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ORIGINAL RESEARCH

Prognostic Value of Functional Capacity in Different Exercise Protocols

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BACKGROUND: Functional capacity is associated with mortality, although the prognostic value of achieved estimated metabolic equivalents (METs) across various exercise protocols is not established. We sought to determine whether achieved METs had different prognostic implications according to the protocol employed.

METHODS AND RESULTS: From 1991 to 2015, we identified 120 705 consecutive patients from a stress testing registry who underwent the following 7 different standardized exercise protocols: Bruce, modified Bruce, Cornell 0%, Cornell 5%, Cornell 10%, Naughton, and modified Naughton. The primary outcome was all-cause mortality. There were 74 953 Bruce, 8368 modified Bruce, 2648 Cornell 0%, 9972 Cornell 5%, 20 425 Cornell 10%, 1226 Naughton, and 3113 modified Naughton protocols. During a mean follow-up of 8.7 years, a total of 8426 deaths (6.9%) occurred. When compared with the Bruce protocol, after multivariable adjustment for clinical risk factors, medications, and functional capacity, test protocol was independently associated with mortality (modified Naughton [hazard ratio (HR), 2.51; 95% CI, 2.26–2.8], Naughton [HR, 1.79; 95% CI, 1.57–2.04], Cornell 0% [HR, 1.79; 95% CI, 1.59–2.01], modified Bruce [HR, 1.62; 95% CI, 1.48–1.76], Cornell 5% [HR, 1.61; 95% CI, 1.47–1.75], and Cornell 10% [HR, 1.32; 95% CI, 1.22–1.42]). Across all protocols, higher estimated METs were associated with lower mortality, although the equivalent METs achieved were associated with a worse prognosis in less-demanding protocols.

CONCLUSIONS: Higher estimated METs are reliably associated with lower mortality in all exercise protocols, although the prognostic value is not transferable across different tests. Consequently, the prognostic value of METs achieved during a stress test should be considered protocol dependent.

Key Words: exercise stress testing ■ mortality ■ stress testing protocol

Stress testing is an important prognostic tool in the evaluation and management of patients with known or suspected heart disease.[1,2] Despite various modalities to assess the response to stress, exercise testing is often preferred because exercise capacity is independently associated with death and adverse cardiac events.[3–6] Defined as the maximal oxygen uptake for a given workload, exercise capacity is typically expressed in estimated metabolic equivalents (METs), which represent multiples of the basal rate of oxygen consumption at rest.[7–9] Importantly, the prognostic value of exercise capacity has been predominantly validated for both men and women using the Bruce protocol.[8,10,11] Despite frequent use in clinical practice, the association between non-Bruce protocols and prognosis is limited.[12,13] In general, a protocol is chosen to achieve 8 to 12 minutes of exercise, and alternative protocols may be selected as many patients cannot exercise for this duration with a standard Bruce protocol.[14] Of note, the relationship between estimated METs on less-demanding protocols with equivalent METs on a Bruce protocol, and the differential association with mortality, has not been investigated. Therefore, the aim of this study is to assess whether achieved METs is consistently associated with prognosis across different exercise

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CLINICAL PERSPECTIVE

What Is New?

- This study compares whether the prognostic value of estimated metabolic equivalents (METs) achieved is transferable between 7 different exercise stress protocols studied in a large cohort of 120 705 patients.
- Our study suggests that achieved METs are not comparable between exercise stress protocols, and the same achieved METs can have variable prognosis depending on the protocol.
- However, regardless of the exercise protocol chosen, higher estimated METs are associated with lower mortality.

What Are the Clinical Implications?

- The numerical MET value of METs should be interpreted within the confines of the specific exercise protocol for men and women.
- The demands of each non-Bruce exercise protocol compared with the Bruce protocol is as important as the METs achieved in determining patient prognosis.
- Estimated METs by exercise stress testing is not the gold standard, and the exercise stress test protocol chosen affects the estimation of METs.

Nonstandard Abbreviations and Acronyms

HR	hazard ratio
METs	estimated metabolic equivalents

protocols and whether this prognostic value is transferable between protocols.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Initial screening included all consecutive patients who underwent stress testing at our institution from January 1, 1991 to February 27, 2015. If a patient had undergone >1 stress test, only the first stress test was selected. The stress testing modalities in the initial screening cohort included exercise electrocardiography (without imaging) and exercise or pharmacological stress with associated imaging (stress echocardiography or stress radionuclide myocardial perfusion imaging). We excluded patients referred for pharmacological testing (echocardiography or myocardial perfusion imaging [n=38 828; 23.3% of total]). In addition, any patients who started the protocol with exercise and were converted to pharmacologic as the result of inadequate heart rate were also excluded (n=467; 0.3% of total). Finally, we excluded patients whose exercise field was missing (n=5651; 3.4% of total) and patients where sex information was missing (n=796; 0.5% of total). After exclusions, the cohort included a total of 120 705 patients (72.5% of total). At the time of stress testing, patient demographics, comorbidities, and medications are prospectively entered into a stress database. Full details of the study cohort have been reported previously.[15] The institutional review board approved the study with a waiver of the requirement for informed consent.

Exercise Stress Testing

Patients underwent symptom-limited treadmill testing according to standardized protocols, designed to achieve at least 8 to 12 minutes of exercise, and the test was performed as recommended by established exercise testing guidelines.[16] The peak estimated (METs) was determined based on treadmill grade and speed at peak exercise. For heart rate recovery calculation, the heart rate at 1-minute postexercise was subtracted from the peak heart rate. Recovery forms differed between modalities, with patients undergoing exercise electrocardiography with no imaging and exercise myocardial perfusion imaging having a walking recovery, and those undergoing exercise echocardiogram having a supine recovery. Therefore, an abnormal heart rate recovery was defined as ≤12 beats/min for the former modalities and ≤18 beats/min for the latter.[17–19] The chronotropic reserve index was calculated as ([peak heart rate−resting heart rate]/[age-predicted peak heart rate−resting heart rate]).[20]

Outcome

The primary outcome studied was all-cause mortality. Death was determined from the Social Security Death Index[21] in addition to supplementation by the institutional death index (expiration summary in patient's chart). In particular, supplementation was necessary for the time period of November 2011 to June 2016 when restrictions for the Social Security Death Index were implemented. The final censoring date was June 10, 2016.

Statistical Analysis

Numeric data are presented as mean±SD. Categorical data are presented as n (%). Student *t* tests or Wilcoxon-rank sum tests for continuous

variables and χ^2 tests or Fisher exact tests for categorical variables were used to examine between group differences, as appropriate. Unadjusted and adjusted analyses for associations with all-cause mortality were performed with Cox proportional hazard models and satisfied the assumption of proportional hazards. Restricted cubic spline plots were used to depict the associations of exercise capacity (estimated METs) with mortality. Covariates for the multivariable Cox models were chosen a priori based on known associations with mortality and included age, sex, coronary artery disease, diabetes mellitus, statin use, hypertension, smoking, end-stage renal disease, and body mass index. Adjusted analyses were also performed with propensity score based analyses. Specifically, 22 covariates related to patient demographics, comorbidities, and medications were used to create propensity scores for a Bruce protocol. In matched analyses, 1-to-1 greedy matching was performed without replacement with a caliper of ≤0.2 SDs of the logit of the propensity score. All analyses were performed using R 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria), and 2-sided $P<0.05$ were considered statistically significant.

RESULTS

A total of 120 705 patients underwent exercise stress testing. The mean age of the cohort was 53.3 years (±12.5 years), and 59% were men. There were 74 953 Bruce, 8368 modified Bruce, 2648 Cornell 0%, 9972 Cornell 5%, 20 425 Cornell 10%, 1226 Naughton, and 3113 modified Naughton individual protocols (Figure S1). Overall, 45 752 patients had non-Bruce protocols. During a mean follow-up of 8.7 years, a total of 8426 deaths (6.9%) occurred. Patients with a non-Bruce protocol were significantly older, more likely to be women, had a higher burden of comorbidities, and were more likely to be on cardiac medications. Non-Bruce protocol patients also had a higher resting blood pressure and hazard ratio (HR) as well as lower peak estimated METs and peak HR (Table 1).

Table 1. Baseline Characteristics by Protocol

Variable	Bruce (n=74 953)	Non-Bruce (n=45 752)	*P* Value
Age, mean±SD, y	49.4±11.3	59.8±11.8	<0.001
Male, n (%)	48 448 (64.6)	22 793 (49.8)	<0.001
CAD, n (%)	6525 (8.7)	12 552 (27.4)	<0.001
DM, n (%)	5729 (7.6)	8079 (17.7)	<0.001
Hypertension, n (%)	31 250 (41.7)	33 139 (72.4)	<0.001
Hyperlipidemia, n (%)	11 996 (16.3)	7012 (15.6)	0.001
Smoker, n (%)	30 679 (40.9)	23 982 (52.4)	<0.001
ESRD, n (%)	387 (0.7)	946 (2.3)	<0.001
BMI, mean±SD	28.2±5.3	29.7±6.5	<0.001
Resting SBP, mean±SD, mm Hg	126.6±17.3	132±20.8	<0.001
Resting HR, mean±SD, bpm	72.1±13.6	73.6±14.2	<0.001
Peak SBP, mean±SD, mm Hg	174.6±26.2	177±30.4	<0.001
Peak HR, mean±SD, bpm	162.6±17.8	144±23.3	<0.001
METs, mean±SD	10.3±2.4	7.2±2.1	<0.001
Abnormal HRR, n (%)	7109 (9.5)	13 530 (29.6)	<0.001
Chronotropic reserve index, mean±SD	0.92±0.16	0.83±0.34	<0.001
Beta blocker use, n (%)	12 273 (16.4)	16 667 (36.4)	<0.001
Nondihydro calcium channel blocker use, n (%)	2097 (3.4)	3729 (9)	<0.001
Statin use, n (%)	16 763 (22.4)	14 839 (32.4)	<0.001
Aspirin, n (%)	20 438 (27.3)	19 371 (42.3)	<0.001
ACEI/ARB, n (%)	13 574 (18.1)	15 178 (33.2)	<0.001
Insulin, n (%)	1281 (1.7)	2228 (4.9)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, heart rate; HRR, heart rate response; METs, estimated metabolic equivalents; and SBP, systolic blood pressure.

In analyses adjusted for comorbidities and estimated METs, less-intense protocols were associated with a higher hazard of mortality compared with the Bruce protocol (modified Naughton [HR, 2.51; 95% CI, 2.26–2.8], Naughton [HR, 1.79; 95% CI, 1.57–2.04], Cornell 0% [HR, 1.79; 95% CI, 1.59–2.01], modified Bruce [HR, 1.62; 95% CI, 1.48–1.76], Cornell 5% [HR, 1.61; 95% CI, 1.47–1.75], and Cornell 10% [HR, 1.32; 95% CI, 1.22–1.42] (Figure 1, Tables 2 and 3). Similarly, a Bruce protocol was associated with lower mortality compared with non-Bruce protocols (adjusted HR, 0.67; 95% CI, 0.64–0.72; $P<0.001$). Overall, regardless of the protocol, higher estimated METs remained associated with lower mortality (Figure 2, Table 3) (adjusted HR, 0.46; 95% CI, 0.44–0.48; $P<0.001$). In propensity-matched patients, the results were similar (modified Naughton [METs HR, 0.73; 95% CI, 0.69–0.78], Naughton [METs HR, 0.87; 95% CI, 0.83–0.91], Cornell 0% [METs HR, 0.85; 95% CI, 0.82–0.89], modified Bruce [METs HR, 0.82; 95% CI, 0.80–0.84], Cornell 5% [METs HR, 0.82; 95% CI, 0.80–0.85], Cornell 10% [METs HR, 0.79; 95% CI, 0.77–0.81]). Less-intense protocols were associated with higher mortality, and higher estimated METs were associated with lower mortality across protocols (Figures S2A through S7B, Table S1).

Table 2. Multivariable HR: Bruce Versus Non-Bruce

	All (n=120 705)		Female (n=49 464)		Male (n=71 241)	
	HR With 95% CI	*P* Value	HR With 95% CI	*P* Value	HR With 95% CI	*P* Value
Age, y	1.42 (1.38–1.47)	<0.001	1.45 (1.36–1.54)	<0.001	1.4 (1.35–1.46)	<0.001
METs (1 kcal/kg per h)	0.4 (0.39–0.42)	<0.001	0.4 (0.38–0.43)	<0.001	0.42 (0.4–0.43)	<0.001
Male	2.28 (2.15–2.4)	<0.001	…	…	…	…
Statin use	0.6 (0.55–0.64)	<0.001	0.59 (0.51–0.68)	<0.001	0.6 (0.55–0.65)	<0.001
Hypertension	1.14 (1.07–1.22)	<0.001	1.19 (1.07–1.33)	0.002	1.1 (1.02–1.19)	0.011
Diabetes mellitus	1.21 (1.15–1.28)	<0.001	1.32 (1.19–1.47)	<0.001	1.17 (1.09–1.24)	<0.001
CAD	1.23 (1.17–1.29)	<0.001	1.45 (1.31–1.6)	<0.001	1.17 (1.1–1.24)	<0.001
Smoker	1.33 (1.26–1.39)	<0.001	1.45 (1.33–1.58)	<0.001	1.28 (1.21–1.36)	<0.001
ESRD	2.27 (2.03–2.55)	<0.001	3.3 (2.59–4.21)	<0.001	2.12 (1.87–2.4)	<0.001
Bruce vs non-Bruce	0.67 (0.63–0.72)	<0.001	0.65 (0.56–0.74)	<0.001	0.67 (0.62–0.72)	<0.001

CAD indicates coronary artery disease; ESRD, end-stage renal disease; HR, hazard ratio; and METs, estimated metabolic equivalents.

Finally, the results were consistent when the analyses were performed separately in men and women. Specifically, although women had lower mortality compared with men, the Bruce protocols were similarly associated with lower mortality in women compared with non-Bruce protocols (HR, 0.65; 95% CI, 0.56–0.74) (Tables 2 and 3).

DISCUSSION

There are 2 main findings from this study. First, across 7 different exercise protocols with various workloads, lower exercise capacity was associated with higher mortality irrespective of protocol, even after robust adjustment. Second, an equivalent estimated functional capacity (METs) does not confer the same prognostic value across different protocols. Specifically, with a Bruce protocol as the reference standard, the same estimated functional capacity is associated with a worse prognosis in less-intense protocols. These findings can be used to recalibrate our understanding of METs achieved and prognostic implications in different clinically used stress protocols. Across stress tests, including even the least-demanding protocols, the good prognostic value of higher estimated functional capacity is maintained. However, for similar patients achieving identical METs, the prognosis is worse with less-intense protocols.

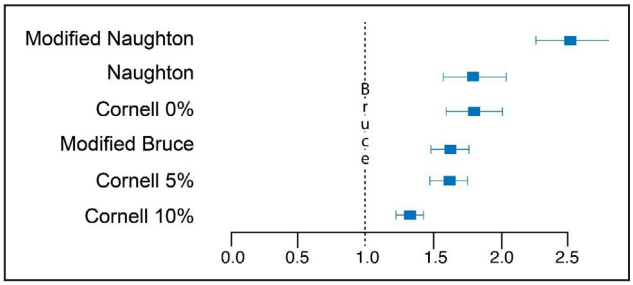

Figure 1. Adjusted hazard ratio of death by protocol selected vs Bruce.
Adjusted for protocol, age, sex, hypertension, diabetes mellitus, coronary artery disease, end-stage renal disease, smoking, and statin use.

Our study raises 2 fundamental issues regarding stress testing. First, prognostic data have been derived mainly from Bruce testing. Second, data correlating estimated METs to actual measured METs across protocols are limited. As an example, the original study to validate the Cornell series of protocols with the Bruce protocol included only 150 patients.[22] However, the advantage of non-Bruce protocols such as the Cornell series of protocols is that many patients with physical or orthopedic limitations would not be able to exercise for a sufficient period of time on the Bruce protocol to achieve a diagnostic study. Importantly, if a patient's estimated functional capacity is limited by orthopedic or physical limitations, as opposed to aerobic limitations, the diagnostic yield of the test in predicting actual aerobic capacity is necessarily decreased. Unfortunately, many studies comparing exercise protocols have been limited by small sample sizes.[23,24] In one prior study of 20 patients who performed both the Naughton and Bruce protocols, the only significant difference between the 2 studies was that the Naughton protocol allowed for a longer exercise duration.[23] In a study of 50 consecutive patients with a ramp-style protocol and subsequent breath-to-breath analysis with a metabolic cart to measure VO_2, there was consistent overestimation between estimated METs measured by exercise duration and the true measured METs.[24] Additional studies have shown that this overestimation is worse after an exercise training protocol and in younger patients.[25,26] Previous studies have also shown that estimates of METs from protocols with large incremental stages

Table 3. Multivariable HR: Bruce Versus Individual Non-Bruce Protocols

	All (n=120 705)		Female (n=49 464)		Male (n=71 241)	
	HR With 95% CI	*P* Value	HR With 95% CI	*P* Value	HR With 95% CI	*P* Value
Age, y	1.47 (1.43–1.52)	<0.001	1.48 (1.4–1.58)	<0.001	1.46 (1.41–1.52)	<0.001
METs	0.46 (0.44–0.48)	<0.001	0.49 (0.45–0.53)	<0.001	0.46 (0.44–0.48)	<0.001
Male	2.17 (2.06–2.3)	<0.001	…	…	…	…
Statin use	0.61 (0.57–0.66)	<0.001	0.62 (0.53–0.71)	<0.001	0.61 (0.56–0.67)	<0.001
Hypertension	1.13 (1.06–1.2)	<0.001	1.14 (1.02–1.28)	0.0211	1.1 (1.02–1.18)	0.0182
Diabetes mellitus	1.23 (1.16–1.3)	<0.001	1.32 (1.18–1.47)	<0.001	1.18 (1.11–1.26)	<0.001
CAD	1.18 (1.11–1.24)	<0.001	1.39 (1.25–1.55)	<0.001	1.12 (1.06–1.19)	<0.001
Smoker	1.34 (1.28–1.41)	<0.001	1.47 (1.35–1.6)	<0.001	1.29 (1.22–1.37)	<0.001
ESRD	2.17 (1.93–2.44)	<0.001	3.1 (2.4–4.01)	<0.001	2.04 (1.79–2.32)	<0.001
Cornell 0.0% vs Bruce	1.79 (1.59–2.01)	<0.001	2.1 (1.72–2.57)	<0.001	1.6 (1.38–1.86)	<0.001
Cornell 10.0% vs Bruce	1.32 (1.22–1.42)	<0.001	1.24 (1.05–1.47)	0.0096	1.37 (1.25–1.5)	<0.001
Cornell 5.0% vs Bruce	1.61 (1.47–1.75)	<0.001	1.77 (1.51–2.08)	<0.001	1.57 (1.41–1.74)	<0.001
Modified Bruce vs Bruce	1.62 (1.48–1.76)	<0.001	1.65 (1.4–1.96)	<0.001	1.63 (1.47–1.81)	<0.001
Modified Naughton vs Bruce	2.51 (2.26–2.8)	<0.001	3.5 (2.84–4.31)	<0.001	2.29 (2.02–2.6)	<0.001
Naughton vs Bruce	1.79 (1.57–2.04)	<0.001	2.07 (1.64–2.61)	<0.001	1.64 (1.4–1.93)	<0.001

CAD indicates coronary artery disease; ESRD, end-stage renal disease; HR, hazard ratio; and METs, estimated metabolic equivalents.

do not correlate as well with actual METs compared with ramp protocols.[14,27,28] Of note, the modified Bruce protocol and many others are often chosen before cardiac rehabilitation or to created exercise prescriptions or when estimated functional capacity is perceived to be low. Nonetheless, to date, there have been no prognostic studies to support this. Our study represents the largest cohort of exercise stress tests using non-Bruce protocols.

Several possible factors may explain the higher HR associated with non-Bruce protocols. A major factor is the protocol choice by the exercise physiologist which likely reflects many factors that are not captured by the variables collected, such as the patient's perceived

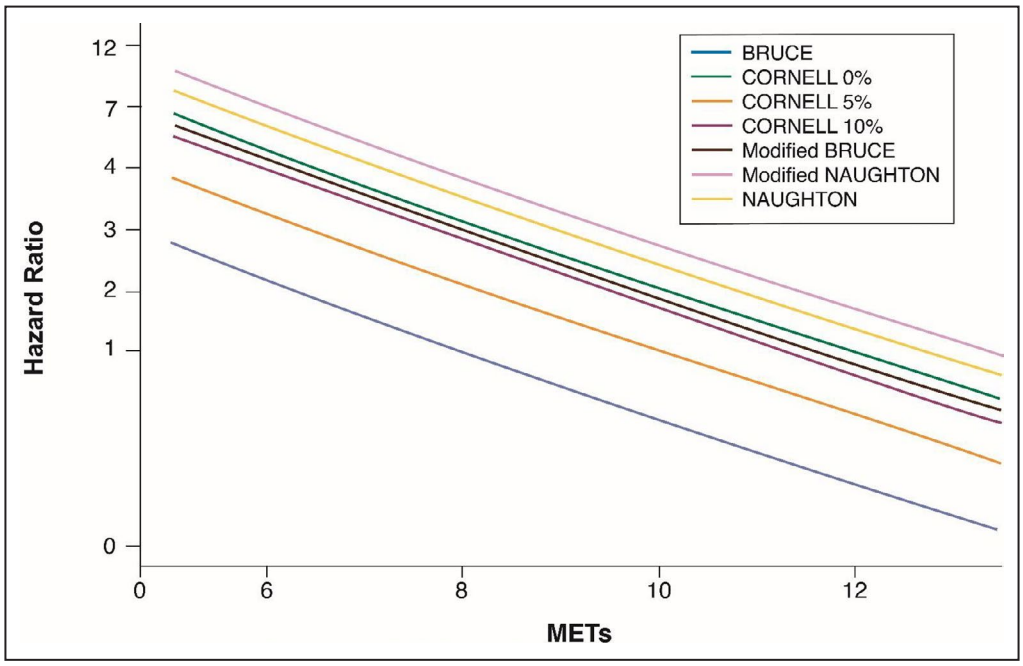

Figure 2. Association of METs with mortality across 7 different exercise protocols.
METs indicates estimated metabolic equivalents.

frailty and bedside assessment. The bedside assessment may characterize features of impairment that are not reflected in our collected variables. The participants in the non-Bruce protocol are older and are more likely to be women, which could be attributed to selection bias on the part of the exercise physiologist. In addition, for historical reasons, the heart failure patients may have been more likely to be tested on the Naughton protocol and healthier patients on the Cornell 10% or standard Bruce.

Part of the differences in mortality risks between the different protocols can be explained by the inherent inaccuracies associated with predicting METs from exercise stress testing. Unfortunately, in our data set, peak VO_2 was not directly measured. A recent article by Kokkinos et al[29] that used directly measured VO_2 highlighted the inaccuracy in the American College of Sports Medicine equations commonly used. The article proposed new equations (Fitness Registry and the Importance of Exercise: A National Data Base [FRIEND]) that were more accurate than the American College of Sports Medicine equations currently used (mean errors 5.1% versus 21.4% for the FRIEND and American College of Sports Medicine, respectively). Our study includes different protocols from those studied in the Kokkinos et al study; however, it is likely that the error in deriving METs is the same. This type of error in estimating METs among the different protocols could contribute to the wide variability in HRs depending on the protocol.

Limitations

Our study has several notable limitations. First, the study spanned a 25-year period, and the patient population referred to stress testing may have changed during this time. To evaluate these concerns, we examined the median age of the patients over time and the number of pharmacological stress tests (Figures S8 and S9). Age appears largely stable during the 25-year period; however, the number of patients referred for pharmacological testing has increased during the same period of time. This referral pattern may have affected the type of protocol ordered, as earlier in the 25-year period more frail patients may have been referred to non-Bruce protocols as opposed to pharmacological stress testing. Second, our cohort is from a single-center referral institution, and our findings need to be validated in diverse, external populations. Third, there is selection bias with regard to the protocol ordered, as patients who are subjectively more aerobically fit as judged by the exercise technician are more likely to be referred to Bruce protocol versus other non-Bruce protocols. Our analysis controls for several variables that could account for reduced exercise tolerance, but it does not account for frailty, which may influence the clinician's selection of exercise test. Finally, electrocardiographic and imaging data were not included in multivariable adjustments, and residual confounding is possible.

CONCLUSIONS

In a large cohort of patients, we have provided insights regarding the prognostic value of numerous exercise protocols. Importantly, regardless of the protocol, lower functional capacity is associated with higher mortality. However, the prognostic value of a specific functional capacity (METs) is not transferable across protocols. In particular, our results suggest that the available exercise protocols are variable with regard to the prognostic value in part because of their poor estimate of the maximum VO_2 in individuals. Alternatively, metabolic exercise stress tests provide an accurate VO_2 assessment and should be considered.

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Disclosures

None.

Supplementary Materials

Table S1
Figures S1–S9

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SUPPLEMENTAL MATERIAL

Table S1. Cox proportional hazard models in propensity matched patients adjusted according to protocol and exercise capacity in estimated metabolic equivalents (METs).

	HR (95% CI)	*p* value
Modified Bruce	1.40 (1.27-1.55)	<0.0001
METs	0.82 (0.80-0.84)	<0.0001
Naughton	1.63 (1.28-2.07)	<0.0001
METs	0.87 (0.83-0.91)	<0.0001
Modified Naughton	1.78 (1.31-2.44)	<0.0001
METs	0.73 (0.69-0.78)	<0.0001
Cornell 0.0%	2.39 (1.94-2.96)	<0.0001
METs	0.85 (0.82-0.89)	<0.0001
Cornell 5.0%	1.77 (1.58-1.97)	<0.0001
METs	0.82 (0.80-0.85)	<0.0001
Cornell 10.0%	1.29 (1.19-1.40)	<0.0001
METs	0.79 (0.77-0.81)	<0.0001

HR = hazard ratio, CI = confidence interval.

Figure S1. Number of Patients Divided by Individual Stress Protocols.

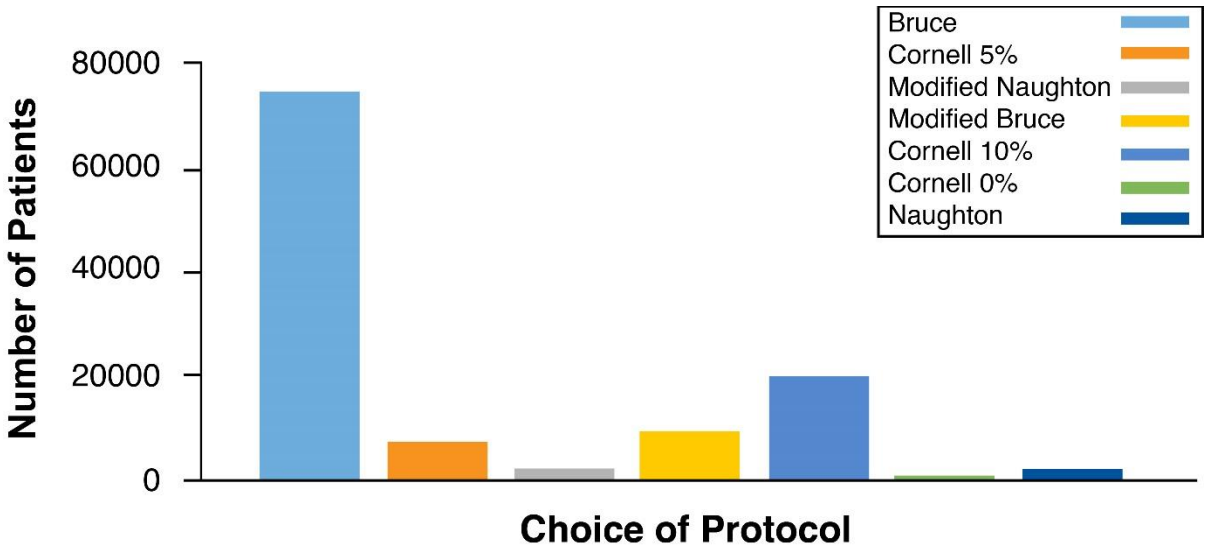
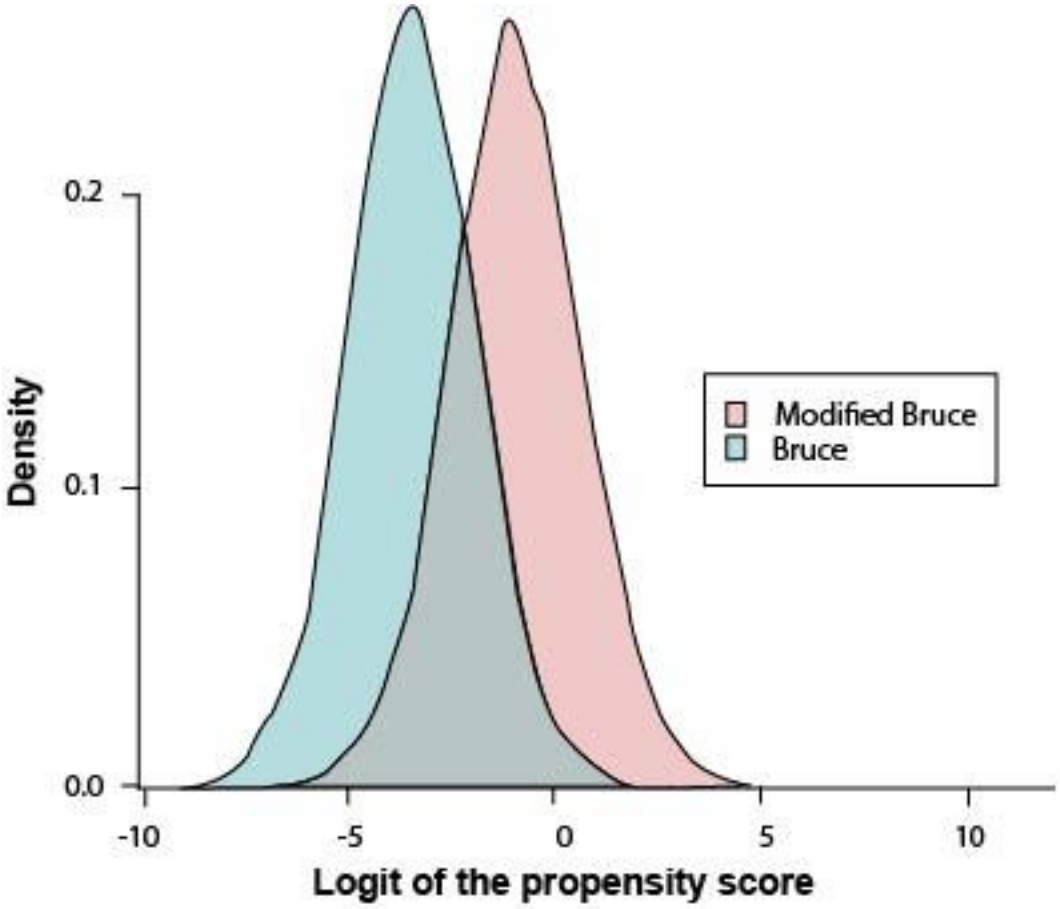


Figure S2. Propensity Score Matching Analysis Between Patients who Underwent Modified Bruce and Bruce Protocols

A. Distribution of Logit of Propensity Score in Patients who Underwent Modified Bruce and Bruce Protocol



B. Standardized difference of covariates before and after matching in patients with modified Bruce and Bruce tests. Of 8,377 patients with modified Bruce testing, 7,300 were matched using a caliper < 0.2 standard deviations of the logit of the propensity score.

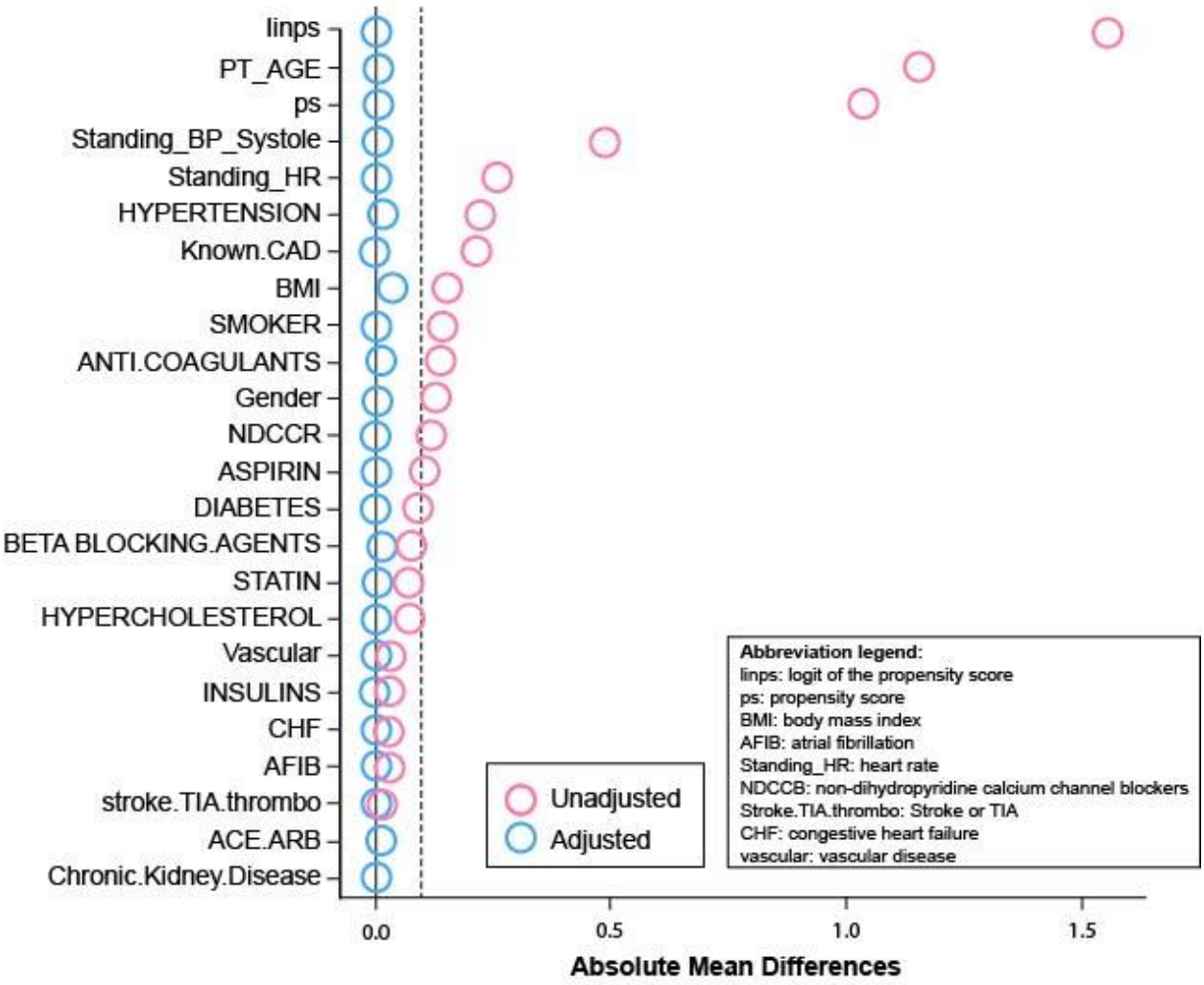
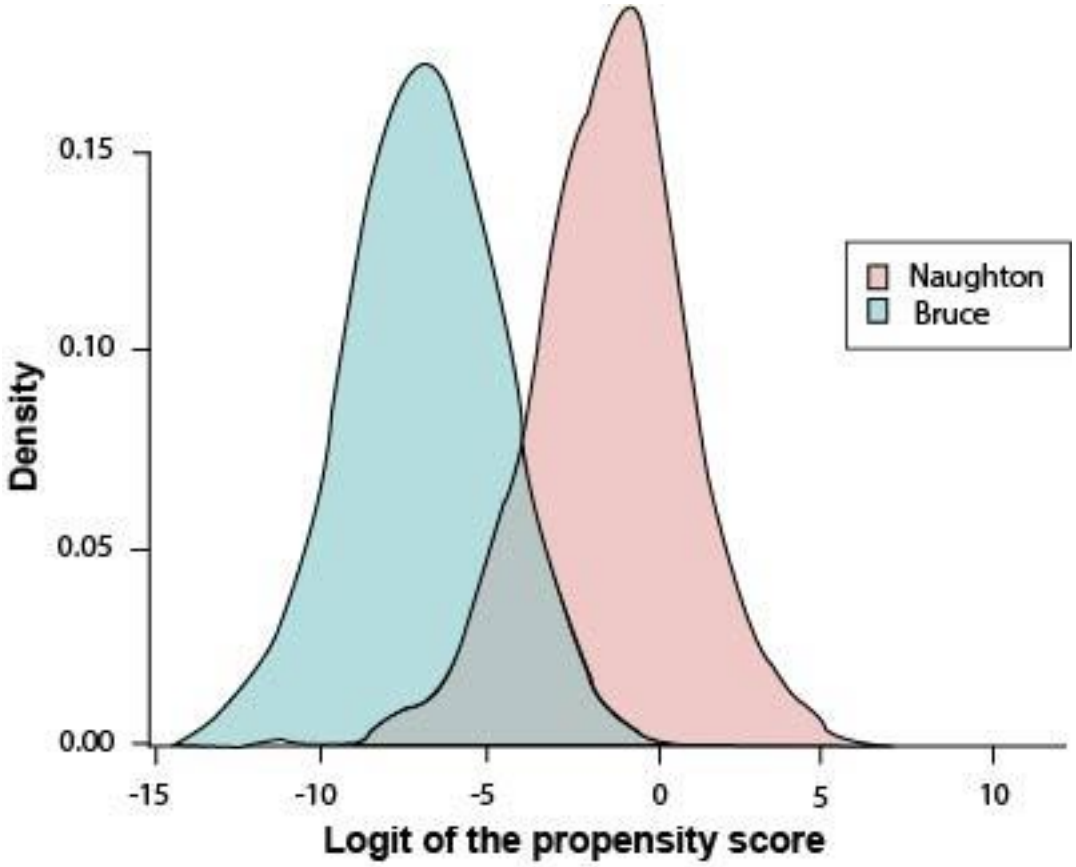


Figure S3. Propensity Score Matching Analysis Between Patients who Underwent Naughton and Bruce Protocols

A. Distribution of Logit of Propensity Score in Patients who Underwent Naughton and Bruce Protocols.



B. Standardized difference of covariates before and after matching in patients with Naughton and Bruce tests. Of 1,230 patients with Naughton testing,1,045 were matched using a caliper ≤ 0.2 standard deviations of the logit of the propensity score.

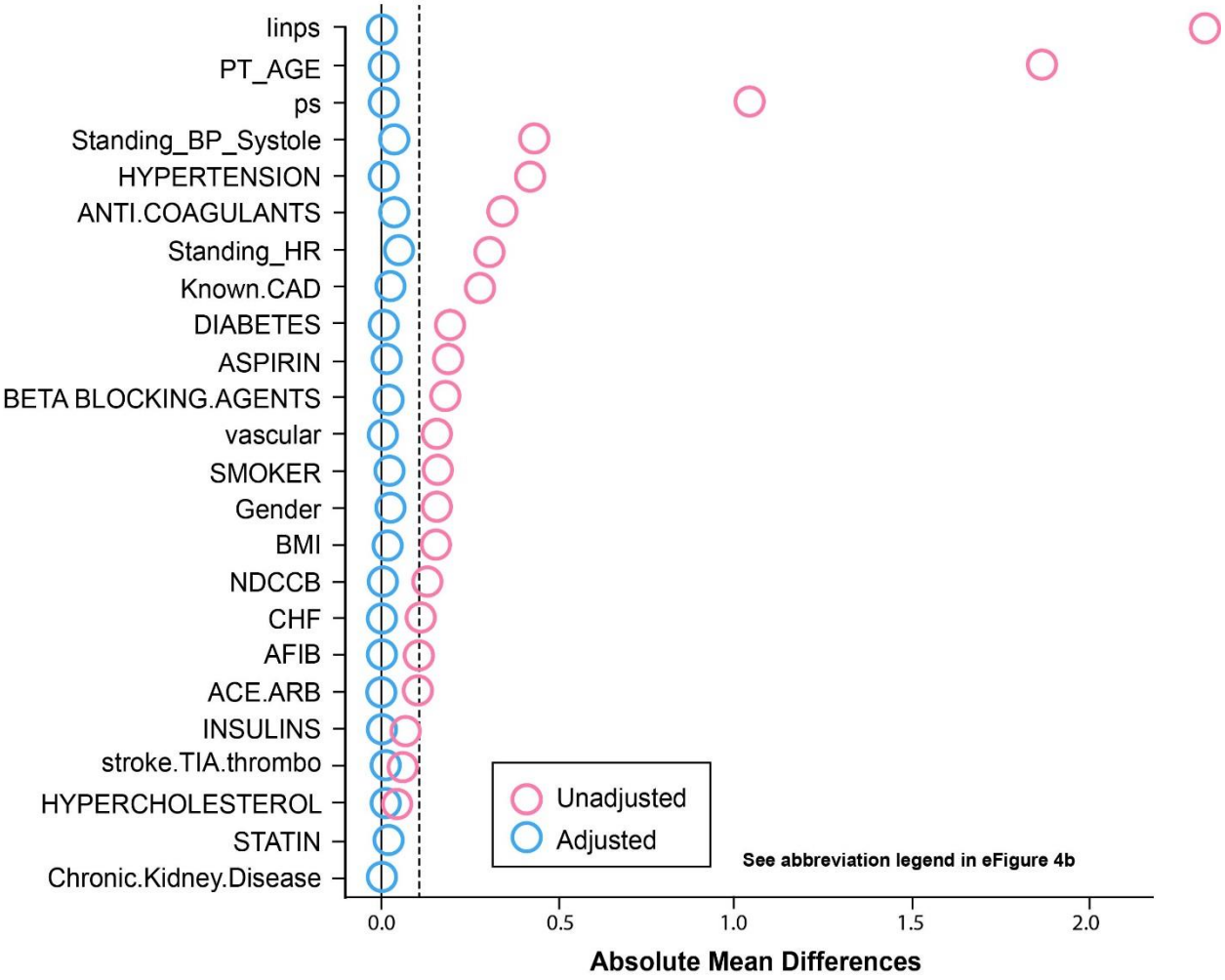
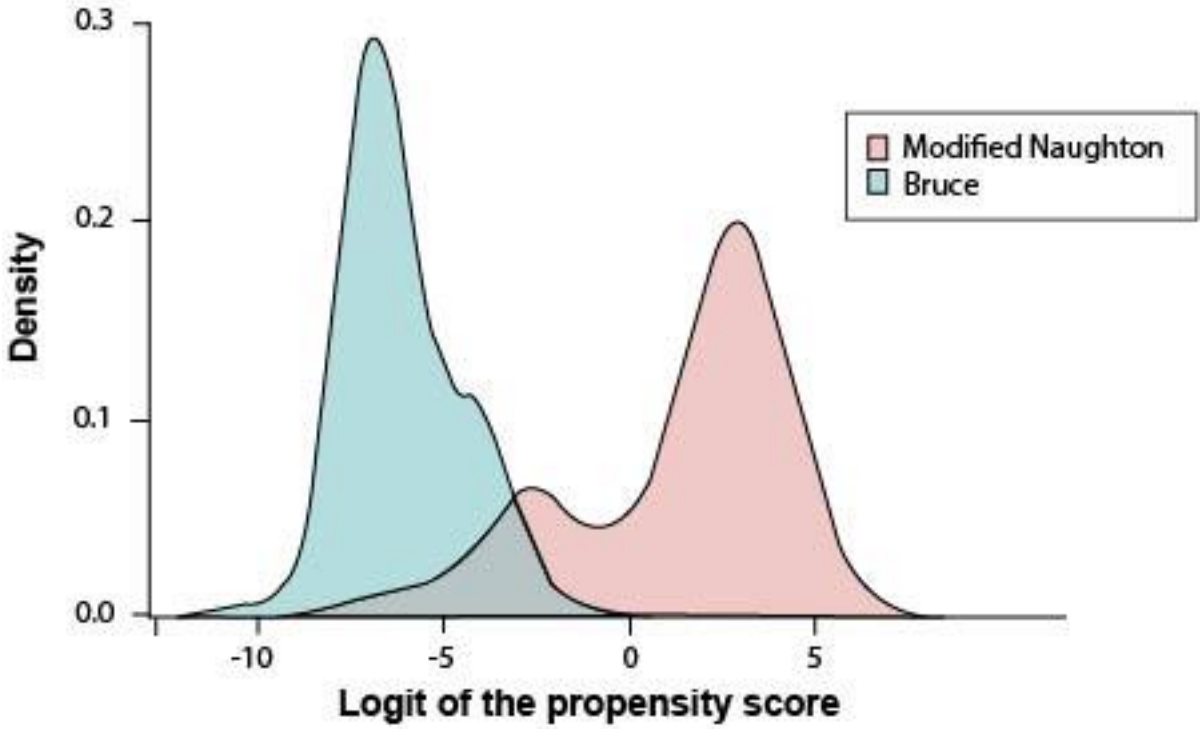


Figure S4. Propensity Score Matching Analysis Between Patients who Underwent Modified Naughton and Bruce Protocols

A. Distribution of Logit of Propensity Score in Patients who Underwent Modified Naughton and Bruce Protocols.



B. Standardized difference of covariates before and after matching in patients with modified Naughton and Bruce tests. Of 3,113 patients with modified Naughton testing, 1,112 were matched using a caliper ≤ 0.2 standard deviations of the logit of the propensity score.

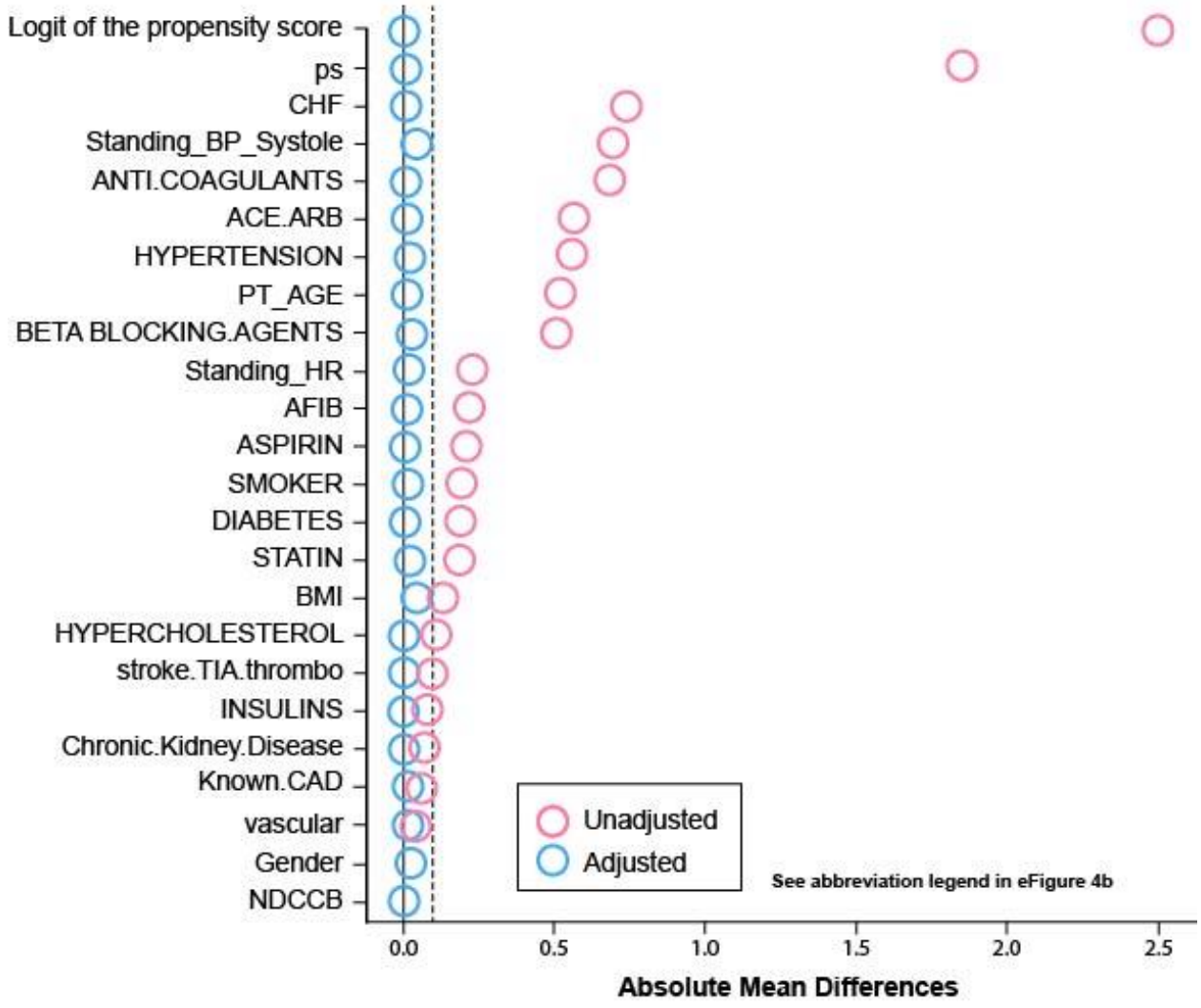
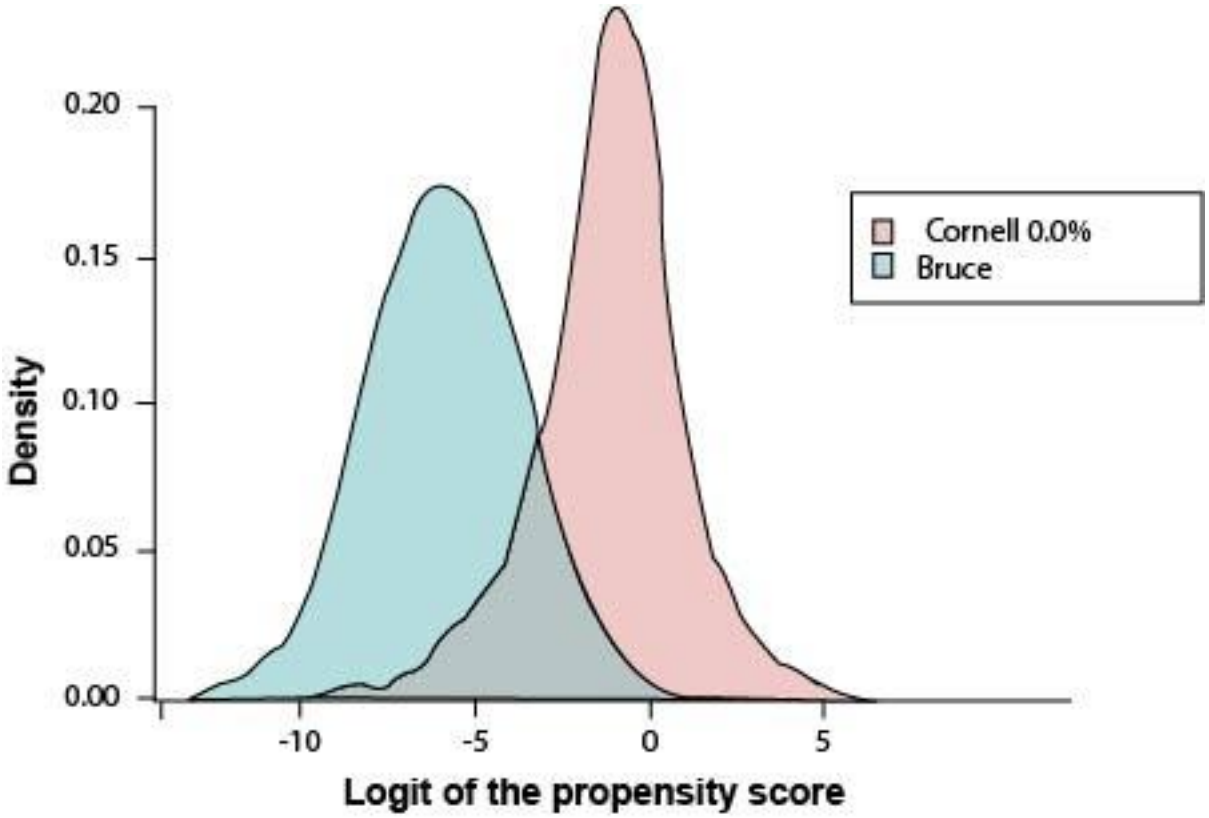


Figure S5. Propensity Score Matching Analysis Between Patients who Underwent Cornell 0% and Bruce Protocols

A. Distribution of logit of propensity score in patients who underwent modified Cornell 0% and Bruce protocols.



B. Standardized difference of covariates before and after matching in patients with Cornell 0% and Bruce tests. Of 2,657 patients with Cornell 0% testing, 2,277 were matched using a caliper ≤ 0.2 standard deviations of the logit of the propensity score.

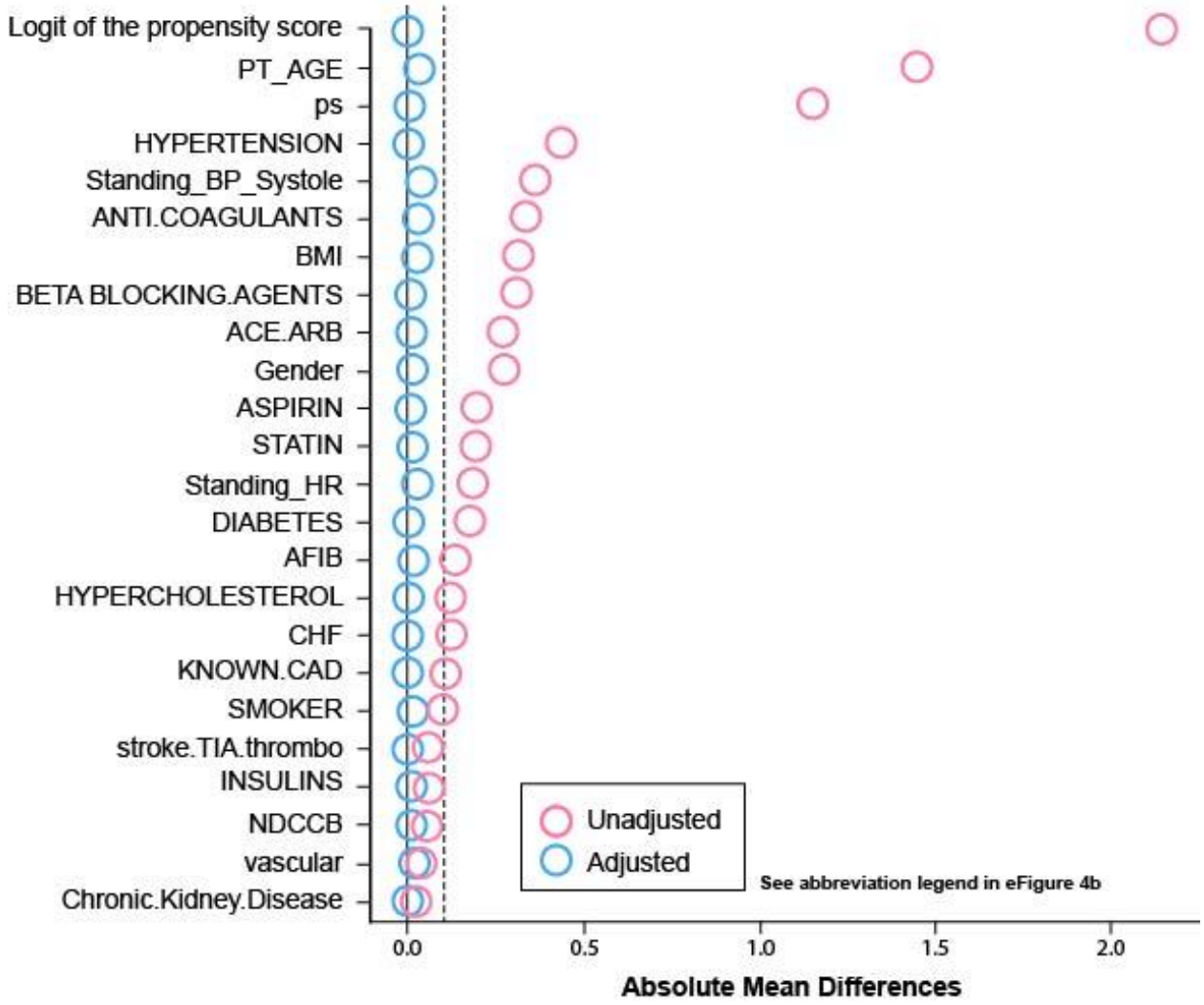
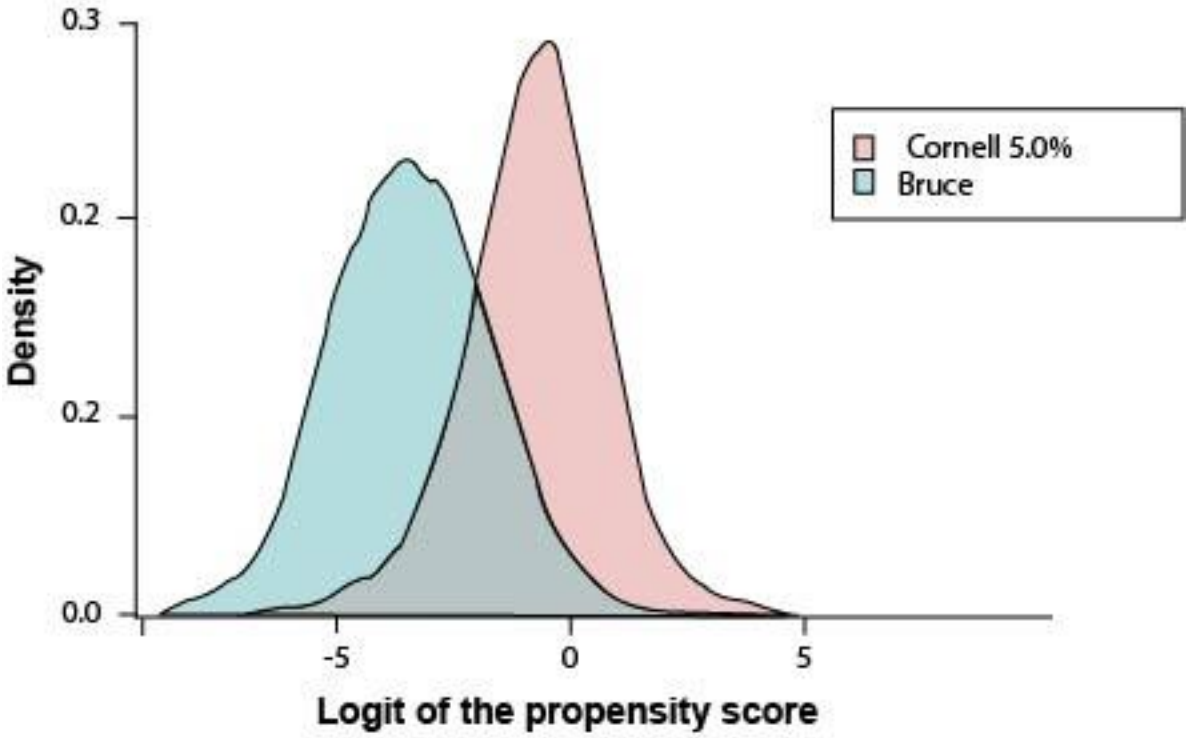


Figure S6. Propensity Score Matching Analysis Between Patients who Underwent Cornell 5% and Bruce Protocols

A. Distribution of logit of propensity score in patients who underwent modified Cornell 5% and Bruce protocols.



B. Standardized difference of covariates before and after matching in patients with Cornell 5% and Bruce tests. Of 9,995 patients with Cornell 5.0% testing, 8,636 were matched using a caliper ≤ 0.2 standard deviations of the logit of the propensity score.

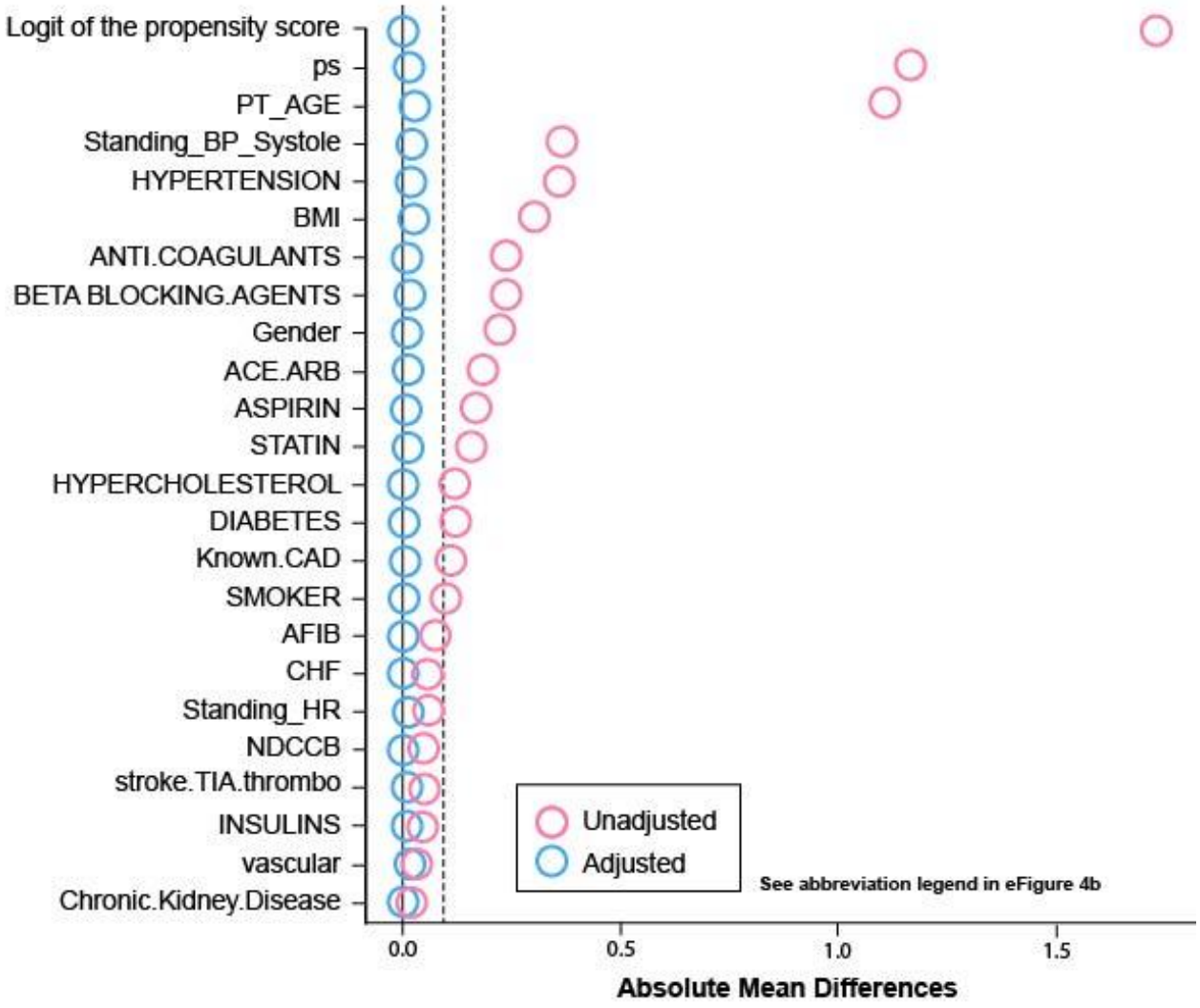
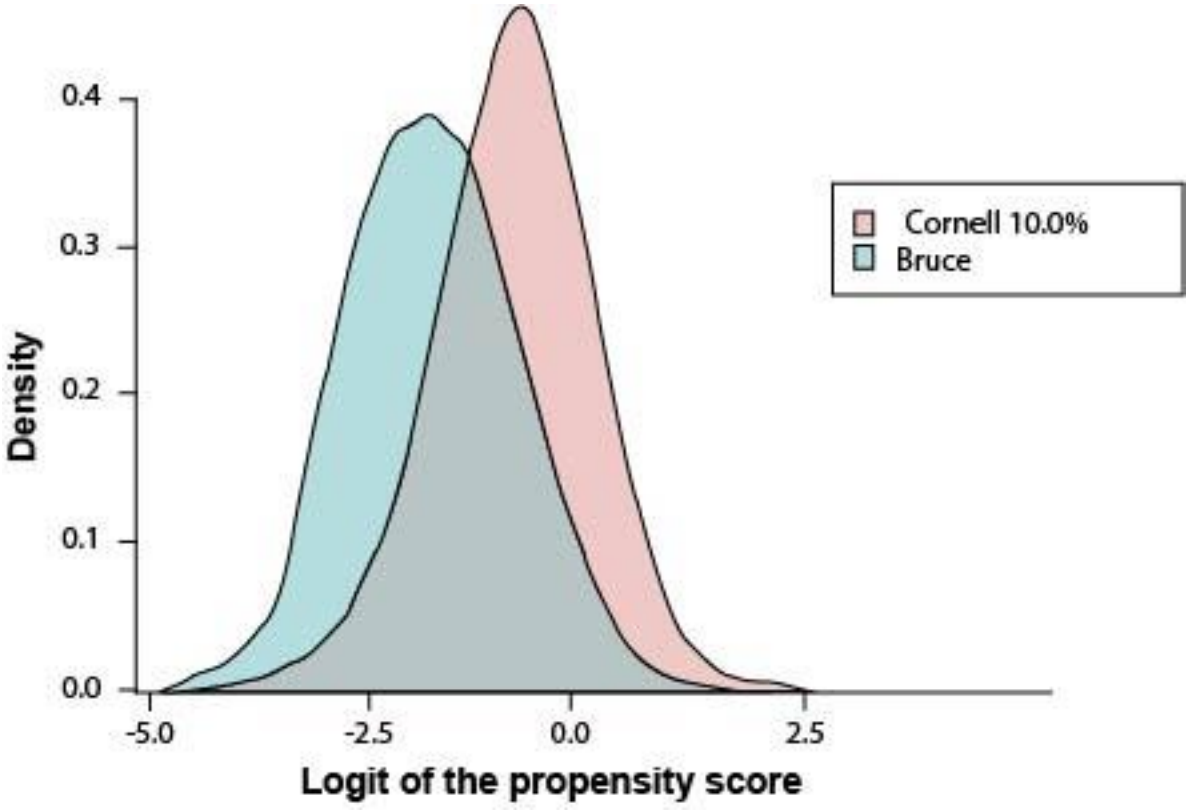


Figure S7. Propensity Score Matching Analysis Between Patients who Underwent Cornell 10% and Bruce Protocols

A. Distribution of logit of propensity score in patients who underwent modified Cornell 10% and Bruce protocols.



B. Standardized difference of covariates before and after matching in patients with Cornell 10% and Bruce tests. Of 20,471 patients with Cornell 10.0% testing, 19,813 were matched using a caliper ≤ 0.2 standard deviations of the logit of the propensity score.

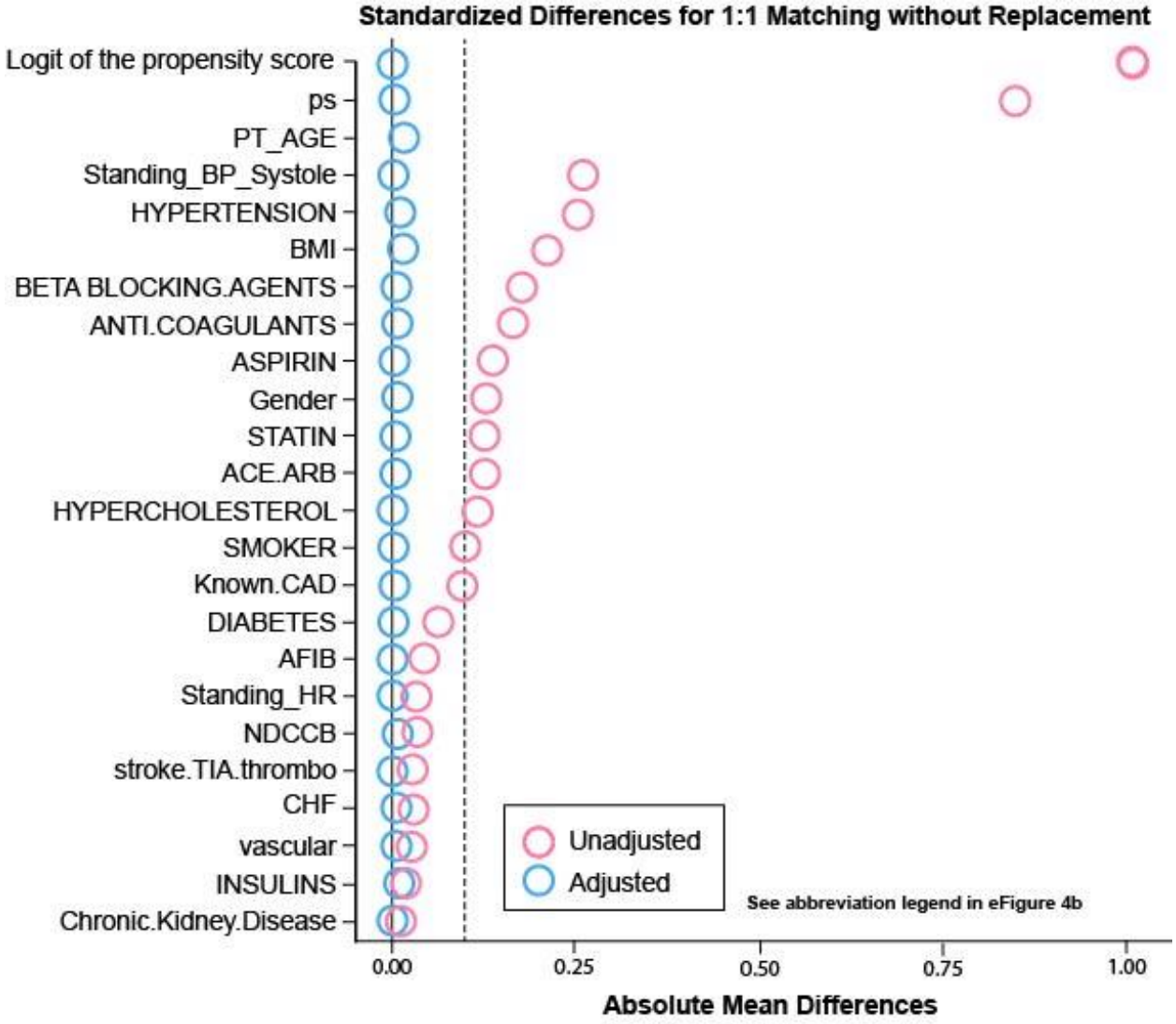


Figure S8. Proportion of Exercise vs Pharmacologic Stress by Year

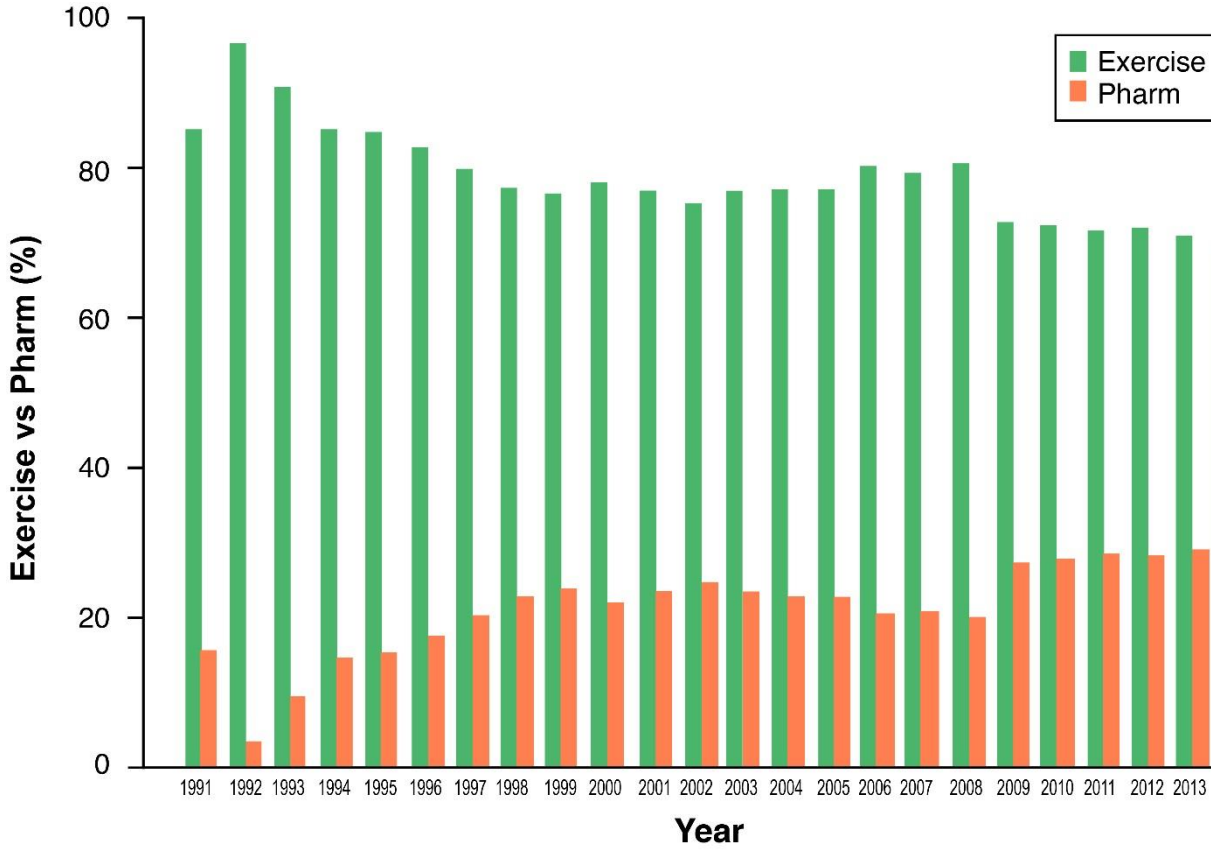


Figure S9. Median Age by Year