577	0.6477
0.02371	0.1421	0.8872

Bonferroni Corrected P-Value
7.131e-112
5.436e-93
3.122e-42
2.602e-34
1.654e-33
9.611e-31
2.369e-29
8.454e-27
1.772e-26
7.563e-26
3.265e-23
1.105e-21
3.865e-21
1.86e-18
4.827e-17
1.591e-16
6.133e-14
2.708e-12
3.182e-11
9.047e-11
1.951e-10
0.0002994
0.0006318
0.001271
0.001328
0.002248
0.003459
0.008761
0.01026
0.01049
0.0177
0.06988
0.09404
0.127
0.1422
0.7315
1
1
1
1
1
1
1

Bonferroni Corrected P-Value
1
1
1
1
1

Table 21: Table continues below

SNP	mean_early_onset_vitiligo	se_early_onset_vitiligo
RS10087240	0.05808	0.05446
RS10200159	0.3497	0.1055
RS1031034	0.1601	0.06356
RS1043101	0.09845	0.05494
RS10774624	0.2133	0.05499
RS10986311	0.2021	0.05535
RS11021232	0.3263	0.06368
RS11079035	0.1316	0.06937
RS1126809	0.3865	0.06805
RS114448410	0.8344	0.05655
RS117744081	0.4754	0.1383
RS12203592	0.08542	0.08551
RS12421615	0.1328	0.05805
RS12482904	0.2412	0.06196
RS12771452	0.2598	0.06624
RS13076312	0.2854	0.05455
RS145954018	1.548	0.08546
RS148136154	0.2306	0.07674
RS1635168	0.358	0.09341
RS16843742	0.1424	0.0667
RS2017445	0.2889	0.05586
RS2111485	0.4064	0.05882
RS2247314	0.3294	0.06138
RS229527	0.3004	0.05452
RS2304206	0.207	0.0661
RS231725	0.1808	0.05679
RS2476601	0.3139	0.08276
RS2687812	0.08084	0.0544
RS301807	0.1737	0.05435
RS34346645	0.1665	0.05564
RS35161626	0.09485	0.05492
RS35860234	0.1304	0.05989
RS41342147	0.134	0.08555
RS4268748	0.4451	0.0693
RS4308124	0.198	0.0549
RS4807000	0.1331	0.05492
RS6012953	0.04761	0.05501
RS60131261	0.4748	0.05594
RS6059655	0.4368	0.1289
RS6583331	0.1657	0.05515
RS706779	0.3213	0.05577
RS71508903	0.07325	0.06719

SNP	mean_early_onset_vitiligo	se_early_onset_vitiligo
RS72928038	0.08278	0.07053
RS78037977	0.3184	0.07334
RS78521699	0.1834	0.09639
RS8083511	0.1896	0.06649
RS8192917	0.2149	0.06135
RS9611565	0.2079	0.06723

mean_late_onset_vitiligo	se_late_onset_vitiligo	predicted_early_onset
0.1818	0.05471	0.1642
0.4222	0.1032	0.3811
0.1272	0.06349	0.1148
0.2101	0.0549	0.1897
0.2305	0.05542	0.2081
0.09541	0.05608	0.08612
0.239	0.06574	0.2158
0.1043	0.07042	0.09417
0.3418	0.0676	0.3085
0.4679	0.05534	0.4224
0.5677	0.1342	0.5125
0.1051	0.08696	0.09486
0.1012	0.05818	0.09136
0.3998	0.06041	0.361
0.1211	0.06417	0.1093
0.2639	0.05491	0.2382
0.4743	0.1252	0.4282
0.2032	0.07807	0.1835
0.3382	0.09356	0.3053
0.1889	0.06812	0.1705
0.2494	0.05635	0.2252
0.2639	0.05768	0.2382
0.2028	0.05997	0.1831
0.2745	0.05477	0.2478
0.1888	0.06611	0.1704
0.148	0.05739	0.1336
0.3601	0.0819	0.325
0.2269	0.05479	0.2048
0.1471	0.05474	0.1328
0.2322	0.05635	0.2096
0.2078	0.05557	0.1876
0.1118	0.06032	0.1009
0.2516	0.09004	0.2271
0.2435	0.06614	0.2198
0.08322	0.05542	0.07513
0.1299	0.05541	0.1173
0.1518	0.05517	0.1371
0.3899	0.05687	0.352
0.3359	0.1255	0.3033
0.1699	0.05542	0.1534
0.2865	0.05574	0.2586
0.1945	0.06526	0.1756

mean_late_onset_vitiligo	se_late_onset_vitiligo	predicted_early_onset
0.1887	0.06872	0.1703
0.2528	0.07505	0.2282
0.1921	0.09753	0.1734
0.1846	0.06688	0.1667
0.2242	0.06152	0.2024
0.3172	0.06938	0.2863

Below, I have plotted the effect estimates in the early-onset and late-onset group together. If the other loci have generally equivalent effects in both groups, we expect that the points should generally fall around the y=x line (denoted in red). If, on the other hand, there is effect size dilution in the early-onset group, we expect that the slope will be <1.