Prevalence of Cardiovascular Disease after Traumatic Brain Injury (TBI): A Comparison Between the TBI Model Systems and National Health and Nutrition Examination Survey (NHANES)

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Rationale for the Study

- Cardiovascular disease (CVD) is a leading cause of death in the United States
- CVD and CVD risk factors are associated with cognitive decline and dementia in general population
  - Important to identify these treatable risk factors in persons with TBI

Primary objective: To compare the prevalence of cardiovascular conditions in a those with moderate to severe TBI enrolled in the TBI Model Systems (TBIMS) to a propensity-matched community-based control cohort using the National Health and Nutrition Examination Survey (NHANES) database.

Data Sources

- TBI Model Systems
  - Moderate to severe TBI
  - Enrolled during/after inpatient rehabilitation
  - Followed at years 1, 2, 5, and every 5 years thereafter
  - Self-reported questions regarding health conditions harmonized to NHANES at follow-up
- NHANES
  - Random sample of the general population in the United States
  - Cross-sectional survey
- Included those aged 18-years-old and older with interviews between January 2015 and March 2020

Pinto SM, Thakur B, Kumar RG, Rabinowitz A, Zafonte R, Walker WC, Ding K, Driver S, Venkatesan UM, Moralez G, Bell KR. Prevalence of Cardiovascular Conditions after Traumatic Brain Injury (TBI): A Comparison Between the TBI Model Systems (TBIMS) and National Health and Nutrition Examination Survey (NHANES). *Journal of the American Heart Association*. 2024 May 7; 13(9):e033673.

Propensity Score Matching

- Variables
  - Age
  - Sex
  - Race
  - Ethnicity
  - Body mass index (BMI)
  - Education – high school or greater vs less than high school
  - Current smoking status
- 1:1 Matching

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Propensity Score Matching (PSM)

- To reduce confounding and balance covariates between the TBI patients (TBIM) and the community-dwelling healthy controls (NHANES).
- To replace the RCTs to establish the causation (PMID: 38577204)
- The scores were estimated using a ***probit*** regression model that includes the following covariates: age, BMI, sex, race, ethnicity, education, and smoking status.
- We implemented ***one-to-one nearest neighbor propensity score matching*** without replacement, applying a ***caliper of 0.01*** on the propensity score to ensure that matched pairs were closely comparable.
- Units outside the caliper range were excluded from the matched set. After matching, balance on covariates was assessed between treatment groups.
- Primary outcomes included ***Hypertension***, ***Congestive Heart Failure***, ***Heart Attack***, ***Stroke***, **and** ***Diabetes***, measured as binary indicators.
- By default, ***psmatch2*** calculates approximate standard errors on the group effects assuming independent observations, fixed and equal weights, and homoskedasticity of the outcome variable within the treated and within the control groups, and that the variance of the outcome does not depend on the propensity score.
- Other options: heteroskedasticity-consistent analytical standard errors, bootstrap

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Propensity Score Matching (PSM)

	datatype	_pscore	_treated	pair	paircount
1	Control	.01418306	Untreated	1	2
2	TBI	.01891479	Treated	1	2
3	Control	.03370356	Untreated	4	2
4	TBI	.03358849	Treated	4	2
5	Control	.04002255	Untreated	7	2
6	TBI	.03991302	Treated	7	2
7	Control	.05060349	Untreated	10	2
8	TBI	.04907716	Treated	10	2
9	Control	.07730531	Untreated	21	2
10	TBI	.07763169	Treated	21	2
11	Control	.08044875	Untreated	24	2
12	TBI	.08022781	Treated	24	2
13	TBI	.0936193	Treated	37	2
14	Control	.09337281	Untreated	37	2
15	TBI	.10075676	Treated	43	2
16	Control	.10043055	Untreated	43	2
17	Control	.10783716	Untreated	51	2
18	TBI	.10824928	Treated	51	2
19	TBI	.11219585	Treated	54	2
20	Control	.11205261	Untreated	54	2

Based on the propensity score, this looks like perfect matching!

Should similarity be judged only by the propensity score?

What about the covariates' balance within a matched pair?

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Propensity Score Matching (PSM)

	AGEF	BMIF	SexF	Race	EthnicityF	edu	smk_yes...	datatype	_pscore	_treated	pair	paircount
1	74	60.6	Female	Black	Non-Hispanic	High School and Above	Yes	Control	.01418306	Untreated	1	2
2	64	99.6	Male	White	Non-Hispanic	less than high school	No	TBI	.01891479	Treated	1	2
3	38	59.4	Female	White	Hispanic	High School and Above	Yes	Control	.03370356	Untreated	4	2
4	80	32.2	Female	Black	Hispanic	High School and Above	Yes	TBI	.03358849	Treated	4	2
5	53	61.7	Female	Black	Non-Hispanic	less than high school	Yes	Control	.04002255	Untreated	7	2
6	56	51.4	Female	Others	Hispanic	High School and Above	Yes	TBI	.03991302	Treated	7	2
7	48	61.1	Female	Black	Non-Hispanic	less than high school	Yes	Control	.05060349	Untreated	10	2
8	35	73.5	Male	Black	Non-Hispanic	High School and Above	Yes	TBI	.04907716	Treated	10	2
9	50	45.9	Female	Others	Hispanic	High School and Above	Yes	Control	.07730531	Untreated	21	2
10	34	41.8	Female	Black	Hispanic	High School and Above	Yes	TBI	.07763169	Treated	21	2
11	59	47.6	Female	Black	Non-Hispanic	High School and Above	Yes	Control	.08044875	Untreated	24	2
12	57	34.3	Female	Asian/Pacific Islander	Non-Hispanic	High School and Above	Yes	TBI	.08022781	Treated	24	2
13	50	49.4	Female	Black	Non-Hispanic	High School and Above	Yes	TBI	.0936193	Treated	37	2
14	77	37.9	Female	Black	Non-Hispanic	High School and Above	Yes	Control	.09337281	Untreated	37	2
15	43	45.3	Female	Others	Hispanic	High School and Above	Yes	TBI	.10075676	Treated	43	2
16	41	46.2	Female	Others	Hispanic	High School and Above	Yes	Control	.10043055	Untreated	43	2
17	58	44	Female	Black	Non-Hispanic	High School and Above	Yes	Control	.10783716	Untreated	51	2
18	56	44.8	Female	Black	Non-Hispanic	High School and Above	Yes	TBI	.10824928	Treated	51	2
19	80	21.7	Female	Asian/Pacific Islander	Hispanic	less than high school	No	TBI	.11219585	Treated	54	2
20	62	51.2	Male	Black	Non-Hispanic	High School and Above	Yes	Control	.11205261	Untreated	54	2

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Prior to matching

Factor	Level	Control	TBI	p-value
N		15685	11063	
Age in years at screening, mean (SD)		49.0 (18.6)	47.4 (17.0)	<0.001
SexF	Female	8080 (51.5%)	2965 (26.8%)	<0.001
	Male	7605 (48.5%)	8094 (73.2%)	
Body Mass Index (kg/m**2), mean (SD)		29.7 (7.4)	27.2 (5.8)	<0.001
Race	White	7479 (47.7%)	7470 (67.5%)	<0.001
	Black	3820 (24.4%)	1883 (17.0%)	
	Asian/Pacific Islander	1898 (12.1%)	299 (2.7%)	
	Others	2488 (15.9%)	1411 (12.8%)	
EthnicityF	Non-Hispanic	11701 (74.6%)	9578 (87.0%)	<0.001
	Hispanic	3984 (25.4%)	1434 (13.0%)	
edu	less than high school	3124 (20.9%)	2347 (21.3%)	0.47
	High School and Above	11807 (79.1%)	8676 (78.7%)	
smk_yes_no	No	3527 (55.9%)	7920 (72.0%)	<0.001
	Yes	2784 (44.1%)	3076 (28.0%)	

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After matching

Factor	Level	Control	TBI	p-value
N		4690	4690	
Age in years at screening, mean (SD)		52.3 (17.3)	52.1 (16.6)	0.58
SexF	Female	1641 (35.0%)	1629 (34.7%)	0.79
	Male	3049 (65.0%)	3061 (65.3%)	
Body Mass Index (kg/m**2), mean (SD)		28.9 (6.5)	29.0 (6.6)	0.22
Race	White	2688 (57.3%)	2590 (55.2%)	0.22
	Black	1068 (22.8%)	1116 (23.8%)	
	Asian/Pacific Islander	230 (4.9%)	233 (5.0%)	
	Others	704 (15.0%)	751 (16.0%)	
EthnicityF	Non-Hispanic	3825 (81.6%)	3807 (81.2%)	0.63
	Hispanic	865 (18.4%)	883 (18.8%)	
edu	less than high school	1048 (22.3%)	1103 (23.5%)	0.18
	High School and Above	3642 (77.7%)	3587 (76.5%)	
smk_yes_no	No	2845 (60.7%)	2756 (58.8%)	0.061
	Yes	1845 (39.3%)	1934 (41.2%)	

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Analytical Strategies

- Various recommended analytical methods for matched data
- Considering independent groups
  - Independent t-test, Chi-square/Fisher's exact test, logistic regression, etc.
- Based on considering matched pairs
  - Paired t-test, McNemar's chi-square, conditional logistic, etc.
- It has been recommended to analyze the PSM data in the same way as we do for RCT.
- Mixed-effect model considering matched pairs as random effects could be one of the alternative methods.

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Analytical Strategies for Binary Outcome Example: Hypertension

1. *logit HypertensionF datatype, or*
2. *logit HypertensionF datatype _pscore, or*
3. *logit HypertensionF datatype pair, or*
4. *logit HypertensionF datatype, or cluster(pair)*
5. *clogit HypertensionF datatype, group(pair) or*
6. *clogit HypertensionF datatype, group(pair) or vce(bootstrap)*
7. *clogit HypertensionF datatype, group(pair) or vce(robust)*

8. *xtmelogit HypertensionF datatype || pair: , or*
9. *xtmelogit HypertensionF datatype || pair: , or covariance(unstructured)*

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Analytical Strategies

- For PS matching, the variability of the estimated treatment effect is affected by the correlation between outcomes of patients in a matched set because patients within a matched set are more likely to be similar compared to unmatched patients. (PMID: 30276839)
- In case of matching without replacement, this correlation can be accounted for with a cluster-robust standard error estimator, which treats the matched sets as clusters. (PMID: 35387508)
- Such standard errors can be obtained from generalized estimating equations or generalized linear mixed models, or with analytic formulas (see *Greifer* for implementations in R).
- They recommended including pair ID as random effects in a logistic regression model, using the coefficient on treatment (here TBI) as the effect estimate.

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Strength linked with Mixed Effects model

1. Treat the matched sets as a random draw from a larger population of potential matched sets, allowing for estimation of variance components at the matched set level.
2. Can handle situations with varying numbers of individuals.
3. Can include all groups, even those with all outcomes that are the same.
4. Acknowledges the inherent dependence of observations within matched sets.
5. Gain efficiency in the computed estimates compared to ignoring the clustering.
6. Control for the measured matching factors through the design and account for potential residual confounding or unmeasured shared factors within sets through the random effects.
7. Random effects allow us to model the variability in the outcome or the exposure-outcome relationship across different matched sets.

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Population

TBIMS Database
(n = 14,870)

Patients excluded
(n = 3,807)

Reason for exclusion: (n = 3,807)

1. Ethnicity did not exist:	47
2. CVD health status was unknown/NA:	260
3. CVD health status reported as did not exist:	211
4. Archived outcome data is unknown/NA:	3,147
5. Cases with all the final outcomes are missing:	52
6. Followed up age missing:	18
7. Year of Interview missing:	64
8. Age at follow up < 18 years:	8

Included patients from
TBIMS (n = 11063)

NHANES
(n = 25,531)

Patients excluded
(n = 9,846)

Reason for exclusion: (n = 9,846)
1. Age at interview < 18 years: 9,846

Included patients from
NHANES (n = 15,685)

Matched Sample based on Propensity Score
Matched Analysis

Matched patients from
TBIMS (n = 4,690)

Matched patients from
NHANES (n = 4,690)

	NHANES (N = 15685)	TBIMS (N=11063)
Age at time of interview; Mean (SD)	47.4 (17.7)	47.7 (17.7)
Female Sex; n (%)	8080 (51.8)	2965 (26.8)
Body Mass Index (kg/m^2); Mean (SD)	29.5 (7.2)	27.2 (5.8)
Race; n (%)		
▪ White	7479 (71.6)	7470 (67.5)
▪ Black	3820 (11.5)	1883 (17.02)
▪ Asian/Pacific Islander	1898 (5.9)	299 (2.7)
▪ Other	2488 (11.0)	1411 (12.7)
Hispanic Ethnicity; n (%)	3984 (16.0)	1434 (13.0)
Education; n (%)		
▪ Completed High School	11807 (87.2)	8676 (78.7)
▪ Less than High School	3124 (12.8)	2347 (21.3)
Current Cigarette Smoker; n (%)†	2784 (44.1)	3076 (28.0)
Year of Interview; n (%)		
▪ 2015 – 2016	5992 (49.2)	3035 (27.4)
▪ 2017 – March 2020	9693 (50.8)	8028 (72.6)
TBI Injury Severity		
▪ GCS; Mean (SD); Median; IQR	-----	9.4 (4.6); 10 (5 – 14)
▪ PTA Days; Mean (SD); Median, IQR	-----	22.8 (22.1); 18 (7 – 32)
Years post-TBI: Mean (SD); Median; IQR	-----	7.8 (6.2); 5 (2 – 10)
Cardiovascular Disease Estimates; n (%)		
▪ Hypertension	5661/15667 (31.7)	3879/11060 (35.1)
▪ Heart Failure	575/14917 (2.5)	331/11056 (3.0)
▪ Heart Attack	683/14928 (3.5)	421/11055 (3.8)
▪ Stroke	696/14930 (3.2)	924/11057 (8.4)
▪ Diabetes	2268/15676 (11.1)	1372/11056 (12.4)

Results

	NHANES (N=4690)	TBIMS (N=4690)	p-value
Age at time of interview; Mean (SD)	52.3 (17.3)	52.1 (16.6)	0.58
Female Sex; n (%)	1641 (35.0%)	1629 (34.7%)	0.79
Body Mass Index (kg/m^2); Mean (SD)	28.9 (6.5)	29.0 (6.6)	0.22
Race; n (%)			0.22
▪ White	2688 (57.3%)	2590 (55.2%)	
▪ Black	1068 (22.8%)	1116 (23.8%)	
▪ Asian/Pacific Islander	230 (4.9%)	233 (5.0%)	
▪ Other	704 (15.0%)	751 (16.0%)	
Hispanic Ethnicity; n (%)	865 (18.4%)	883 (18.8%)	0.63
At Least High School Education; n (%)	3642 (77.7%)	3587 (76.5%)	0.18
Current Cigarette Smoker; n (%)	1845 (39.3%)	1934 (41.2%)	0.061

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Results

	NHANES (N=4690)	TBIMS (N=4690)
TBI Injury Severity		
▪ **GCS; Mean (SD); Median (IQR)**	-----	9.99 (4.5); 11 (6 – 14)
▪ **PTA Days; Mean (SD); Median (IQR)**	-----	21.7 (21.2); 17 (5 – 32)
Years post-TBI: Mean (SD); Median (IQR)	-----	8.2 (6.4); 5; (2 – 10)
Cardiovascular Disease Estimates; n (%)		
▪ **Hypertension**	1926 (41.1%)	2109 (45.0%)
▪ **Heart Failure**	240 (5.1%)	196 (4.2%)
▪ **Heart Attack**	322 (6.9%)	218 (4.6%)
▪ **Stroke**	293 (6.2%)	475 (10.1%)
▪ **Diabetes**	735 (15.7%)	800 (17.1%)

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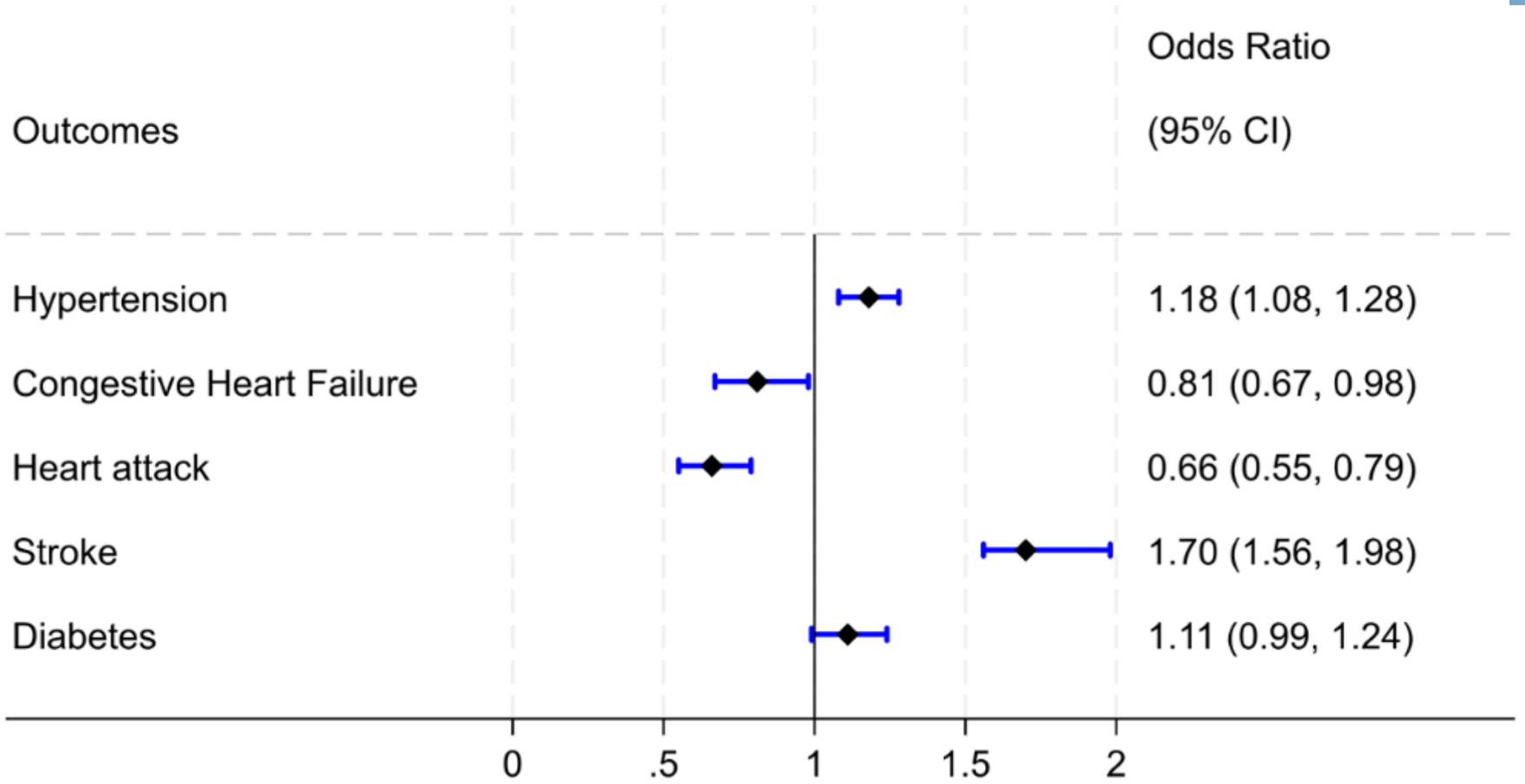
Results



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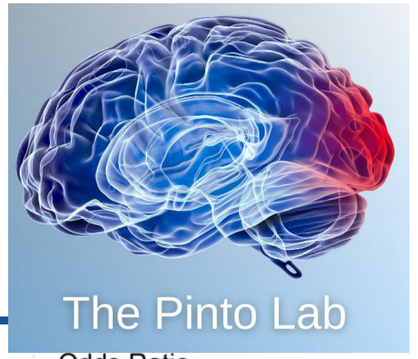

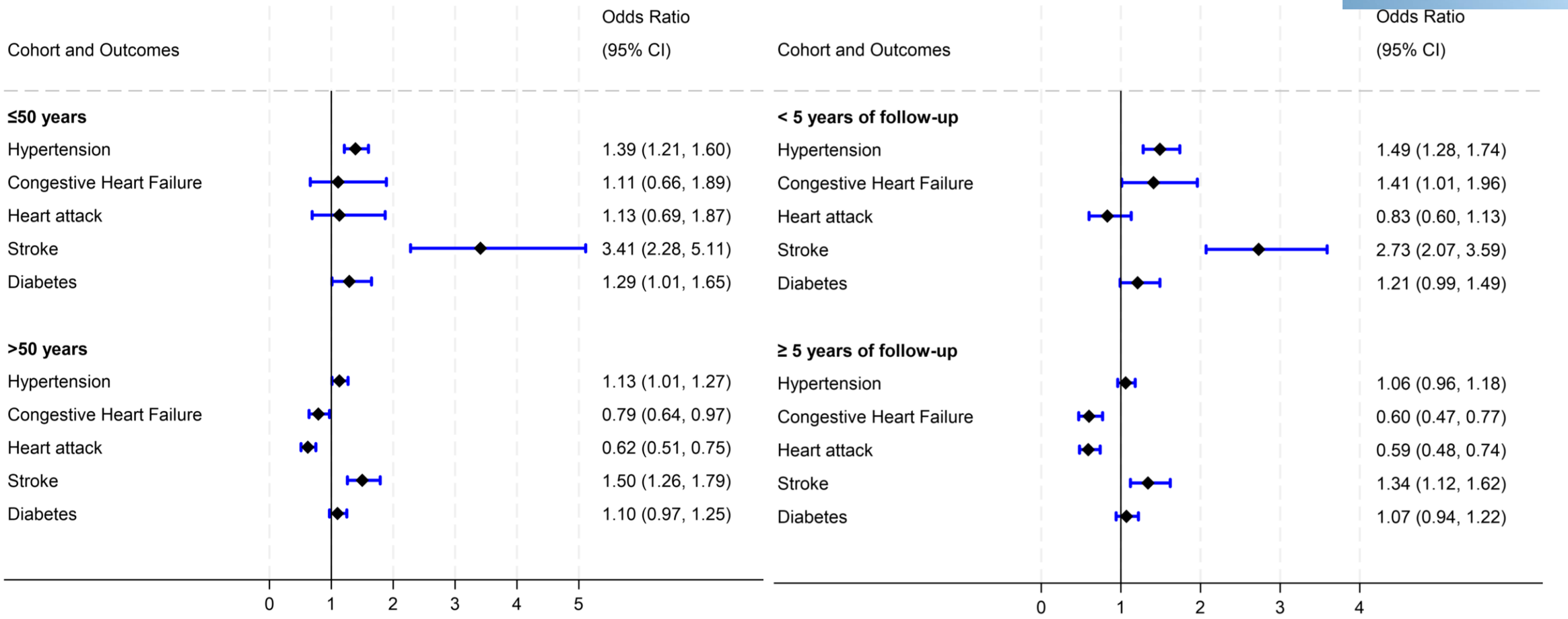

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Cause of Death for Those Died Before Year 1

Primary Cause of Death	<=50 years	>50 years
N died/N injured (percent mortality)	**504/11165 (4.5%)**	**1094/5435 (20.1%)**
Ischemic heart disease	14 (2.8%)	94 (8.6%)
Other form of heart disease	29 (5.8%)	99 (9.0%)
Cerebrovascular disease	7 (1.4%)	48 (4.4%)
Other causes of death	336 (66.7%)	683 (62.4%)
Unknown cause of death	118 (23.4%)	170 (15.5%)

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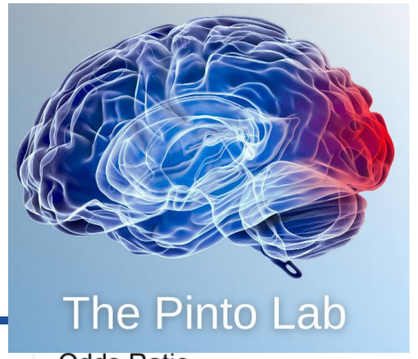

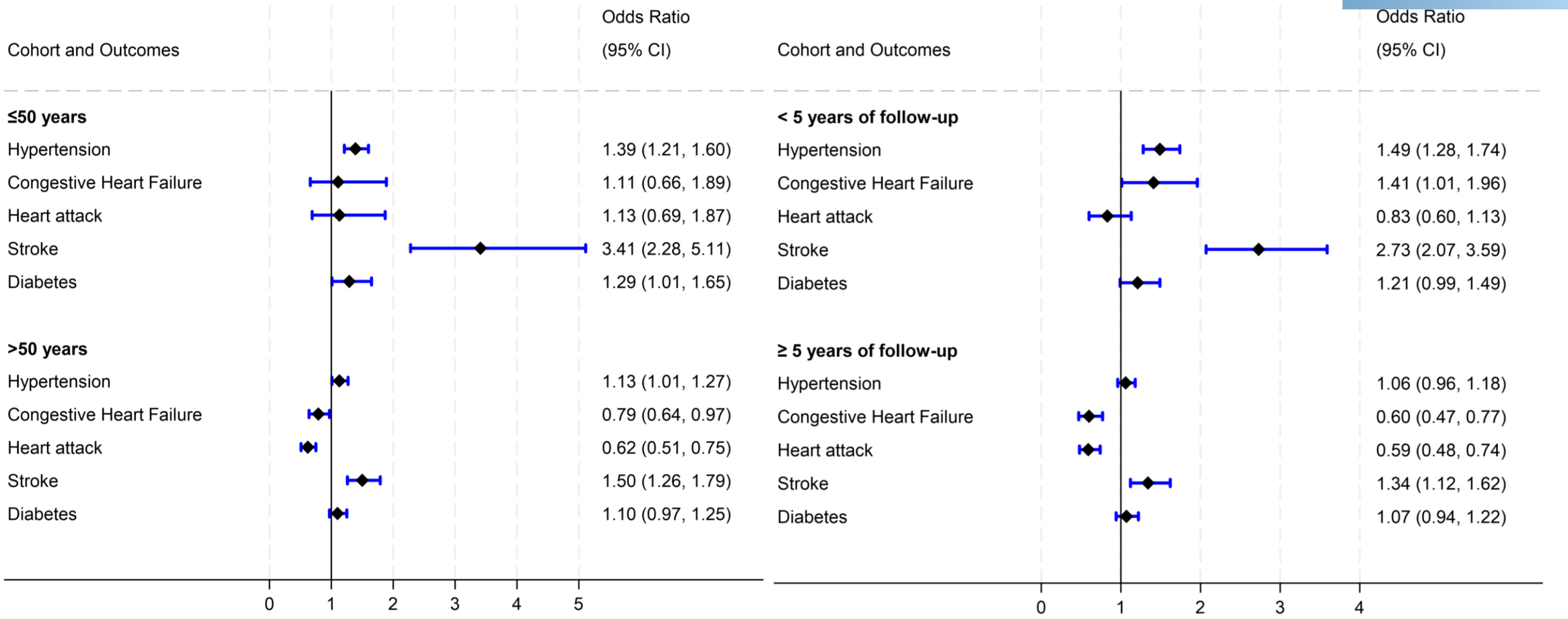

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Conclusions

- Compared with the control cohort, individuals with TBI:
  - ↑ rate hypertension and stroke
  - ↓ rate MI and CHF
    - Lethality of these conditions may have impacted findings
- Limitations
  - Unable to control for alcohol, substance use, or sociodemographic factors due to variability in the way these variables were collected in the two databases
  - Unknown TBI status for those in the NHANES database

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Alcohol Variables

NIAAA concept	TBIMS	NHANES
Abstains	Q1: at least 1 drink in past month	ALQ 111 (do you drink?) = No and ALQ (days drank in 12 months) 121 = 0
Exceeds daily risk (>4/day M; >3/day F (binge drinking)	Exceeds based on answer to either Q3 or Q4 Q3: on days when you drank, how many on average (past month) Q4: How many times >4 M, >3 F (only after 2017)	Exceeds based on any of the following: ALQ 130 (# drinks/day) ALQ 142 (#days binging past year) ALQ 170 (#days binging past 30 days)
Exceeds weekly risk (>14/week M; >7/week F)	Q2: how many drinks per week or per month (past month)	Based on combined responses from ALQ 121 and ALQ 130
Binging past 30 days	Positive based on either Q3 or Q4	ALQ 170
# drinks/month	Q2 # days (up to 30) x Q3 avg/day	Combine responses from ALQ 121 and ALQ 130 (need to use mid-point for some with ranges)

Timing is a problem: **Past month** **Past 12 months**

Credit to John Corrigan for this Table

Clinical Scenario

- 25M drinks 6 beers per day until 3 months ago, now does not drink
  - **TBIMS**: Abstains
  - **NHANES**: Exceeds daily risk (binge) and weekly risks
  - **NHANES Q170** (binge in 30 days): Does not binge
  - **NHANES Drinks/day**: 4.44 = (9 months * 30 days/month * 6 drinks/day)/365 days

Questions?

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