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	1431	34.03	39.08	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

Associations with Vitiligo Risk (Case-Control)

Next, I wanted to verify that the associations looked as I would expect for each of the PRSs. So, I checked the association 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	1.74e-49	2.35	2.1	2.64
vitiligo	eAOO_hap_carrier	2.33e-49	2.43	2.16	2.74
vitiligo	generic_rs9271597	1.90e-97	1.84	1.74	1.95
vitiligo	mhc_class2_only	6.12e-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	9.05e-08	1.61	1.35	1.92
late_onset_vitiligo	eAOO_hap_carrier	2.22e-07	1.62	1.35	1.94
late_onset_vitiligo	generic_rs9271597	1.26e-31	1.59	1.47	1.71
late_onset_vitiligo	mhc_class2_only	1.08e-27	1.3	1.24	1.36
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).

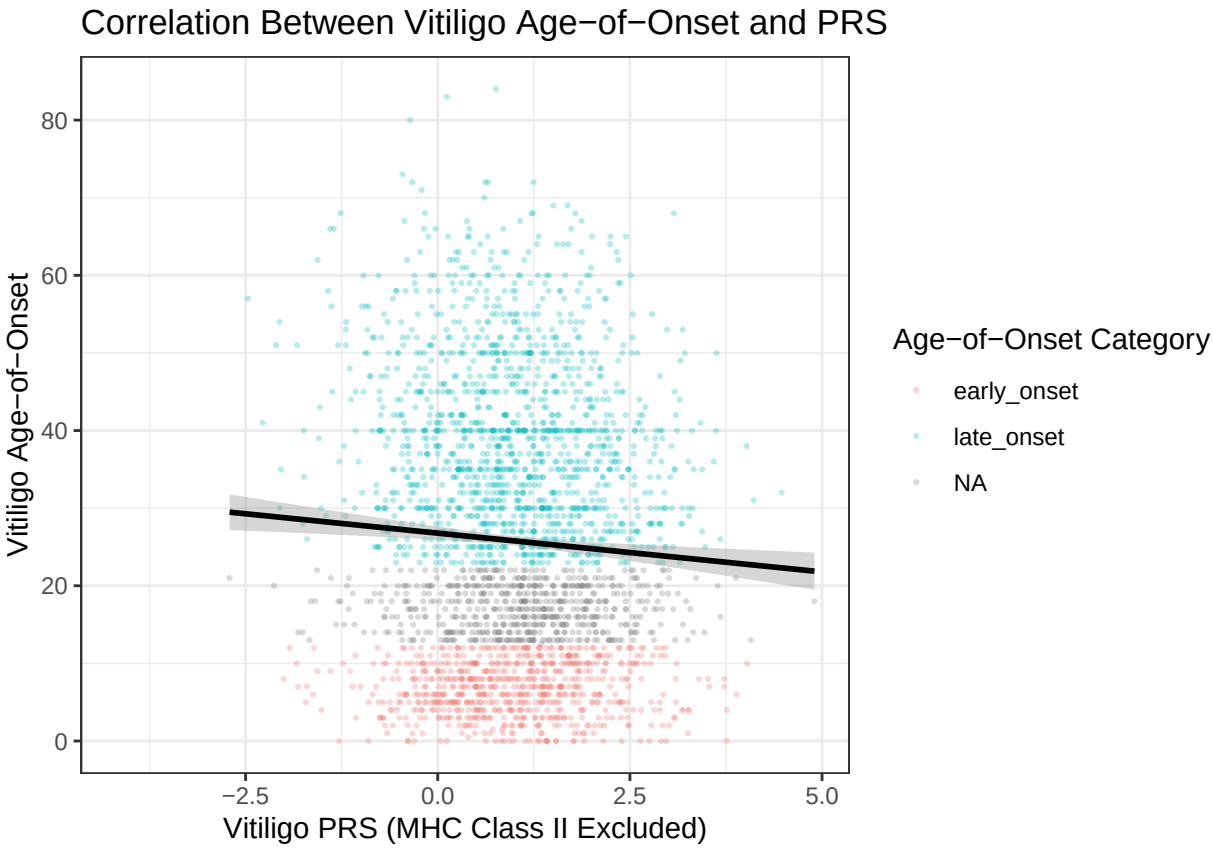
Associations with Vitiligo Age-of-Onset (Case Only)

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

Phenotype	PRS or SNP	pval	estimate	lower_ci	upper_ci
VITageonset	no_mhc_classII	7.30e-04	-1.03	-1.63	-0.43
VITageonset	mhc_class2_only	2.94e-22	-2.59	-3.11	-2.07
VITageonset	CONFIRMED	1.59e-15	-2.37	-2.96	-1.79
VITageonset	eA00_rs145954018	9.74e-18	-7.29	-8.94	-5.64
VITageonset	generic_rs9271597	6.32e-11	-2.91	-3.78	-2.04
VITageonset	eAOO_hap_carrier	3.12e-18	-7.71	-9.44	-5.99

Again, these results look about as I would expect: the MHC Class II only PRS is more strongly associated than the confirmed PRS. 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).



Interaction Test Between High-Risk MHC Haplotype and PRS (excluding MHC Class II SNPs)

My hypothesis was that the vitiligo PRS becomes less relevant when combined with the eAOO high-risk haplotype — essentially, that the genetic risk is already fairly saturated for individuals that carry the high-risk MHC Class II haplotype.

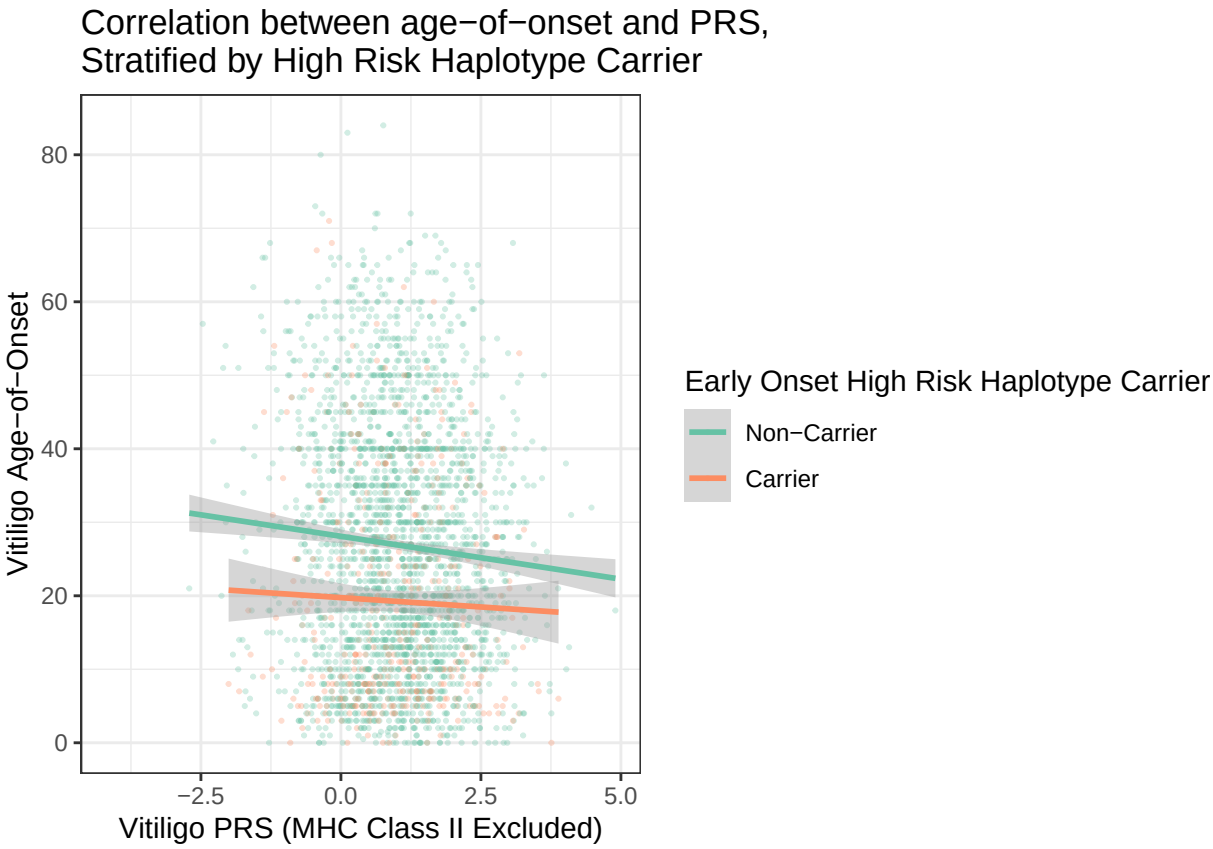
As a result, I expected to observe a correlation slope close to zero for age-of-onset ~ PRS in those *with* the eAOO haplotype, indicating a lack of association. Conversely, for those *without* the high-risk haplotype, I anticipated a correlation slope for age-of-onset ~ PRS significantly less than 1.

The interaction test, which compares slopes between carriers and non-carriers, serves as a formal assessment of this hypothesis. Notably, achieving statistical significance in an interaction test may have inadequate power, as a sample size of ~16X the sample size to detect the main effect is typically needed to detect an interaction effect.

Table 5: Table continues below

outcome	predictor	term
VITageonset	no_mhc_classII_prs_scaled	no_mhc_classII_prs:eAOO_hap_carrier

pval	estimate	std_error	lower_ci	upper_ci
0.38	0.73	0.83	-0.91	2.36



Although there is a trend towards a stronger negative slope for those that do not carry the high-risk eAOO haplotype relative to those that do carry the haplotype (consistent with our hypothesis), the difference is not significant (interaction P = 0.38).

Stratified Association in Early and Late Onset Groups

Due to power limitations in the interaction test, I performed a stratified analysis in the early- and late-onset groups separately.

Table 7: 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	5.34e-01	0.08	-0.17
late_onset	VITageonset	no_mhc_classII	1.36e-06	-1.41	-1.98

upper_ci
0.32
-0.84