Supplemental Data / Analysis

Comparison of SDM treatment to standard of care
Propensity matched Vestrum data

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Introduction

This report contains analyses of propensity score matched data from the Vestrum database.

Throughout, we use the labels "VPT" (Vision Protection Therapy) to indicate treated subjects, treated with standard of care and SDM laser as appropriate, and "SCA" (Standard Care Alone) to indicate the matched eyes from the Vestrum database.

The Vestrum database of 392,250 eyes with visits between 1/4/2016 and 9/30/2020 were initially filtered using study exclusion criteria to obtain a candidate set of 236,302 eyes, including 830 VPT eyes. The following Table outlines the filtering process.

Table 1. Initial filtering of Vestrum database.

Criteria Description	Total Excluded	Total Remaining
Total Number of Eyes in the Database		392,250
Include the eyes with age group 50+	3,594	388,656
Exclude the eyes diagnosed with Wet AMD prior to Dry AMD Diagnosis	38,417	350,239
Exclude the Unilateral Dry AMD Eye, if their fellow eye is Wet AMD	64,926	285,313
Exclude the Eyes Treated with Laser from SCA	4,217	281,096
Exclude the Eyes receiving Injection Before their First Laser	18	281,078
Exclude all patients with DME,DR,Type 1 or Type 2 diabetes mellitus	22,287	258,791
Exclude the eye with RVO Condition	9,469	249,322
Exclude the eyes who received any Injection Prior to the Dry AMD Diagnosis Date	426	248,896
Exclude the eyes with High Myopia, Histoplasmosis & Central Serous Chorioretinopathy	12,594	236,302
Total Number of Eyes Remaining in VPT		830
Total Number of Eyes Remaining in SCA after PS Matching(10:1 ratio)		8,300

After completion of the initial filtering, all VPT eyes were retained, and nearest-neighbor propensity score matching was used to obtain a matched set of control eyes from the SCA. The R Matchit package was used for the matching (R version 4.0.2, Matchit version 3.0.2).

Propensity scores were based on the following covariates:

Table 2. Variables used to perform propensity score matching

Variable
Age
Smoking status
AREDS vitamin use status
Hypertension status
Number of Encounters

Diagnostics from the matching indicated a good overlap of propensity scores between the two groups (see appendix).

The resulting analysis data comprise 830 VPT eyes (from 449 subjects) from the Luttrull practice and 8300 SC National eyes (from 6567 subjects, a 10:1 matched propensity score sample) from other practices within the matched Vestrum data.

Eyes were considered to have "converted" to wet AMD during the follow-up period if both of the following occurred:

- an ICD code for wet AMD was entered into the database
- anti-VEGF injections were initiated

The time of wet AMD conversion was the earliest of the date where the ICD code was entered or the date of the first anti-VEGF injection.

Baseline Tabulations

The following Table summarizes the demographics of the two Groups.

Table 3. Demographics by study group, after propensity score matching.

Factor Level	VPT	SCA
N (study eyes)	830	8300
N (subjects)	449	6567
Gender		
Female	279/449 (62.1%)	4081/6567 (62.1%)
Male	169/449 (37.6%)	2481/6567 (37.8%)
Not Recorded	1/449 (0.2%)	5/6567 (0.1%)
Age (years)		
Mean(SD)	77.0 (10.1)	76.6 (9.7)
Median	77.0	77.0
Min, Max	[50.0, 99.0]	[50.0, 100.0]
Age (category)		
Age: (50,65]	60/449 (13.4%)	870/6567 (13.2%)
Age: (65,70]	66/449 (14.7%)	965/6567 (14.7%)
Age: (70,75]	70/449 (15.6%)	1087/6567 (16.6%)
Age: (75,80]	72/449 (16.0%)	1101/6567 (16.8%)
Age: (80,85]	76/449 (16.9%)	1185/6567 (18.0%)
Age: (85,90]	73/449 (16.3%)	925/6567 (14.1%)
Age: (90,110]	37/449 (8.2%)	415/6567 (6.3%)
Hypertension		
No	199/449 (44.3%)	2769/6567 (42.2%)
Yes	250/449 (55.7%)	3798/6567 (57.8%)
AREDS use		
No	181/449 (40.3%)	2834/6567 (43.2%)
Yes	289/449 (64.4%)	3733/6567 (56.8%)
Smoking		
No	445/449 (99.1%)	6521/6567 (99.3%)
Yes	4/449 (0.9%)	46/6567 (0.7%)

Treatment and Raw Outcomes

The following Table summarizes followup and AMD treatments received.

Table 4. Follow-up and treatment summary by study group, after propensity score matching.

Factor Level	VPT	SCA
N (study eyes)	830	8300
Total Follow-up Days		
Mean(SD)	467.8 (484.3)	676.6 (553.8)
Median	330.0	659.0
Min, Max	[0.0, 1721.0]	[0.0, 1730.0]
Follow Up Years (categories)		
0 ≤ Follow Up Yrs ≤ 1	439/830 (52.9%)	3655/8300 (44.0%)
1 < Follow Up Yrs ≤ 2	171/830 (20.6%)	1473/8300 (17.7%)
Follow Up Yrs > 2	220/830 (26.5%)	3172/8300 (38.2%)
Number of Encounters		
Mean(SD)	9.0 (8.5)	9.2 (9.2)
Median	6.0	6.0
Min, Max	[1.0, 48.0]	[1.0, 63.0]
Treated with SDM Laser		
No	265/830 (31.9%)	N/A
Yes	565/830 (68.1%)	N/A
Number of Laser Treatments		
N	565	N/A
Mean(SD)	5.1 (3.7)	N/A
Median	4.0	N/A
Min, Max	[1.0, 18.0]	N/A
Converted to wAMD		
Yes	10/830 (1.2%)	1246/8300 (15.0%)
No	820/830 (98.8%)	7054/8300 (85.0%)

Survival analysis by PS Stratum

For conversion to wet AMD, the most appropriate method of analysis appears to be survival analysis using the initial diagnosis of dry AMD for the SCA group, or treatment for the VPT group, as time 0, and conversion to wet AMD as the outcome.

Note that other analysis methods were also carried out, but are not reported here (see the appendix for Poisson regression results). These alternative simpler methods produced the same general conclusions as the survival analysis.

The survival analysis was stratified by propensity score quintiles. That is, eyes were divided into five (nearly equal size) groups using the quintiles of the propensity scores.

The following plots show the survival curves by propensity score stratum.

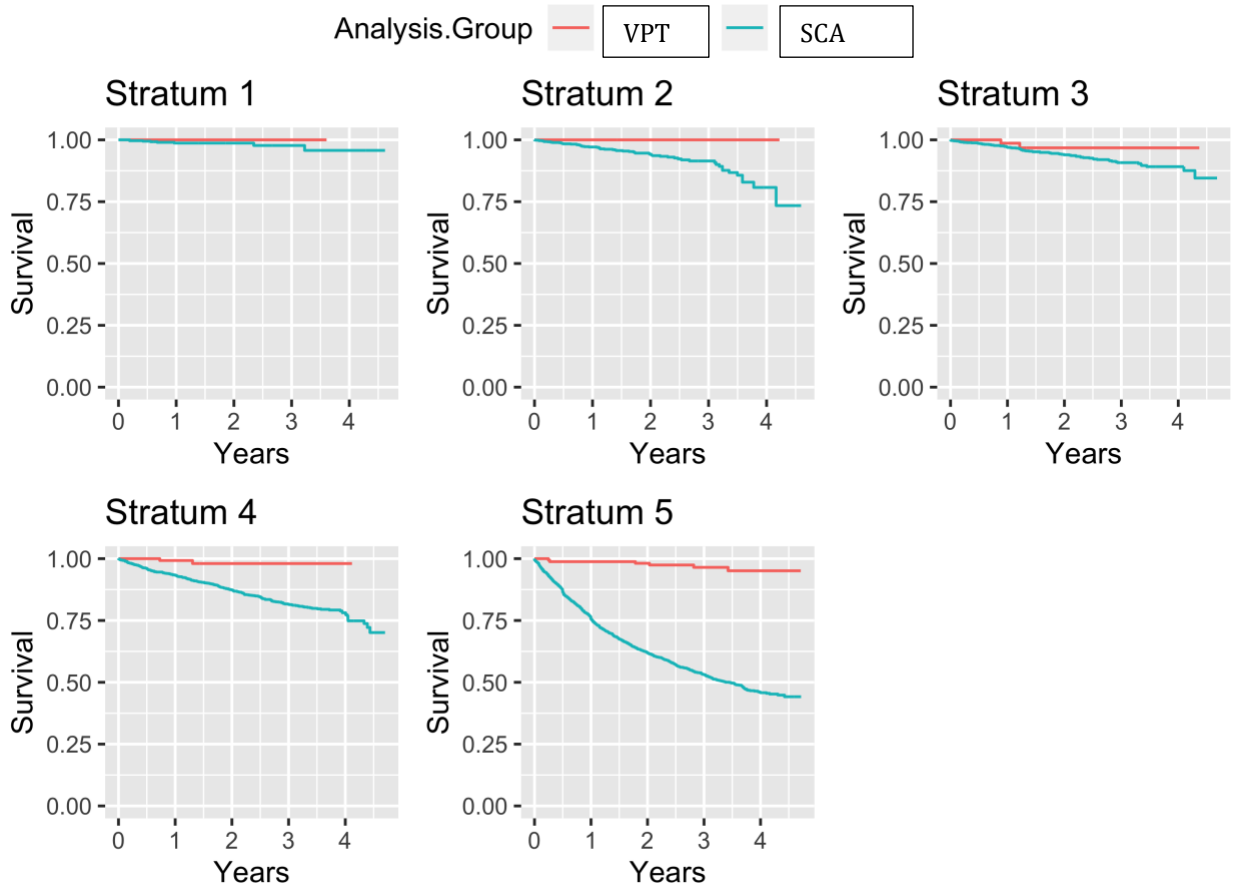

Figure 1. Kaplan-Meier survival plots by propensity score strata.

A test for equality of the survival curves (a stratified log-rank test) shows a very significant difference in survival between the VPT and SCA.

Table 5. Kaplan-Meier test between Groups, stratified by propensity score quintiles. Chisq = 110.148264 on 1 degrees of freedom, p = 0.000000

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
Analysis.Group=VPT	830	10	117.6	98.49	110.1
Analysis.Group=SCA	8300	1246	1138	10.18	110.1

Now we carry out a Cox proportional hazards regression, again stratified by propensity score quintiles.

A test for the proportional hazards assumption shows no strong evidence of non-proportionality (cox.zph(), p = 0.811). Also (see appendix), various diagnostic plots indicate that the Cox PH model appears to fit the data well.

A summary of the survival analysis shows an overall hazard ratio of 13.04.

Table 6. Cox PH summary of survival difference.

	coef	exp(coef)	se(coef)	z	p
Analysis.GroupSC National	2.568	13.04	0.3177	8.084	6.661e-16

Likelihood ratio test=177.3 on 1 df, p=0 n= 9130, number of events= 1256

Summary of Survival Fits

The following plot shows the overall cumulative wet AMD conversion probabilities by group.

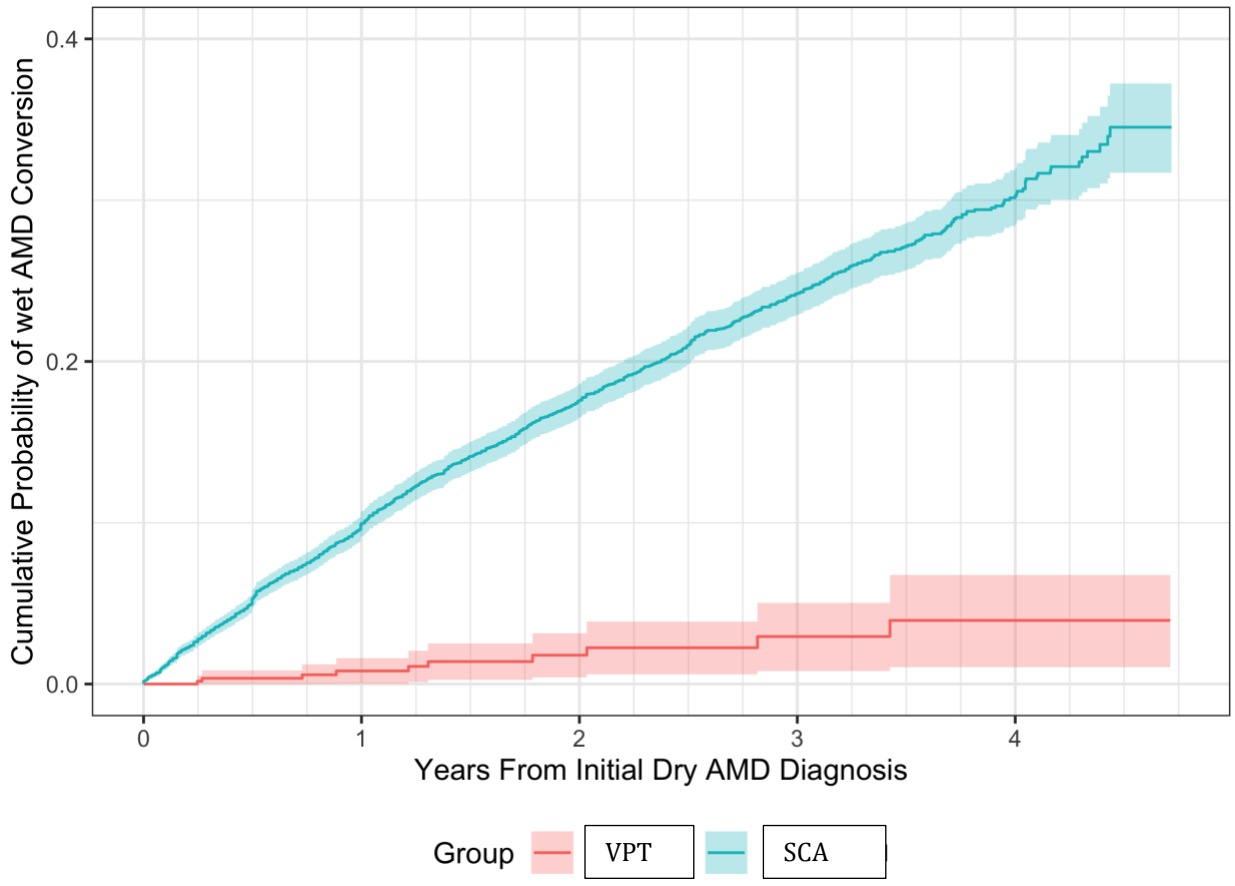

Figure 2. Overall Kaplan-Meier cumulative wet AMD conversion probability by group. Shaded areas indicate 95% confidence intervals.

The following Table shows the cumulative probability of progressing to wet AMD, by year and group.

Table 8. Summary of overall survival by group (unstratified Kaplan-Meier estimates).

Analysis Group	Years From DAMD Diagnosis	n at risk	n events	Cumulative Probability of wet AMD	95% CI
VPT	1	391	4	0.8%	[0.0%, 1.6%]
	2	220	3	1.8%	[0.4%, 3.1%]
	3	123	2	2.9%	[0.8%, 5.0%]
	4	40	1	3.9%	[1.0%, 6.8%]
SCA	1	4645	583	10.0%	[9.2%, 10.7%]
	2	3172	344	17.6%	[16.5%, 18.6%]
	3	1798	209	24.2%	[22.9%, 25.5%]
	4	515	93	30.3%	[28.5%, 32.0%]

The hazard ratio between the two groups is summarized in the following Table. Since there are multiple eyes per person, a clustered bootstrap (clustered by subject) was used to provide a robust check on the confidence interval. The lower bound on the 95% confidence interval for the hazard ratio is above 5 using either method, again providing strong evidence for a hazard ratio greater than 1.

Table 9. Cox proportional hazards estimated hazard ratio and associated confidence intervals. Cox PH model is stratified by propensity score quartiles.

Estimated Hazard Ratio	95% CI (asymptotic)	95% CI (bootstrap[1])
13.0	[7.0, 24.3]	[5.5, 18.5]

1-Bootstrap confidence interval is based on 4,000 cluster (subject level) bootstrap samples.

Visual Acuity

Visual acuity (ETDRS letters or the equivalent) was measured for a subset of subject visits (usually non-treatment visits). The SC National group averaged about 1025.7 VA measurements per month, the SC+SDM group averaged 52.1.

A tabulation of the mean VA by year shows a slight downward trend for the SCA (perhaps due to aging?) but no obvious differences between the two groups.

Table 12. Mean visual acuity (ETDRS letters or equivalent) by Group and Year.

Analysis Group	Mean VA 2016	Mean VA 2017	Mean VA 2018	Mean VA 2019
VPT	78.9	80.8	78.4	81.2
SCA	82.5	82.1	80.5	78.9

The following plot shows the mean VA per month for the SCA and VPT subjects. As expected there is more noise in the much smaller VPT group. Given the amount of noise it is difficult to assess whether there are any differences in VA through time.

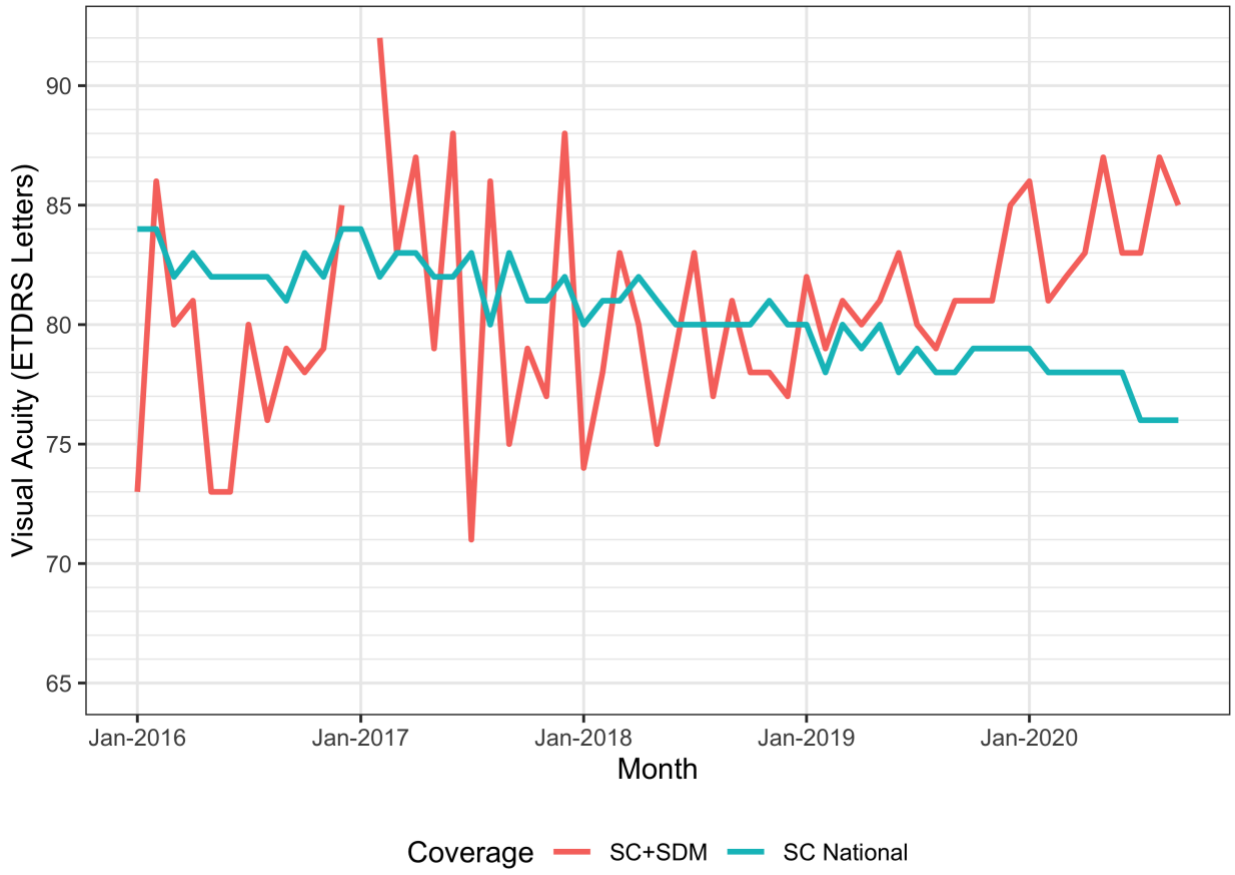

Figure 3. Visual Acuity by month, SC National, SC+SDM Groups.

A loess smoother does not show any clear systematic differences between the two groups. Perhaps the VPT group is showing increasing VA relative to the SCA?

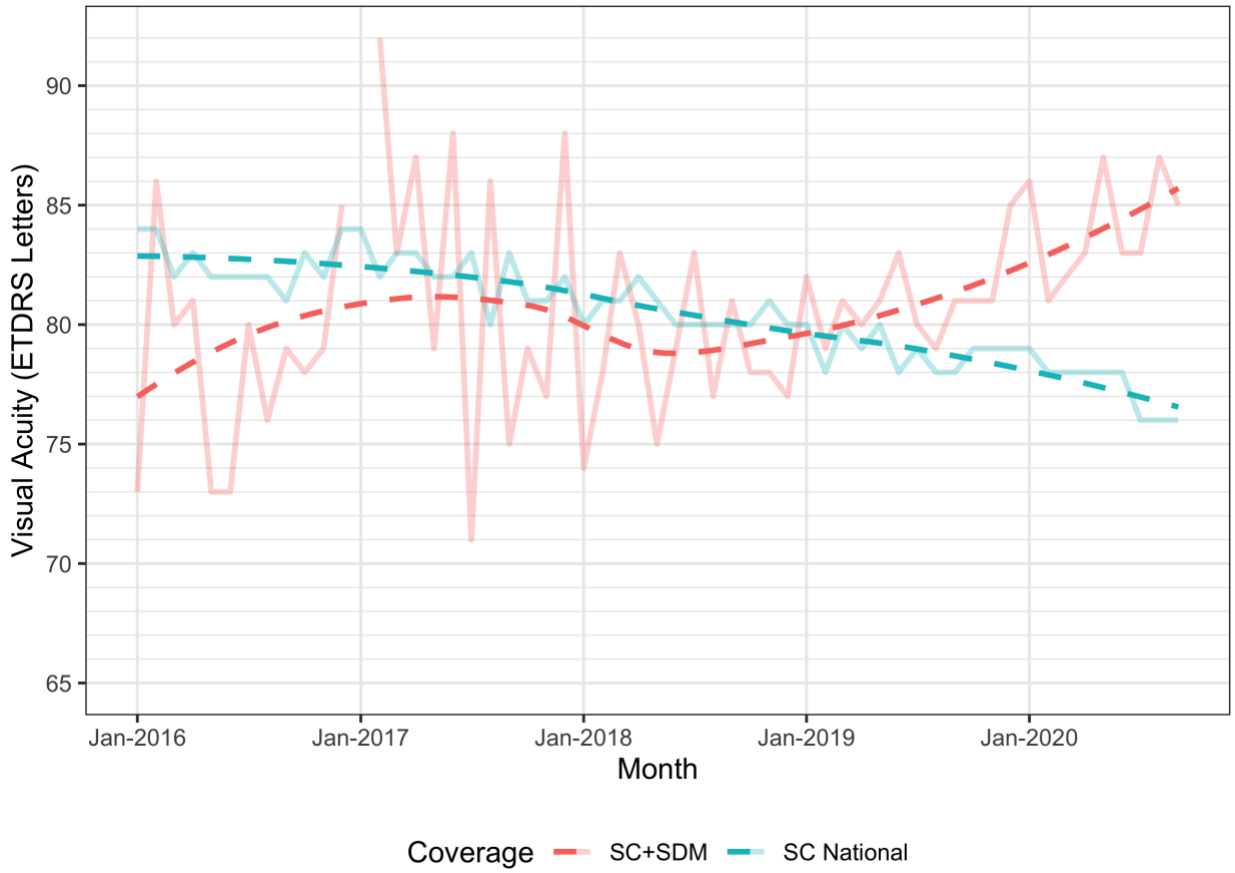

Figure 4. Visual Acuity by month, SCA, VPT Groups, with loess smooths.

Appendix I. Primary analysis with propensity matching including encounter frequency

This appendix includes diagnostic plots and alternative analyses.

Distribution of Follow-Up Time

The following plot shows the follow-up time by group and wet AMD status.

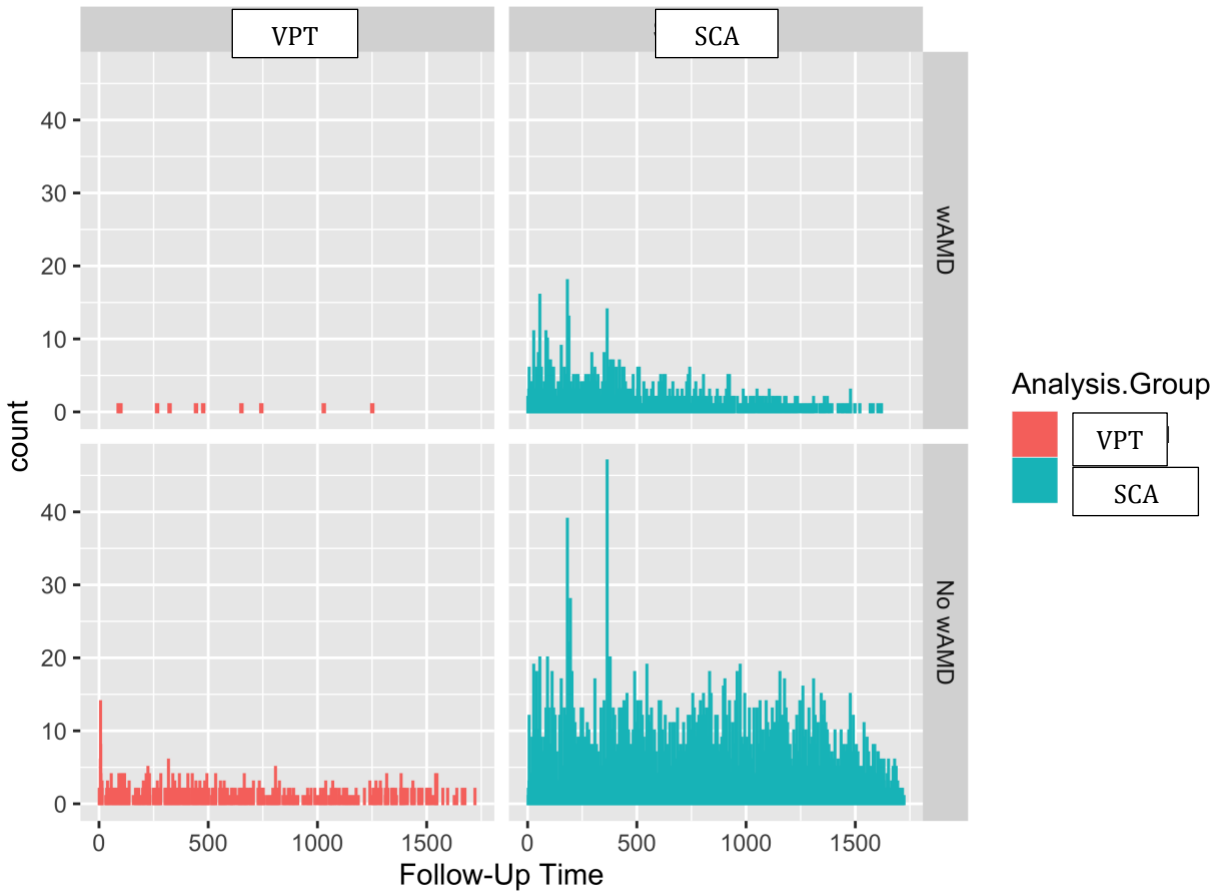

Figure 5. Follow up time by study group and wAMD conversion status. Subjects with 0 days follow-up are excluded.

Diagnostic Plots for Propensity Scores

Propensity score diagnostic plots look good overall. The overall distributions for the propensity scores are quite similar.

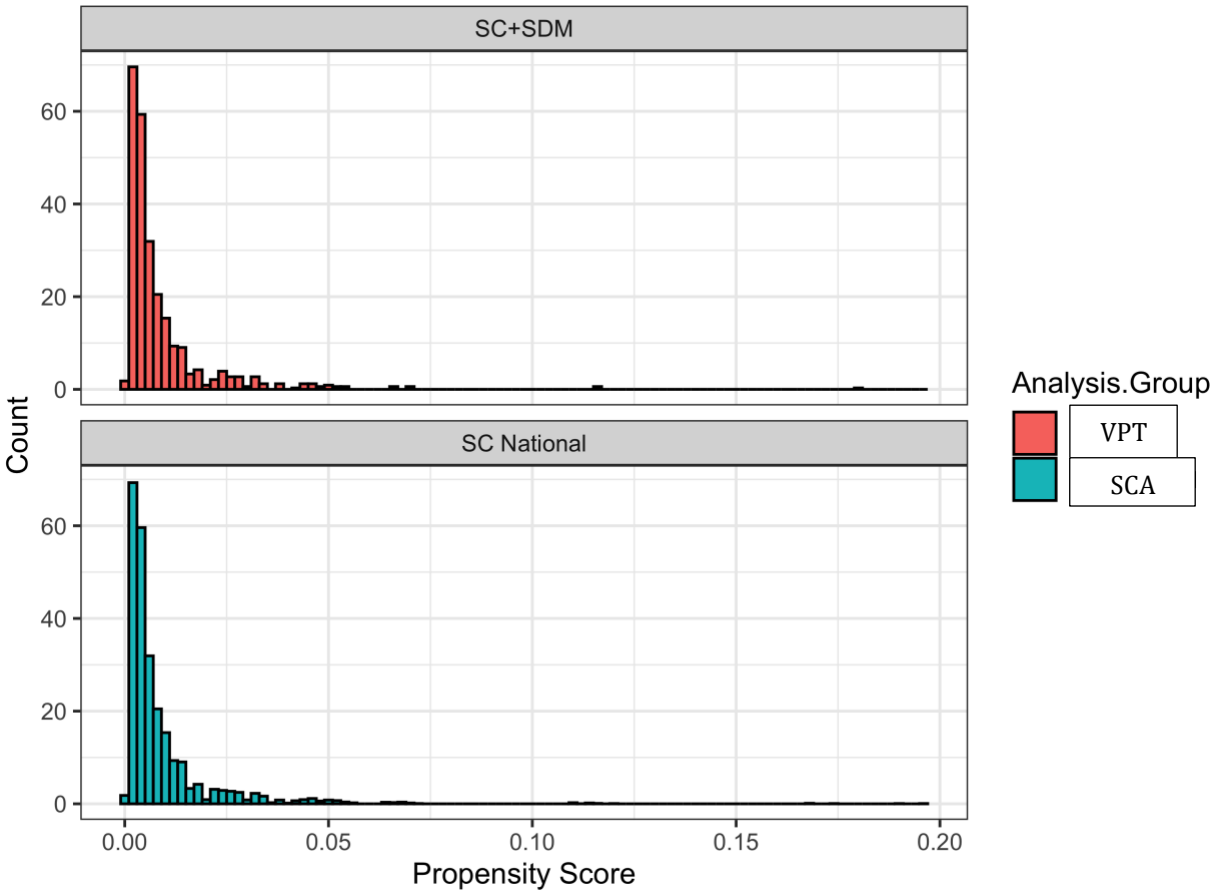

Figure 6. Diagnostic plots for propensity scores, overall distribution.

Propensity scores are also similar within each PS stratum.

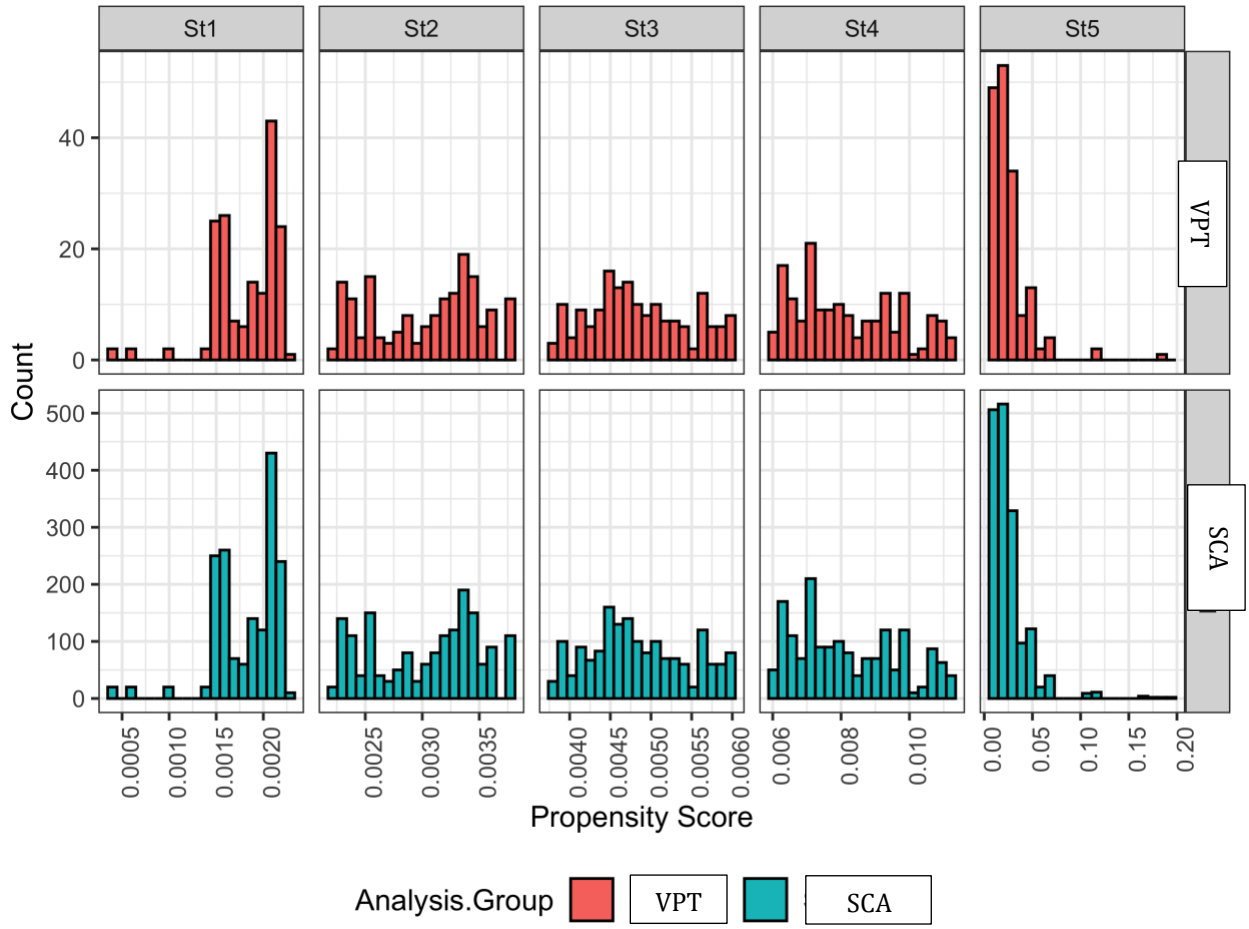

Figure 7. Diagnostic plots for propensity scores, distribution by PS stratum.

Each individual component also looks good. What we want to see is that within each stratum the two groups are similar (e.g. the pairs of orange and yellow bars have good overlap, the pairs of green bars are similar height).

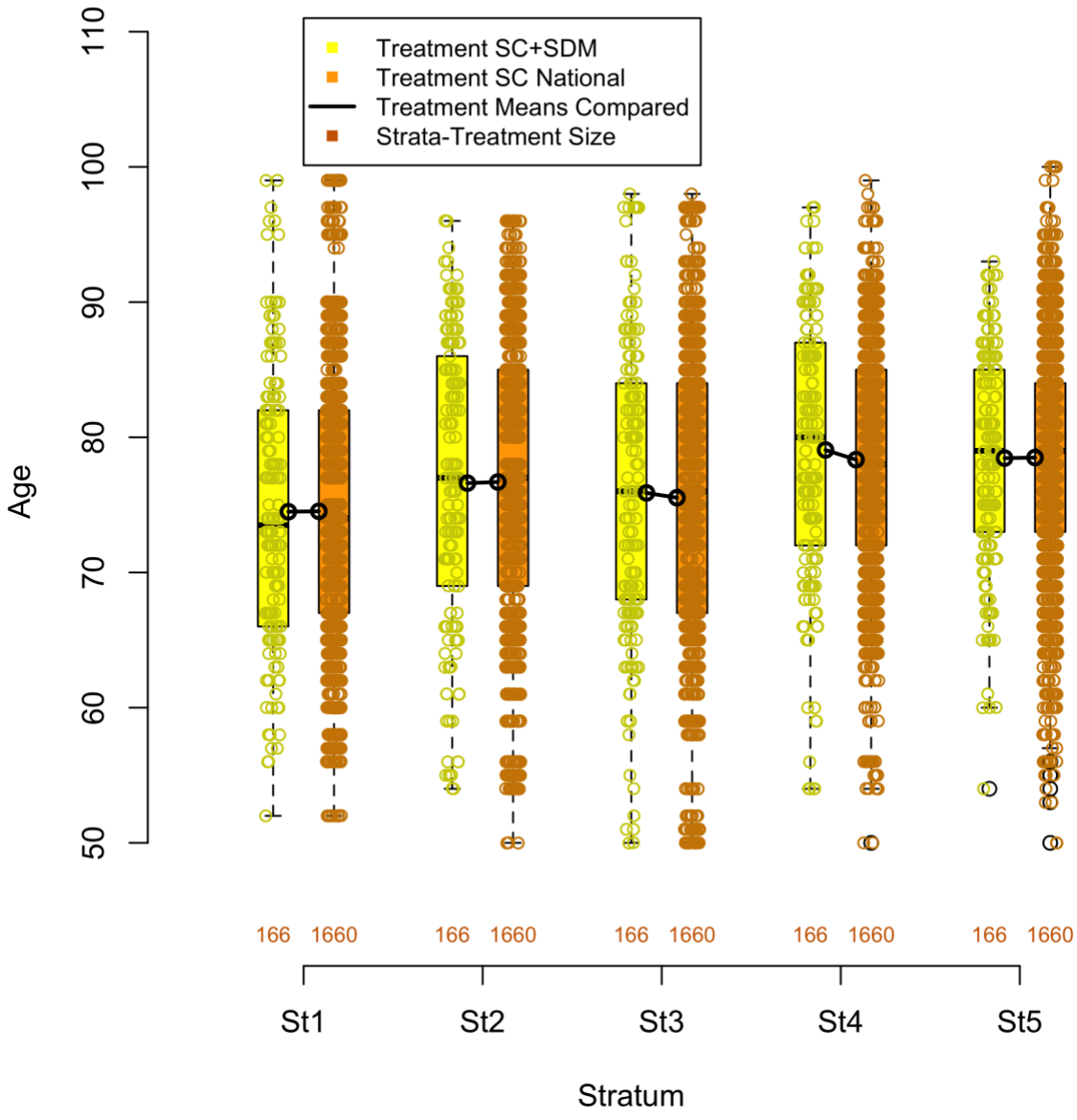

Figure 8. Diagnostic plots for propensity scores, age. SC+SDM = VPT. SC National=SCA

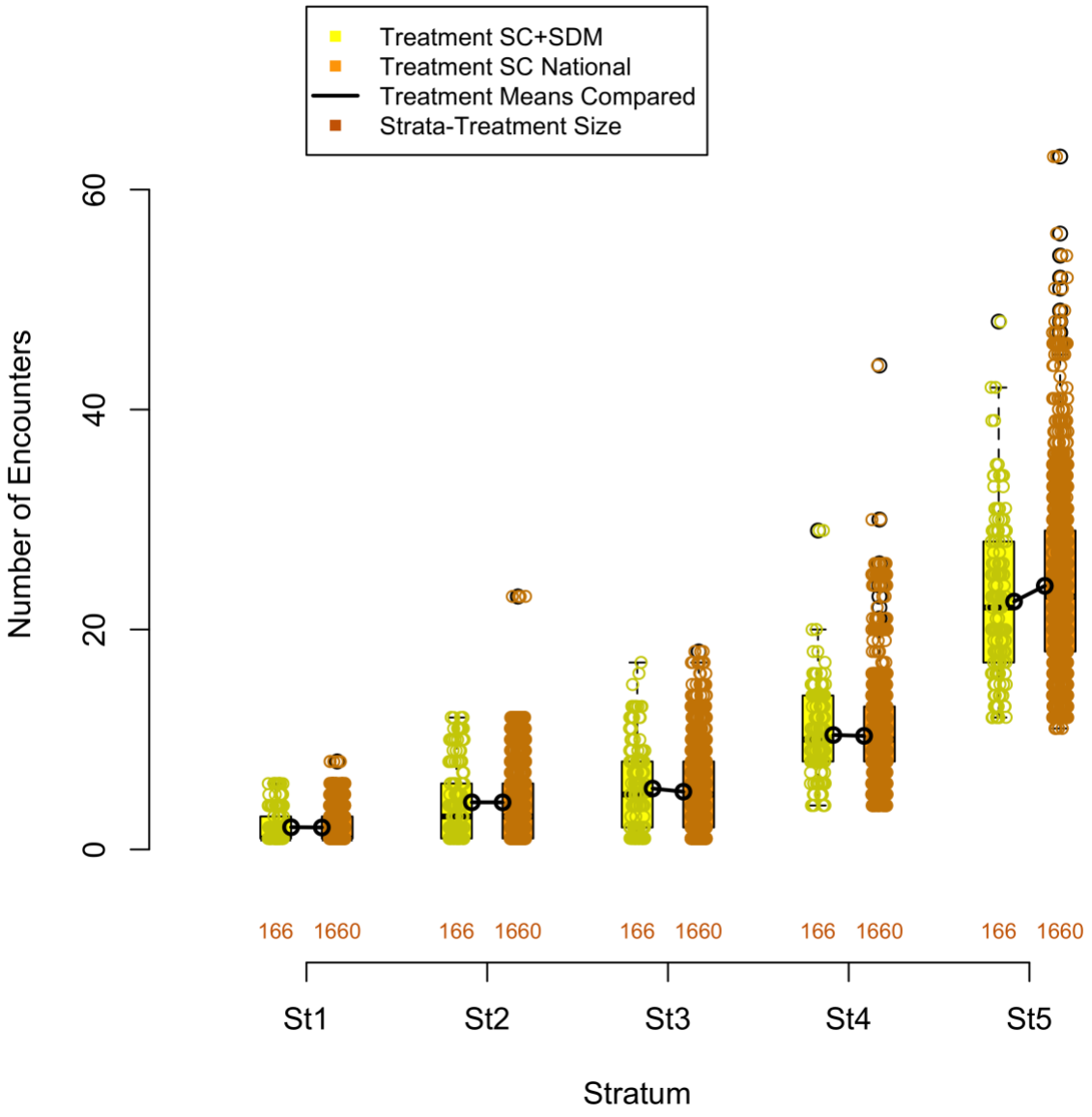

Figure 9. Diagnostic plots for propensity scores, number of encounters. SC+SDM = VPT. SC National = SCA

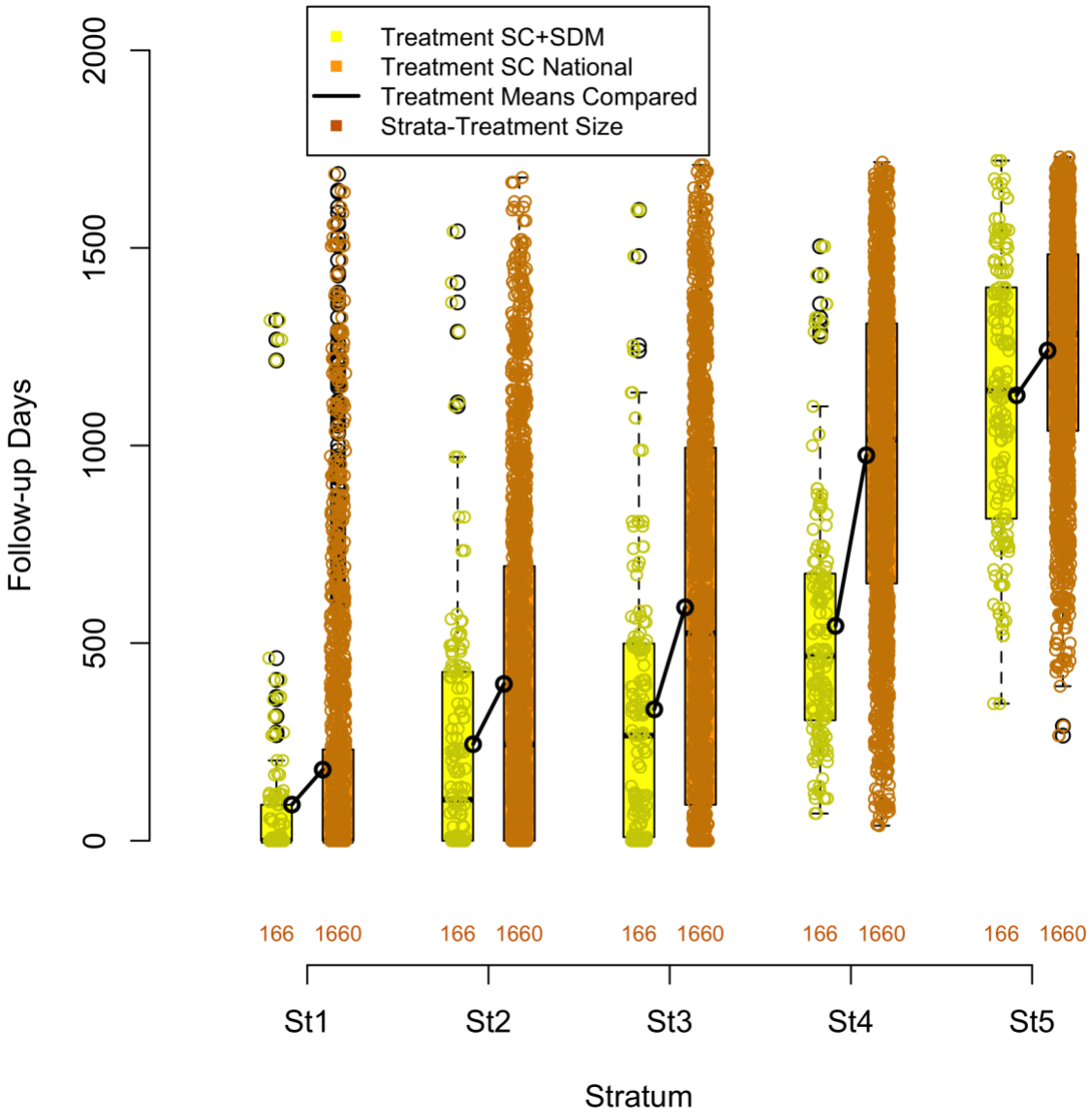

Figure 10. Diagnostic plots for propensity scores, follow-up days. SC+SDM = VPT. SC National = SCA

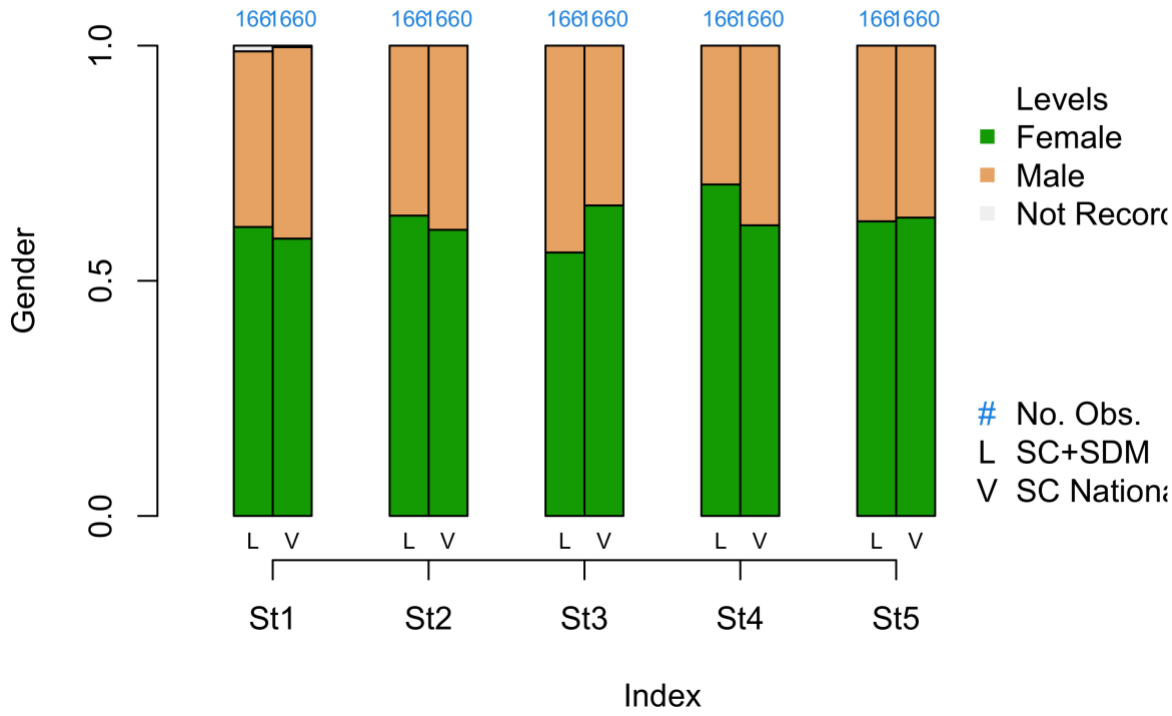

Figure 11. Diagnostic plots for propensity scores, gender. SC+SDM = VPT. SC National = SCA

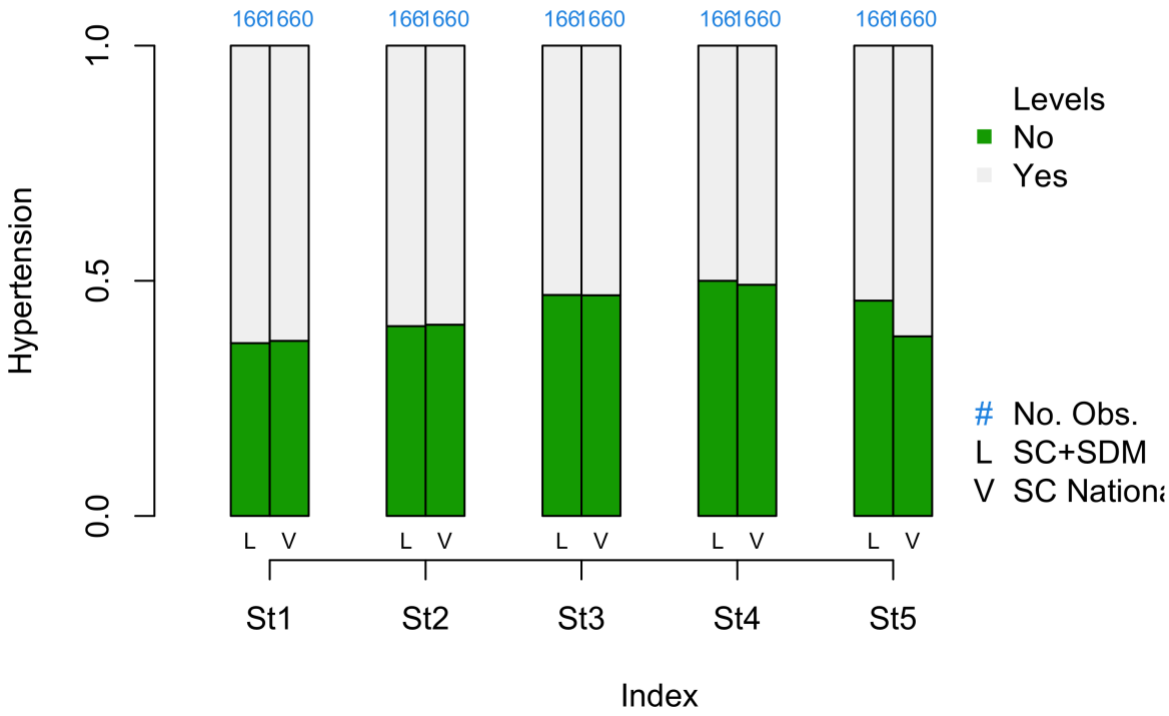

Figure 12. Diagnostic plots for propensity scores, hypertension. SC+SDM = VPT. SC National = SCA

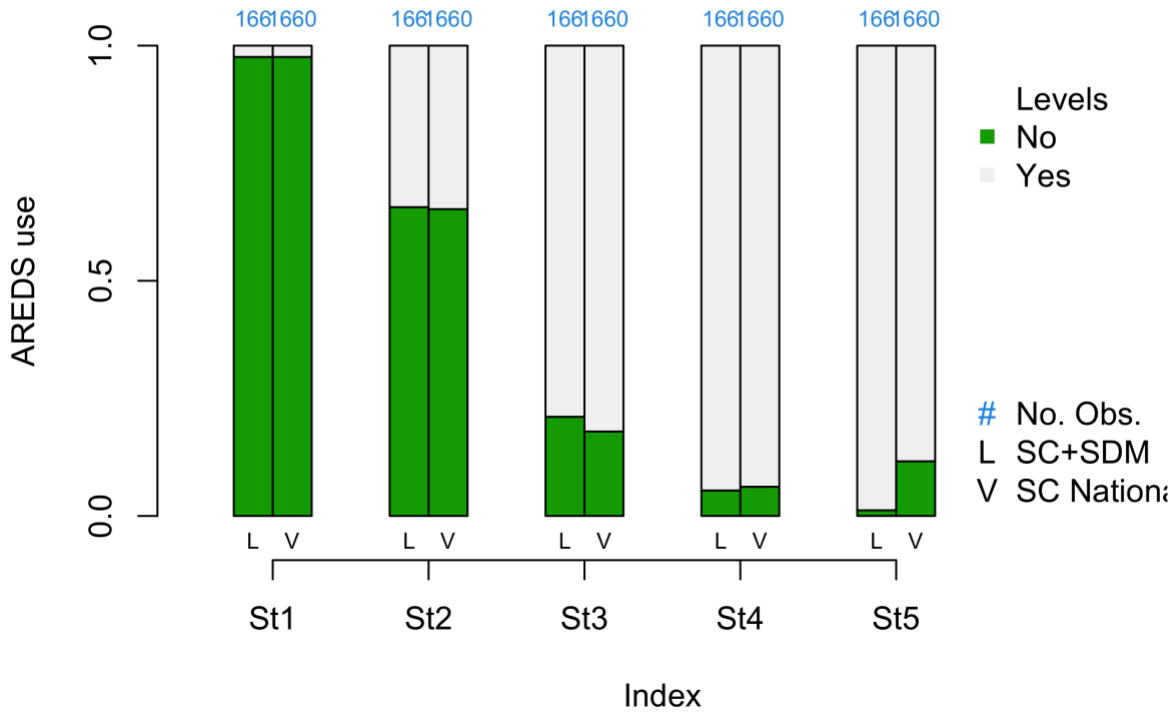

Figure 13. Diagnostic plots for propensity scores, AREDS use. SC+SDM = VPT. SC National = SCA

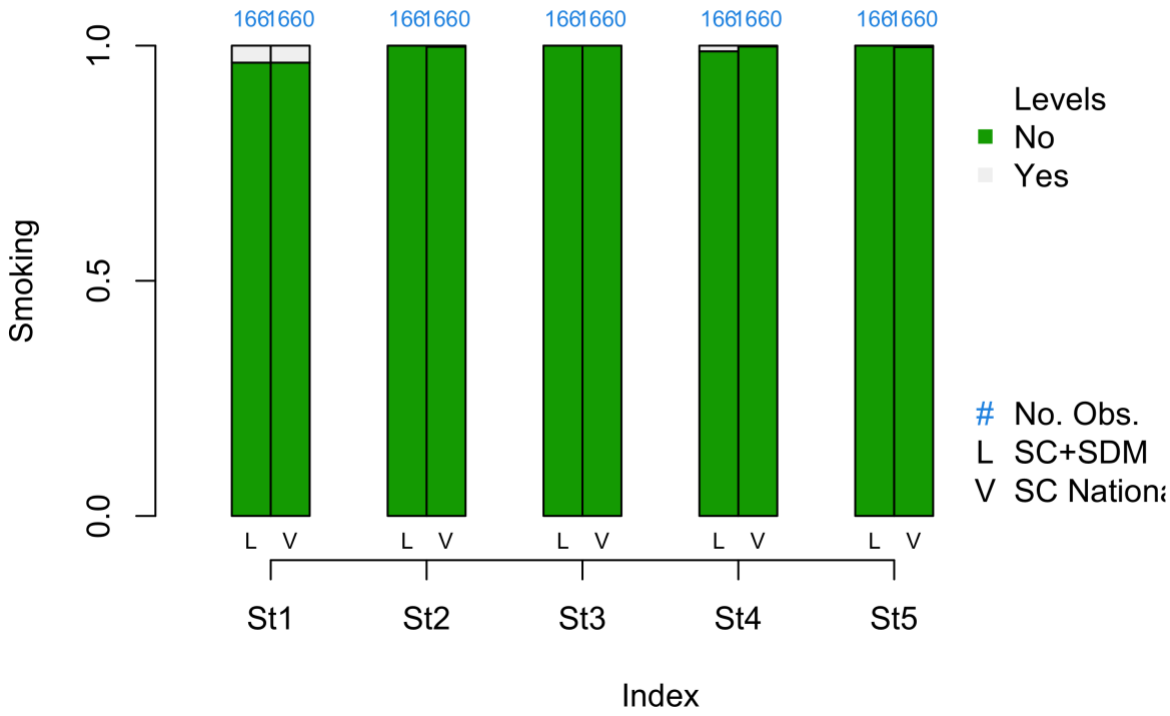

Figure 14. Diagnostic plots for propensity scores, smoking. SC+SDM = VPT. SC National = SCA

Incidence Rates via Poisson Regression

As a simpler alternative to the survival analysis, we can fit a poisson regression model. Poission regression adjusts for the follow-up on each eye individually, so corrects the bias in incidence rates somewhat. We can also easily account for the propensity score strata.

Fitting generalized (poisson/log) linear model: Converted.to.wAMD.n ~ Analysis.Group + PSStratum + offset(Follow.up.Years)

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-9.165	0.4743	-19.32	3.384e-83
Analysis.GroupSC National	2.577	0.3177	8.112	4.977e-16
PSStratumSt2	1.405	0.3757	3.739	0.0001845
PSStratumSt3	1.128	0.3698	3.05	0.002285
PSStratumSt4	1.717	0.3586	4.789	1.677e-06
PSStratumSt5	2.782	0.3553	7.831	4.854e-15

Table 13. Incidence rates from poisson regression (correcting for unequal follow-up in data, and adjusting for stratum differences.)

Analysis.Group	incidence rate	std.error	df	z.ratio	p.value
VPT	0.001161	0.0003784	Inf	-20.74	1.6e-95
SCA	0.01528	0.001214	Inf	-52.63	0

The incidence rate ratio from this fit is 13.2.

Diagnostic Plots for Cox PH Model

The following plots are diagnostics from the Cox proportional hazards fit.

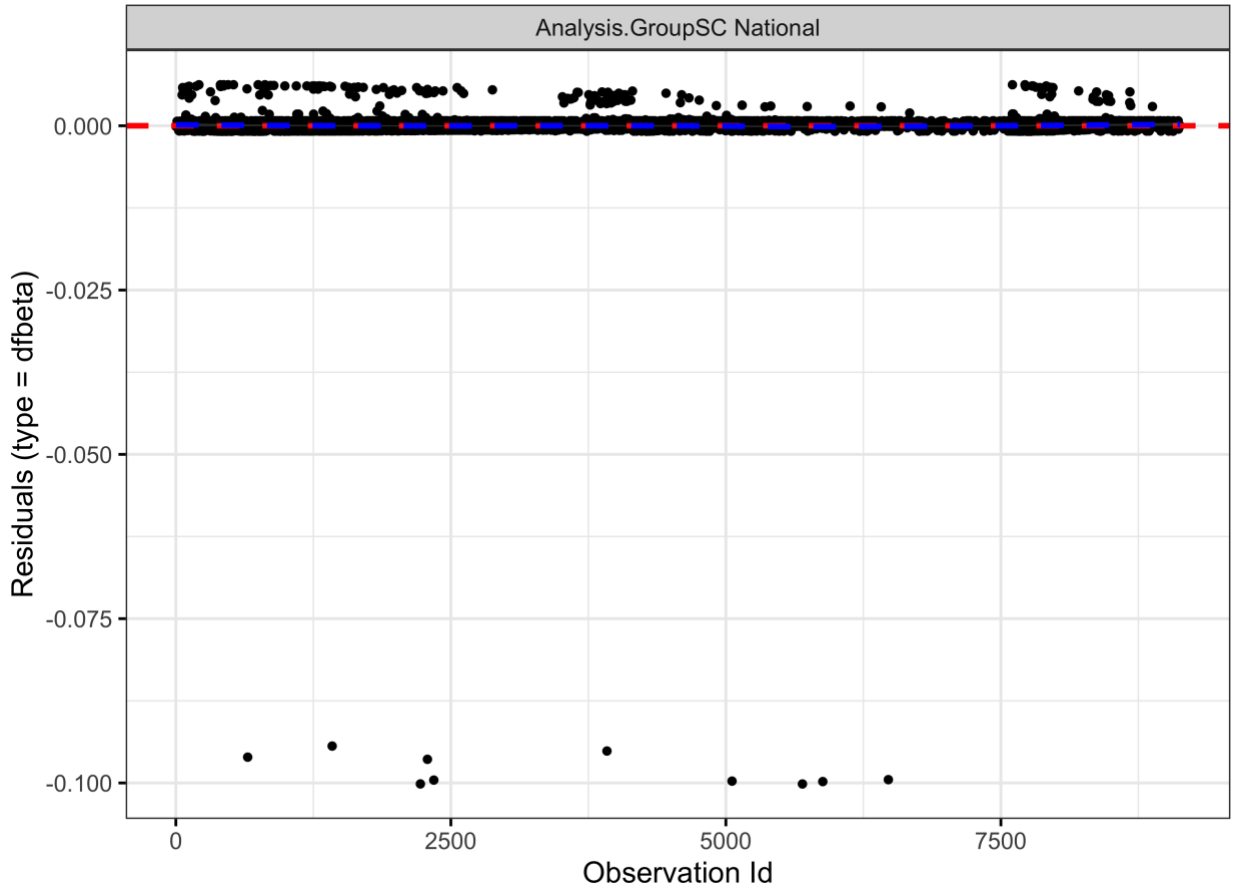

Figure 15. Dfbeta residuals from Cox PH fit. SC National = SCA

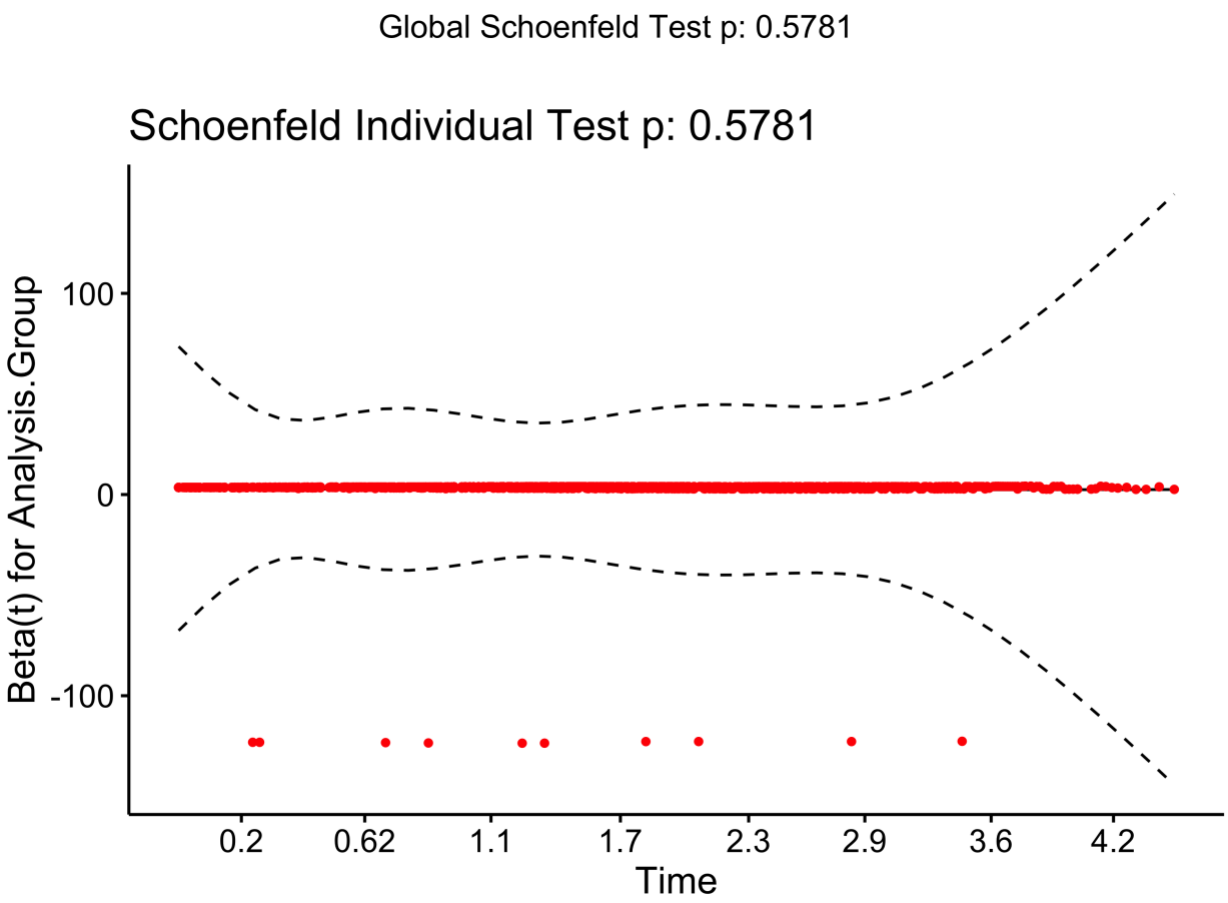

Figure 16. Scaled Schoenfeld residuals vs Time.