Title: Hand grip strength as a predictor of sarcopenia in COPD: an analysis of the UK Biobank

Name: Amy Attaway

Co-investigators:

Joe Zein, MD – has experience with analyzing the UK biobank and has extensive experience with genetic epidemiology studies.

Umur Hatipoglu, MD – the head of the COPD center at Cleveland Clinic with significant clinical expertise with COPD.

Srinivasan Dasarathy, MD – my primary mentor and a physician scientist analyzing the mechanisms of sarcopenia or skeletal muscle loss in chronic diseases like COPD.

Background:

COPD is the 4th most common cause of death in the United States. Sarcopenia, or skeletal muscle loss, afflicts 20-40% of COPD patients and is a major systemic comorbidity that adversely affects survival and physical function. For patients with COPD, skeletal muscle loss can cause symptoms of fatigue and shortness of breath, and can be mistaken for symptoms of airway obstruction. Screening for skeletal muscle loss could be performed on an outpatient basis using handgrip strength testing, which is a simple test that could be used to predict evidence for skeletal muscle loss in order to target those who require interventions like pulmonary rehabilitation.

Objective:

Our study will determine compare handgrip strength in patients with COPD and those without COPD.

Research Question:

Are reductions in handgrip strength associated with COPD (as compared to those without COPD)?

Participants:

The UK biobank is a large long-term study in the United Kingdom which is investigating the respective contributions of genetic predisposition and environmental exposure (including nutrition, lifestyle, medications etc.) to the development of disease. This database has extensive information on anthropomorphic measures including bioelectric impedance, which is one of the most accurate ways to measure sarcopenia and is only performed in research studies. Participants in this study will have a spirometric diagnosis of COPD (based on an FEV1/FVC ratio <0.70). They must also be former smokers. Spirometry must meet acceptability criteria as determined by ATS/ERS criteria. We will exclude those with concurrent asthma or other chronic lung diseases. Those in the control group must also be former smokers. Only adult participants with an age >40 years will be included, as the diagnosis of COPD is less likely in those younger than 40. Because 89% of the UK biobank is Caucasian, we will exclude other races. We will also exclude pregnant women. Our data will include 500 in the COPD group and 2000 in a random sample healthy non-COPD subjects matched for age, sex, and other covariates. This is a retrospective cohort study.

The Exposure:

The exposure will be COPD versus non-COPD. We will compare the COPD group to a non-COPD group. We will plan to have 500 in the COPD group and 2000 in the control group. Subjects with missing data of handgrip strength will be excluded.

The Outcome(s):

The primary outcome is handgrip strength. This is a quantitative variable with kilograms as the unit of measurement.

The Covariates:

The covariates to assist in building the model will include are age, sex, BMI, employment, current tobacco smoking, pack years of smoking, alcohol intake frequency, alcohol addiction, alcohol dependence, substance abuse history, diabetes, cirrhosis, heart failure, renal failure, diagnosis of cancer and what type (in situ / metastatic / uncertain / none), IPAQ activity group based on metabolic equivalent minutes per week, metabolic minutes per week, basal metabolic rate, fat free mass index (a measure of skeletal muscle mass), appendicular skeletal muscle index (a measure of skeletal muscle mass in the extremities). Current smoking status must be matched with controls in particular because current smoking status also causes chronic inflammation which can lead to its own reductions in handgrip strength. The covariates were all measured prior to the decision about applying the exposure of interest.

Getting the Data Set:

This dataset was received in collaboration with an ongoing study by Dr. Zein analyzing the genetic mechanisms of asthma in the UK biobank. We applied to the UK biobank to receive permission to use this data for an analysis of COPD and skeletal muscle loss and our application was accepted by them.

Planned Methods:

Statistical Methods: Appropriate graphical and numerical data summaries across the COPD versus non COPD groups will be performed, followed by propensity score matching and weighting methods to address selection bias. For outcomes analysis, our primary tool will be linear regression on propensity-matched pairs, as well as propensity-weighted (double robust) comparisons of handgrip strength between the COPD and non COPD groups.

Hand grip strength as a predictor of sarcopenia in COPD: an analysis of the UK Biobank

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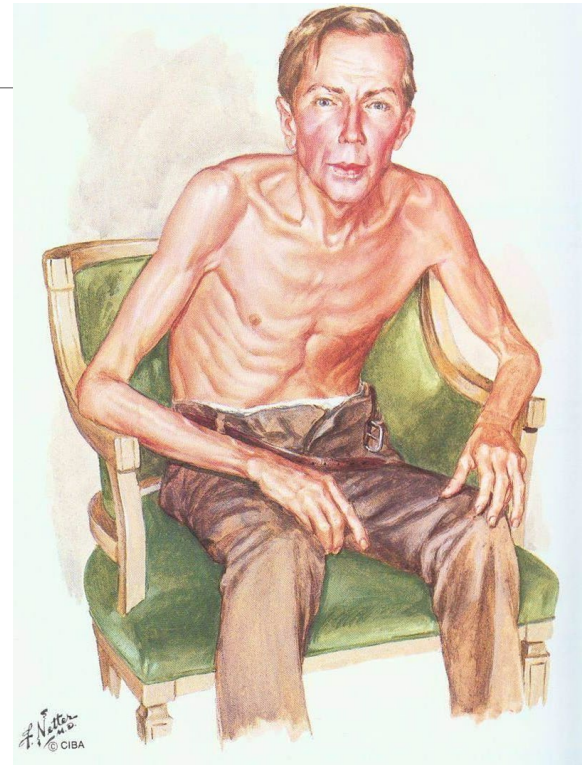
Background

COPD (chronic obstructive pulmonary disease) is a disease of chronic inflammation due to smoking, which has been known to cause skeletal muscle loss or sarcopenia in advanced disease.

HGS (handgrip strength) is a simple measure of upper limb muscle function that can be performed at a clinic visit.



Research question

Is lower handgrip strength associated with a diagnosis of COPD as compared to a propensity matched cohort of subjects without COPD?

Data source

A prospective study of 502,536 adults from the United Kingdom. Goal is to improve the care of many serious and life-threatening conditions.

Participants answered questions about their illnesses, dietary intake, and SES factors. They underwent a physical exam and provided biologic samples during their baseline visit.

Spirometry measurements and handgrip strength were available on majority of participants.

Participants

- Participants in this study had a spirometric diagnosis of COPD (based on FEV1/FVC ratio <0.70).
- Only adult participants with an age >40 years will be included, as the diagnosis of COPD is less likely in those younger than 40.
- We excluded those with chronic lung disease, asthma, and pregnant women.
- All subjects (including controls) were either current or former smokers.
- Because the UK biobank is 89% Caucasian, we chose to study just the Caucasian population.
- Our data will include 500 in the COPD group and 2000 in a random sample healthy non-COPD subjects matched for age, sex, race, and other covariates.

Covariates from UK biobank

Covariates were:

- **Demographics:** age, sex, body mass index (BMI), type of employment
- **Social history:** current tobacco smokers, pack years of smoking, alcohol intake frequency, alcohol dependence, alcohol addicted, substance abuse history
- **Past medical history:** diabetes, cirrhosis, renal failure, heart failure, diagnosis of cancer and what type (in situ / metastatic / uncertain / none)
- **Activity & anthropomorphic measures:** IPAQ activity group (low / medium / high), metabolic minutes per week, basal metabolic rate, fat free mass index, appendicular skeletal mass index.

No variables were imputed.

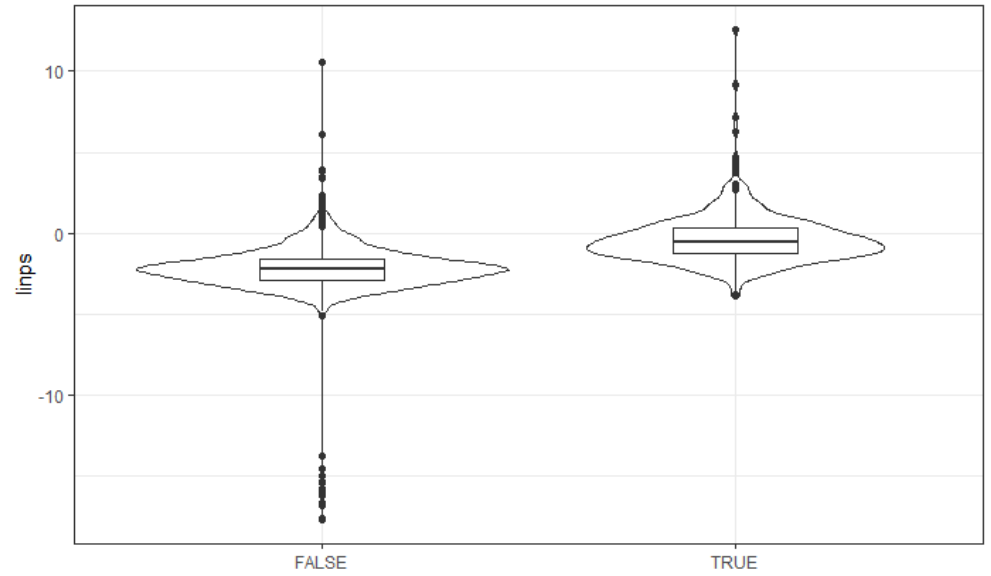
Table #1 (prior to matching)

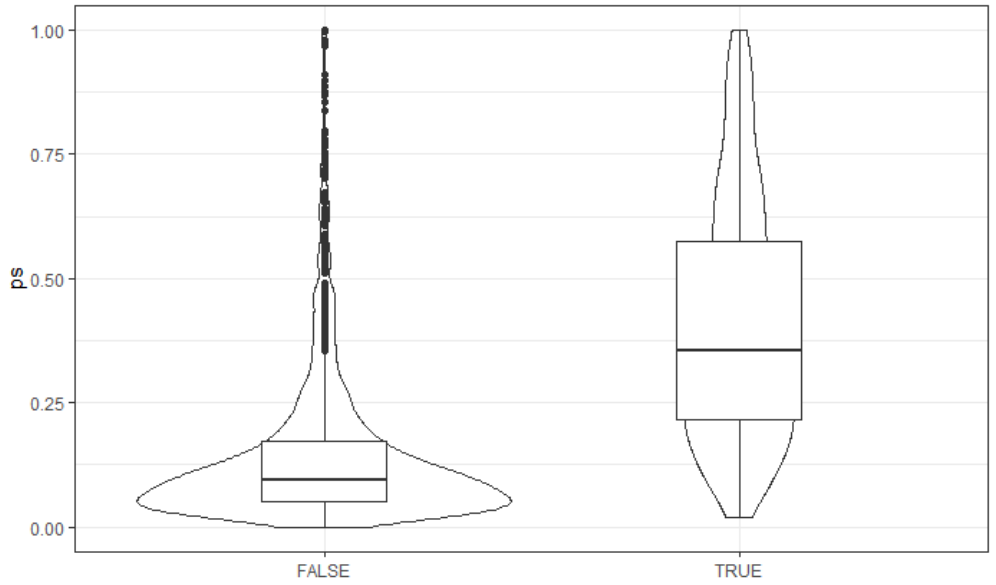
	No COPD	COPD	p test
	2000	500	
Age (mean (SD))	57.10 (8.10)	60.35 (6.85)	<0.001
Male (%)	991 (49.5)	189 (37.8)	<0.001
BMI (mean (SD))	27.48 (4.42)	27.19 (5.28)	0.205
Employment (%)			<0.001
Disabled	54 (2.7)	33 (6.6)	
Employed	1159 (58.0)	206 (41.2)	
Homemaker	42 (2.1)	11 (2.2)	
Retired	707 (35.4)	230 (46.0)	
Unemployed	29 (1.4)	16 (3.2)	
Voluntary work	9 (0.4)	4 (0.8)	

	No COPD	COPD	p test
Current smoker (%)			<0.001
No	1609 (80.5)	300 (60.0)	
Occasional	249 (12.4)	189 (37.8)	
Yes	142 (7.1)	11 (2.2)	
Pack years (mean (SD))	13.36 (19.17)	38.39 (29.25)	<0.001
Alcohol intake frequency (%)			0.001
1 or 2 per week	512 (25.6)	111 (22.2)	
1 or 3 per month	526 (26.3)	104 (20.8)	
3 to 4 times per week	599 (29.9)	175 (35.0)	
Never	172 (8.6)	65 (13.0)	
Special occasions	191 (9.6)	45 (9.0)	
Alcohol dependence (%)	1 (0.0)	1 (0.2)	0.86
Alcohol addicted (%)	15 (0.8)	7 (1.4)	0.261
Substance abuse history (%)	54 (2.7)	18 (3.6)	0.354

	No COPD	COPD	p test
Diabetes (%)	102 (5.1)	33 (6.6)	0.224
Cancer type (%)			0.008
Benign	2 (0.1)	1 (0.2)	
In-Situ	52 (2.6)	14 (2.8)	
Malignant	340 (17.0)	113 (22.6)	
Metastatic	2 (0.1)	1 (0.2)	
None	1595 (79.8)	364 (72.8)	
Uncertain	9 (0.4)	7 (1.4)	

	No COPD	COPD	p test
IPAQ activity group (%)			0.067
High	808 (40.4)	198 (39.6)	
Low	364 (18.2)	113 (22.6)	
Moderate	828 (41.4)	189 (37.8)	
MET minutes per week (mean (SD))	2633.91 (2647.54)	2693.63 (2753.46)	0.655
Basal metabolic rate (mean (SD))	6753.12 (1375.45)	6790.86 (1400.26)	0.585
Fat free mass index (mean (SD))	18.77 (2.57)	18.82 (2.71)	0.709
FEV1% predicted (mean (SD))	96.70 (16.29)	77.21 (17.52)	<0.001
FEV1/FVC ratio (mean (SD))	0.77 (0.06)	0.64 (0.07)	<0.001
Appendicular skeletal muscle index (mean (SD))	8.33 (1.35)	8.34 (1.45)	0.94
Handgrip strength (mean (SD))	32.79 (11.23)	33.06 (11.36)	0.626



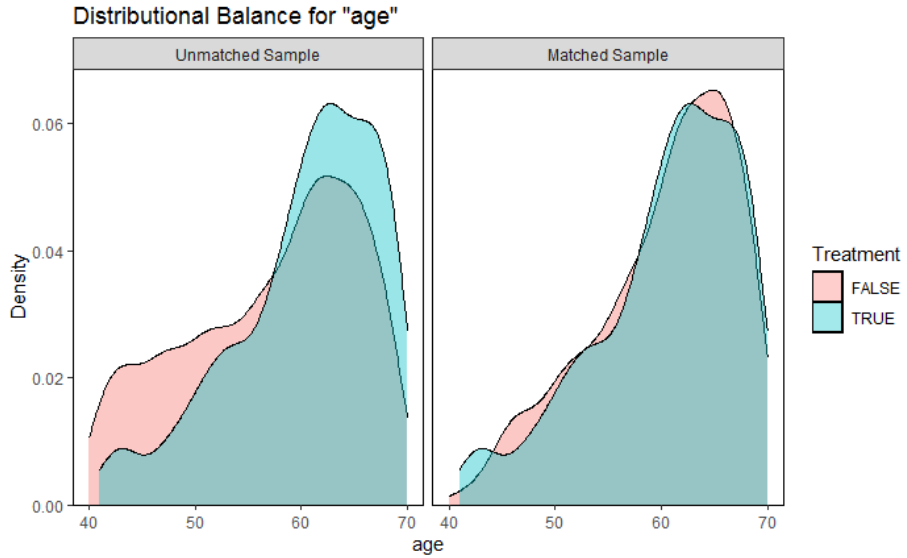


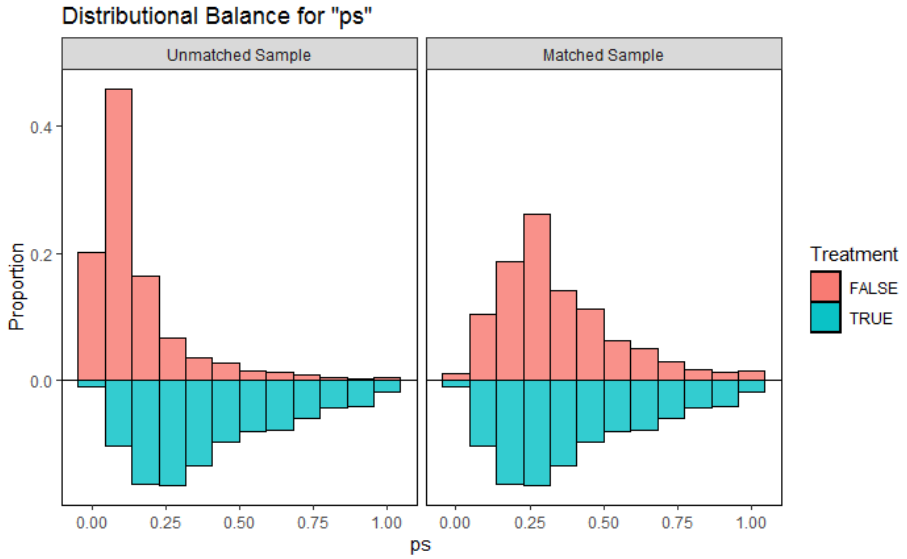
Propensity score distribution

- The propensity score indicates the probability of a diagnosis of COPD based on the covariates.
- Minimum propensity score was 0.02 and maximum is 1.00.

Match #1: 1:1 greedy matching without replacement with the Matching package

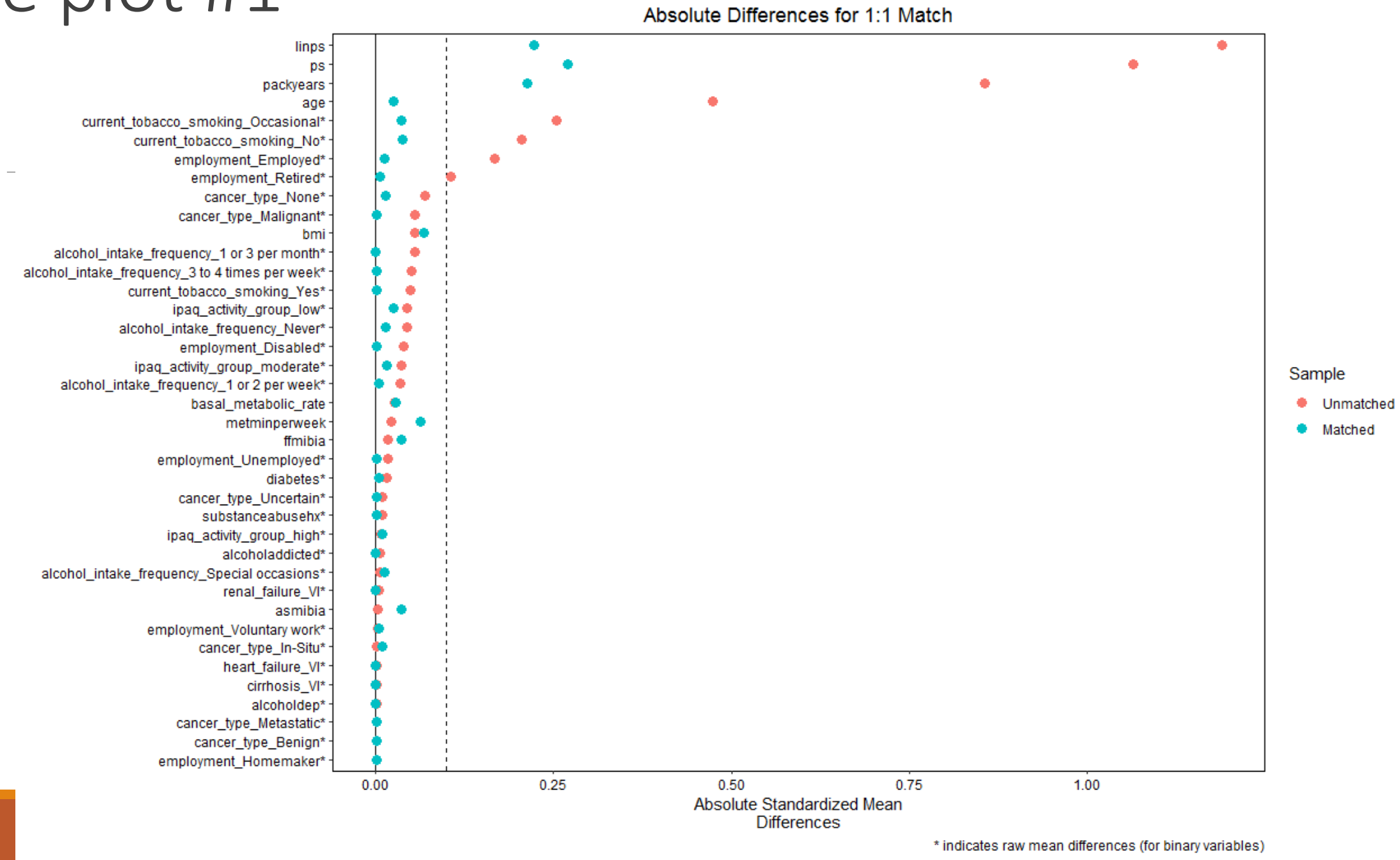
I had 500 matches of control with 500 COPD population.





Rubin's Rules	Unmatched	Match 1
Rule #1	1.19	0.22
Rule #2	0.85	1.65

Love plot #1

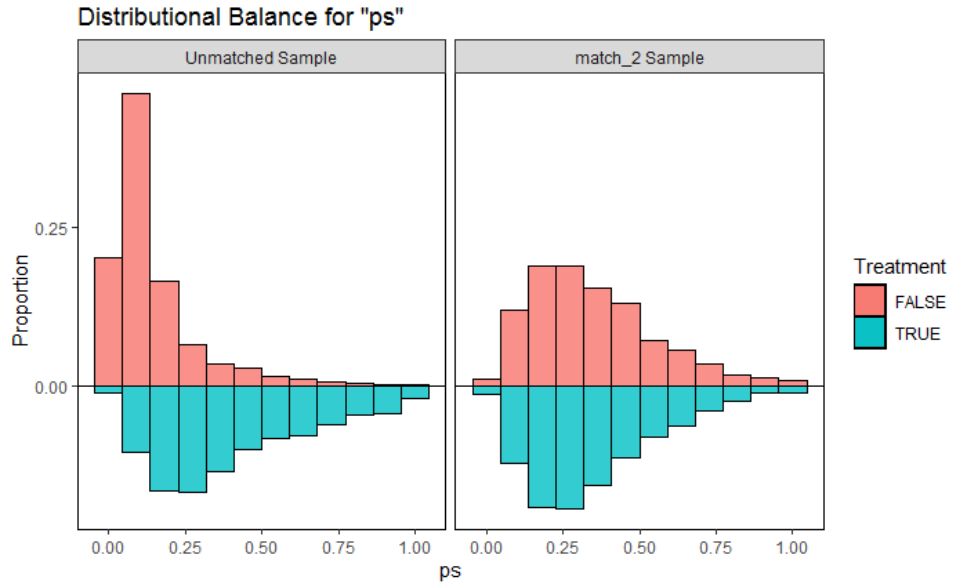

Absolute Differences for 1:1 Match
linps
ps
packyears
age
current_tobacco_smoking_Occasional*
current_tobacco_smoking_No*
employment_Employed*
employment_Retired*
cancer_type_None*
cancer_type_Malignant*
bmi
alcohol_intake_frequency_1 or 3 per month*
alcohol_intake_frequency_3 to 4 times per week*
current_tobacco_smoking_Yes*
ipaq_activity_group_low*
alcohol_intake_frequency_Never*
employment_Disabled*
ipaq_activity_group_moderate*
alcohol_intake_frequency_1 or 2 per week*
basal_metabolic_rate
metminperweek
ffmibia
employment_Unemployed*
diabetes*
cancer_type_Uncertain*
substanceabusehx*
ipaq_activity_group_high*
alcoholaddicted*
alcohol_intake_frequency_Special occasions*
renal_failure_VI*
asmibia
employment_Voluntary work*
cancer_type_In-Situ*
heart_failure_VI*
cirrhosis_VI*
alcoholdep*
cancer_type_Metastatic*
cancer_type_Benign*
employment_Homemaker*
0.00
0.25
0.50
0.75
1.00
Absolute Standardized Mean Differences
Sample
Unmatched
Matched
* indicates raw mean differences (for binary variables)

Match #2: Caliper Matching (1:1 without replacement) with the Matching package

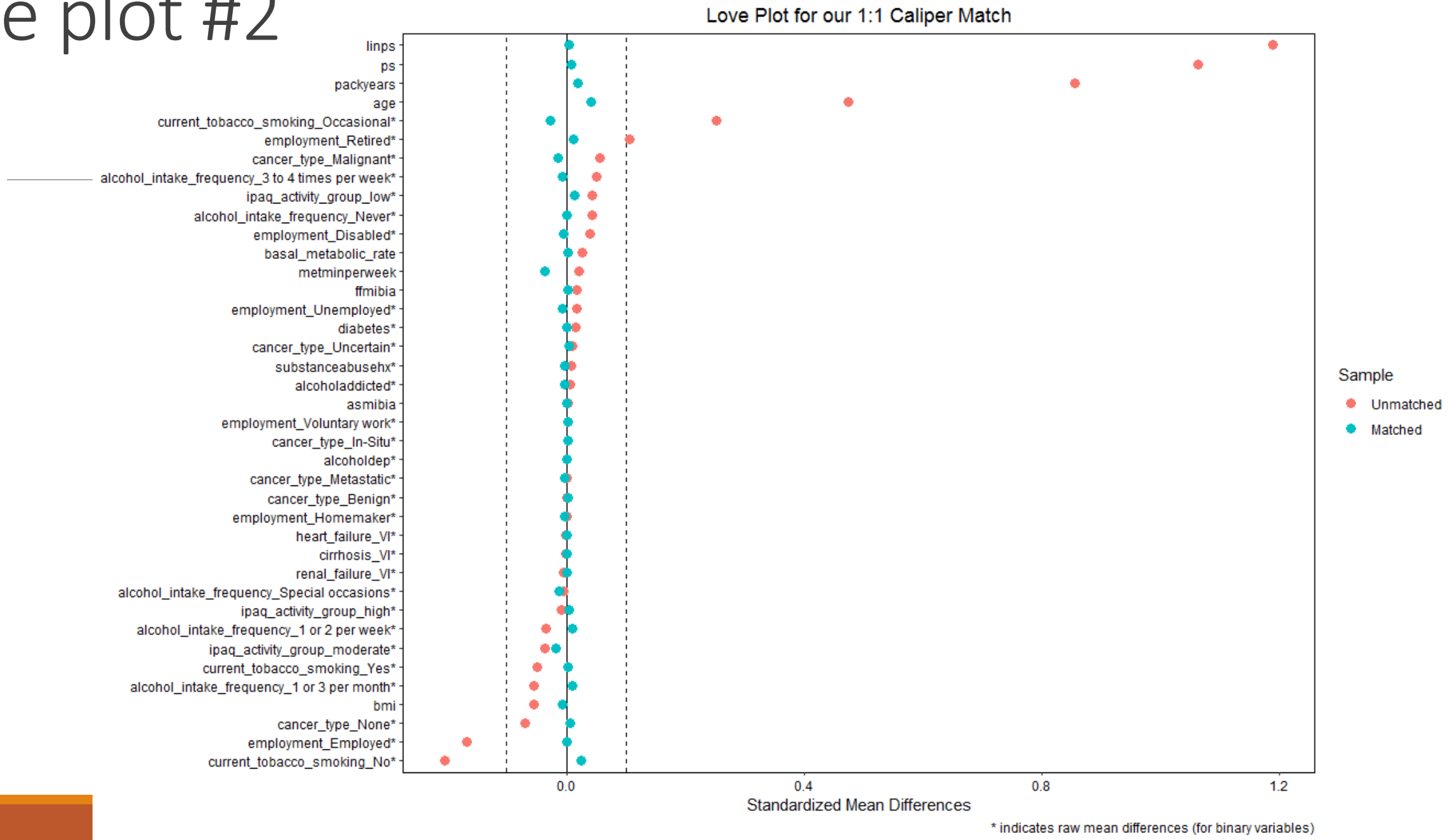
I only accepted matches where the linear propensity score of each match was within 0.2 standard deviations of the linear PS.

The matched number dropped to 433, making my total 866 instead of 1000.

Rubin's Rules	Unmatched	Match 1	Match 2
Rule #1	1.19	0.22	0.00
Rule #2	0.85	1.65	1.01



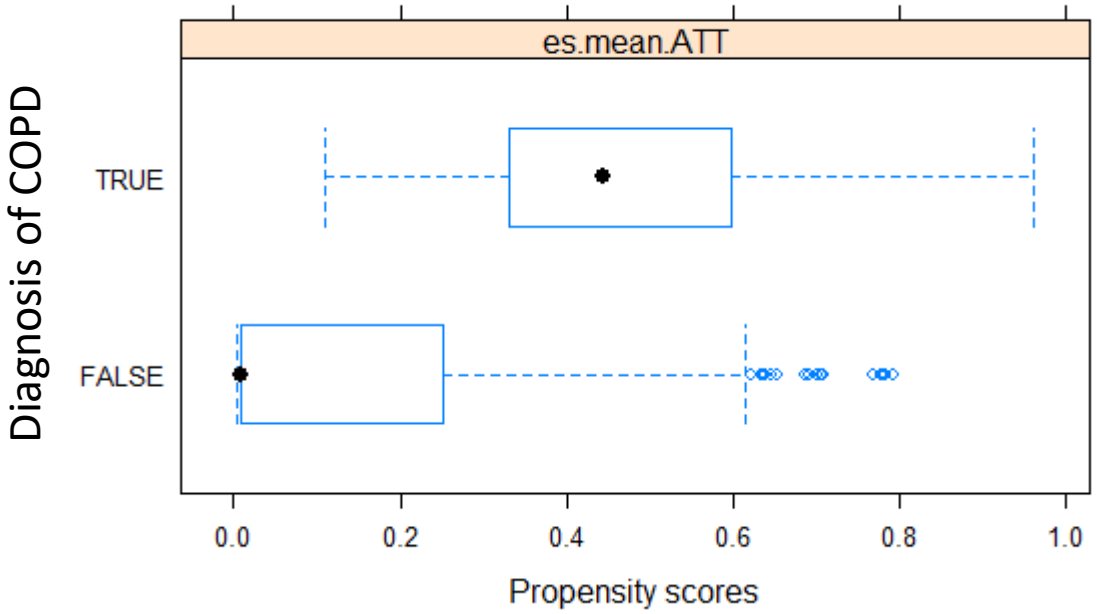
Love plot #2

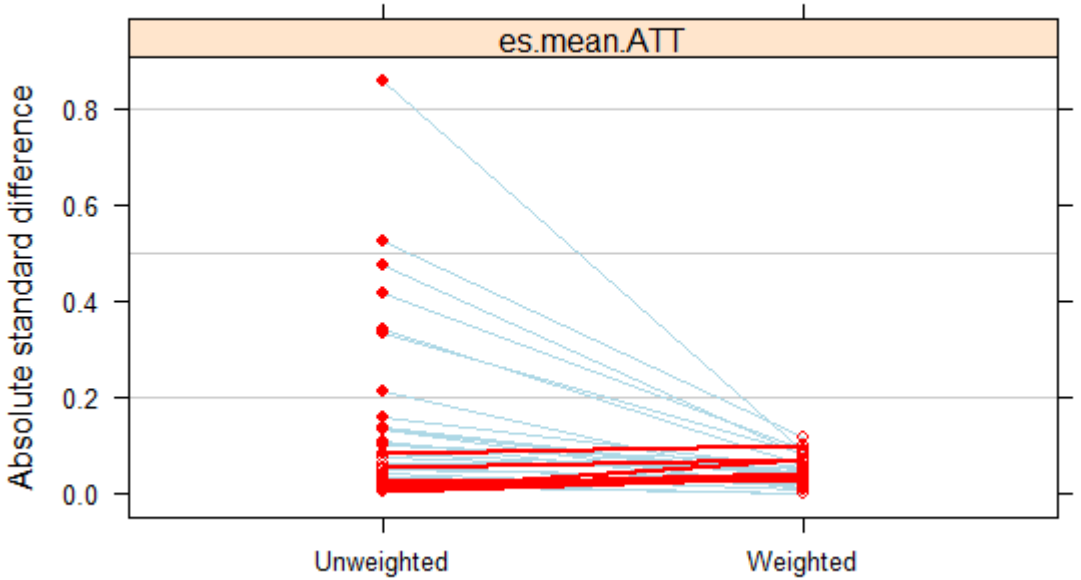

Love Plot for our 1:1 Caliper Match
linps
ps
packyears
age
current_tobacco_smoking_Occasional*
employment_Retired*
cancer_type_Malignant*
alcohol_intake_frequency_3 to 4 times per week*
ipaq_activity_group_low*
alcohol_intake_frequency_Never*
employment_Disabled*
basal_metabolic_rate
metminperweek
ffmibia
employment_Unemployed*
diabetes*
cancer_type_Uncertain*
substanceabusehx*
alcoholaddicted*
asmibia
employment_Voluntary work*
cancer_type_In-Situ*
alcoholdep*
cancer_type_Metastatic*
cancer_type_Benign*
employment_Homemaker*
heart_failure_VI*
cirrhosis_VI*
renal_failure_VI*
alcohol_intake_frequency_Special occasions*
ipaq_activity_group_high*
alcohol_intake_frequency_1 or 2 per week*
ipaq_activity_group_moderate*
current_tobacco_smoking_Yes*
alcohol_intake_frequency_1 or 3 per month*
bmi
cancer_type_None*
employment_Employed*
current_tobacco_smoking_No*
0.0
0.4
0.8
1.2
Standardized Mean Differences
Sample
Unmatched
Matched
* indicates raw mean differences (for binary variables)

Primary outcome results after matching

	Estimate	Standard error	CI low	CI high
COPD (Match #1)	0.96	0.71	-0.43	2.35
COPD (Match #2)	0.45	0.76	-0.60	2.38

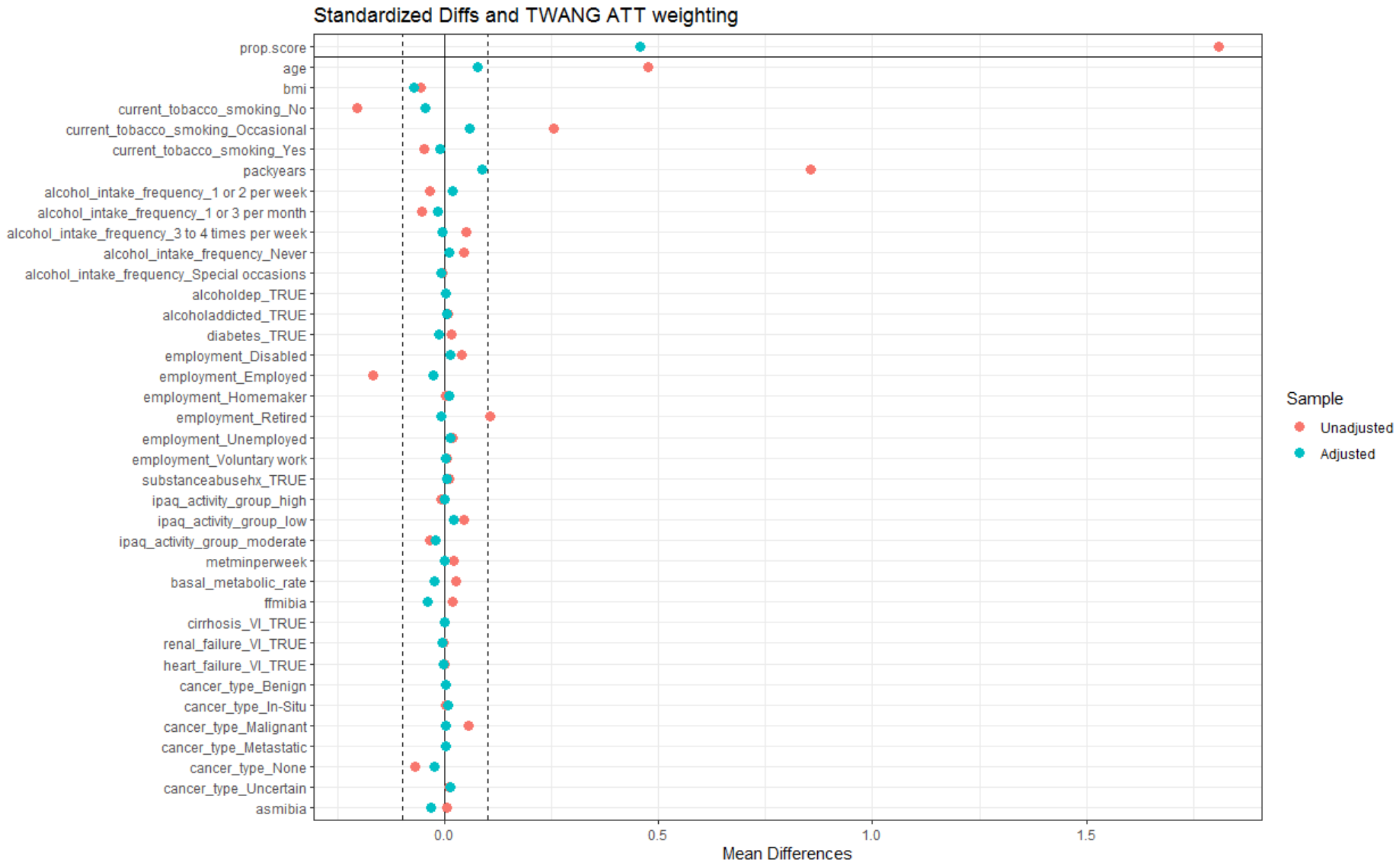
Match #3: Weighting by the inverse PS, then assess covariate balance using ATT approach





Rubin's Rules	Unmatched	Match 1	Match 2	Match 3
Rule #1	1.19	0.22	0.00	0.07
Rule #2	0.85	1.65	1.01	1.22

Love plot #3


Standardized Diffs and TWANG ATT weighting
prop.score
age
bmi
current_tobacco_smoking_No
current_tobacco_smoking_Occasional
current_tobacco_smoking_Yes
packyears
alcohol_intake_frequency_1 or 2 per week
alcohol_intake_frequency_1 or 3 per month
alcohol_intake_frequency_3 to 4 times per week
alcohol_intake_frequency_Never
alcohol_intake_frequency_Special occasions
alcoholdep_TRUE
alcoholaddicted_TRUE
diabetes_TRUE
employment_Disabled
employment_Employed
employment_Homemaker
employment_Retired
employment_Unemployed
employment_Voluntary work
substanceabusehx_TRUE
ipaq_activity_group_high
ipaq_activity_group_low
ipaq_activity_group_moderate
metminperweek
basal_metabolic_rate
ffmibia
cirrhosis_VI_TRUE
renal_failure_VI_TRUE
heart_failure_VI_TRUE
cancer_type_Benign
cancer_type_In-Situ
cancer_type_Malignant
cancer_type_Metastatic
cancer_type_None
cancer_type_Uncertain
asmibia
0.0
0.5
1.0
1.5
Mean Differences
Sample
Unadjusted
Adjusted

Outcome with weighted analysis

	Estimate	Standard error	P value	CI low	CI high
Handgrip strength	-2.91	0.51	1.29*10^-8	-3.91	-1.91

- This suggests that, in patients with COPD as compared to controls, the handgrip strength is reduced by 2.91 kg (1.91-3.91).
- I then performed a sensitivity analysis. The gamma for 1.00 was 0.0907 and therefore this analysis is very sensitive to change from an unobserved covariate.

Conclusion

- My analysis for matches #1 and #2 did not show significant change in handgrip strength comparing COPD subjects with propensity-matched controls.
- Match #3 may have been statistically significant but my sensitivity analysis showed it was very sensitive to bias.
- I would like to analyze this with the full UK biobank cohort to see if a larger cohort may reveal similar findings.
- The UK biobank (on average) early stage COPD patients (FEV1 77.2%), and perhaps the cohort was not severe enough for handgrip strength to be a good predictor.
- Analyses of NHANES and KNHANES has not shown significant changes when analyzing handgrip strength in patients with COPD as compared to controls, and so this analysis is consistent with existing literature.

Statistical conclusions

- What I've learned is that there are many different ways to do matching.
- To me it is useful to try and match in multiple different ways.
- I learned it is tempting to get excited about a statistically significant result however sensitivity analysis is an important step to make sure that your analysis is not sensitive to unmeasured covariates that could easily change your overall conclusion.

Questions?