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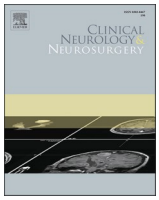

Full length article

Race and sex disparities in acute outcomes of patients with acute ischemic stroke and diabetes mellitus. A national inpatient sample study

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ABSTRACT

Background: Diabetes Mellitus (DM) disproportionately affects racial minority groups and is a well-established risk factor for ischemic stroke and worse stroke outcomes. Whether racial disparities exist in acute outcomes of patients presenting with Acute Ischemic Stroke (AIS) and comorbid DM, including potential differences in the administration of evidence-based reperfusion therapy, remains unclear. We aimed to assess whether racial and sex differences exist in the acute outcomes and treatment of patients with DM presenting with AIS.

Methods: January 2016-December 2018 AIS admissions with diabetes were extracted from the US National Inpatient Sample (NIS). Multivariable logistic regressions assessed the association between race, sex, and differences in in-hospital outcomes (mortality, hospitalisation >4 days, routine discharge, and stroke severity). Further models assessed the relationship between race, sex, and receipt of thrombolysis and thrombectomy. All models were adjusted for relevant confounders, including comorbidities and stroke severity.

Results: 92,404 records representative of 462,020 admissions were extracted. Median (IQR) age was 72 (61−79), with 49 % women, 64 % White, 23 % African American, and 10 % Hispanic patients. African Americans had lower odds of in-hospital mortality compared to Whites (adjusted odds ratio; 99 % confidence interval=0.72;0.61–0.86), but were more likely to have prolonged hospitalisation (1.46;1.39–1.54), be discharged to locations other than home (0.78;0.74–0.82) and have moderate/severe stroke (1.17;1.08–1.27). Additionally, African American (0.76;0.62–0.93) and Hispanic patients (0.66;0.50–0.89) had lower odds of receiving thrombectomy. Compared to men, women had increased odds of in-hospital mortality (1.15;1.01–1.32).

Conclusions: Racial and sex disparities exist in both evidence-based reperfusion therapy and in-hospital outcomes amongst patients with AIS and diabetes. Further measures are needed to address these disparities and reduce the excess risk of adverse outcomes among women and African American patients.

1. Introduction

A two-fold excess risk of incident acute ischaemic stroke (AIS) exists in patients with Diabetes Mellitus (DM), with 37–42 % of stroke cases being attributed to DM and/or hypertension [1]. In comparison to men, this excess risk is more pronounced in women [2], the underlying mechanism of which remains unclear. Disparities by age and race have also been explored regarding the diabetes-stroke relationship [2–5]. Results from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study highlight increased risk for black and white women and white men, in patients with DM in comparison to those without DM [6]. What remains unclear however, is whether such disparities transpire in in-hospital outcomes of patients with AIS and comorbid DM. In light of the large increase in DM prevalence including in

Abbreviations: AIS, Acute Ischaemic Stroke; EVT, Endovascular Thrombectomy; IVT, Intravenous Thrombolysis; HCUP, Healthcare Cost and utilisation Project; ICD-10, International Classification of Disease, tenth edition; LOS, Length of stay; NIHSS, National Institutes of Health Stroke Scale; NIS, National Inpatient Sample; US, United States; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

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the younger population [7], it is important to comprehensively evaluate the effect race and sex may have on stroke outcomes and whether disparities exist. These results are important for personalised medicine and to be able to escalate care in specific groups to achieve equity.

Previous sex-stratified analyses of stroke outcomes in patients with DM report conflicting results. Some studies report lower risks of in-hospital complications in women vs men, with no differences in in-hospital mortality [8], whilst others report a 12 % higher risk of in-hospital mortality after ischaemic stroke in women, despite having no significant differences in receipt of revascularization therapy [9]. Such differences may be attributed to racial differences between the included cohorts. African American, Hispanic, and Asian-American populations, reportedly, have a lower or equal incidence of stroke compared to their White counterparts [4,5]. However, the mortality rate for Hispanic populations from acute stroke is reportedly higher than for the White population [10]. Other reports addressing ethnic and sex disparities in stroke outcomes are limited to small cohorts or samples representative of only one race [10,11]. To the best of our knowledge, no studies exist concurrently conducting race and sex-stratified analysis of post-stroke outcomes in patients with DM.

Using a large administrative database representative of the US population, we aimed to determine the sex and racial disparities in important hospital outcomes (death, prolonged hospitalisation, and routine discharge) amongst patients with ischaemic stroke and DM as well as ascertain whether these differences could be explained by disparities in receipt of revascularisation therapies. Such findings are important to be able to identify specific subgroups along the stroke care continuum that could be targeted for personalised management strategies.

2. Methods

2.1. Study design and data source

This was a retrospective cohort study using data from the largest US all-payer inpatient claims-based database, the National Inpatient Sample (NIS), which represents a 20 % stratified sample of all community hospital admissions [12]. Each record sampled in the NIS is assigned a sampling weight (a measure inversely related to the probability of each hospital discharge being selected into the sample) [13]. Using the provided sampling weight and information regarding the NIS strata, this dataset can provide national estimates for the sampling population, representative of 95 % of the US population [12]. The authors completed the online Healthcare Cost and Utilization project Training Tool, and read and signed the Data Use Agreement. The NIS is an anonymised, publicly available database. Ethical approval was not required. As of October 1st, 2016, reporting of the NIHSS was possible with collection of ICD-10-CM codes [14]. Thus u~~U~~sing admission data files between 2016 and 2018, records with a primary diagnosis of ischemic stroke (International Classification of Diseases, Tenth revision [ICD-10] codes I63.0-I63.9) and a secondary diagnosis of diabetes mellitus (ICD-10 E11.00-E11.9) were extracted.

2.2. Definition of outcomes, exposure, and confounders

2.2.1. Outcomes

The following primary outcomes were analysed: (1) in-hospital mortality, (2) prolonged hospitalisation $>$ 4 days, (3) routine discharge, (4) moderate/severe stroke, defined as National Institutes of Health Stroke Scale (NIHSS) $>$ 5. NIHSS was defined by ICD-10-CM codes R29.700 (NIHSS $=$ 0) – R29.742 (NIHSS $=$ 42) [15]. Secondary outcomes were receipt of (a) Intravenous Thrombolysis (IVT) and (b) Endovascular Thrombectomy (EVT) identified using ICD-10-PCS codes (Table SI). Vital status at discharge (dead/alive) and the length of hospital stay (LOS) serve as standard variables in the NIS [16,17]. Prolonged hospitalisation was defined as LOS$>$ 4 days [18]. Discharge status was coded using provided discharge destinations [19]. Discharge destination was dichotomized into routine discharges and other discharges ("home health care", "short term-hospital," "other facilities including intermediate care and skilled nursing homes," "died in hospital," "discharged against medical advice", "discharged to an unknown population"). Stroke severity was classified into the 5 NIHSS levels: 0, no measured stroke symptoms; 1–4, minor stroke; 5–15, moderate stroke; 16–20, moderate to severe stroke; and 21–42, severe stroke.

2.3. Exposure and confounders

Race is coded in the NIS categories: African American, Hispanic, Asian/Pacific islanders, Native American, other. This study analyses White, African American, Hispanic, Asian/Pacific Islanders, Native American. The 'other' category was excluded as missing. All models were adjusted for the confounders detailed in Table SII.

Adjusting covariates was based on clinical judgement and literature [9]. Elixhauser comorbidities were determined using the Healthcare Cost and Utilization Project Elixhauser comorbidity software [20].

2.4. Statistical analysis

Stata/MP 14.1 analyses were performed[21] using provided discharge weights as probability weights and using survey data analysis techniques stratifying by NIS stratum and admission year[22] to account for patient clustering within hospitals [21]. Given the large sample size, a 1 % threshold of statistical significance ($p < 0.01$) was used.

2.5. Missing data

The NIHSS variable had ~75 % data missing (Table 1). Admissions with missing NIHSS data were significantly older, more likely to be women, and had a higher prevalence of comorbidities. More recent admissions and those to urban teaching centres had less NIHSS data missing. Data missingness was likely dependent only on observed, but not unobserved data and subsequently deemed likely missing-at-random [23]. A multiple imputation by chained equation algorithm with 20 iterations was employed to impute missing NIHSS values using an ordinal logistic regression with the predictors outlined in Table SIII. Sensitivity analyses not including NIHSS adjustment were also undertaken (Table SVI, SVII, SIX). These did not reveal any significant differences, except for women receiving EVT.

2.6. Descriptive statistics

Patient characteristics were compared between racial groups and between sexes. The Mann-Whitney and Pearson's Chi-squared tests were employed to compare characteristics for non-normally distributed continuous and categorical variables, respectively.

2.7. Main analyses

Multivariable logistic regressions were employed to examine: the association between race and sex and the odds of receiving IVT or EVT, the association between race and in-hospital outcomes, and the association between sex and in-hospital outcomes. A model containing an interaction term between race and sex explored potential racial differences in sex disparities. Adjusting covariables are listed in Table SII. A mediation analysis was performed excluding revascularisation therapy from the multivariable adjustments in-order to ascertain whether disparities in receipt of revascularisation may drive disparities in the main outcomes.

Table 1
Patient characteristics on admission for patients with comorbid diabetes mellitus, stratified by race. Further descriptive statistics are detailed in Table SIV and SV.

	Total	White	African American	Hispanic	Asian American	Native American	P value
N	462,020	293,590	105,900	45100	14895	2535	
Age,y, median (IQR)	70.00 (61.00–79.00)	72.00 (63.00–80.00)	65.00 (57.00–74.00)	67.00 (57.00–77.00)	70.00 (61.00–78.00)	64.00 (57.00–70.00)	<0.001
Length of Stay, median (interquartile range)	3.00 (2.00–6.00)	3.00 (2.00–5.00)	4.00 (2.00–7.00)	4.00 (2.00–6.00)	3.00 (2.00–6.00)	4.00 (2.00–6.00)	<0.001
Women n(%)	225980 (48.91)	138005 (47.01)	58310 (55.06)	21000 (46.56)	7365 (49.45)	1300 (51.28)	<0.001
Elixhauser comorbidities, n(%)							
Congestive Heart Failure	88270 (19.11)	56140 (19.12)	22730 (21.46)	6895 (15.29)	2025 (13.60)	480 (18.93)	<0.001
Valvular Disease	41045 (8.88)	29480 (10.04)	7110 (6.71)	3190 (7.07)	1060 (7.12)	205 (8.09)	<0.001
Peripheral vascular disease	41575 (9.00)	28100 (9.57)	8185 (7.73)	3695 (8.19)	1370 (9.20)	225 (8.88)	<0.001
Hypertension	430010 (93.07)	269635 (91.84)	101600 (95.94)	42335 (93.87)	14050 (94.33)	2390 (94.28)	<0.001
Obesity	95940 (20.77)	62045 (21.13)	23965 (22.63)	8255 (18.30)	1175 (7.89)	500 (19.72)	<0.001
Dyslipidemia	319095 (69.07)	206525 (70.34)	69705 (65.82)	30580 (67.80)	10665 (71.60)	1620 (63.91)	<0.001
Atrial Fibrillation	105305 (22.79)	78610 (26.78)	15275 (14.42)	8050 (17.85)	3015 (20.24)	355 (14.00)	<0.001
Smoking	76875 (16.64)	48670 (16.58)	20525 (19.38)	5565 (12.34)	1510 (10.14)	605 (23.87)	<0.001
Liver disease	9725 (2.10)	5970 (2.03)	2075 (1.96)	1250 (2.77)	370 (2.48)	60 (2.37)	<0.001
Metastatic Cancer	5615 (1.22)	3835 (1.31)	1115 (1.05)	440 (0.98)	180 (1.21)	45 (1.78)	0.008
Solid Tumour without metastasis	6985 (1.51)	4695 (1.60)	1465 (1.38)	585 (1.30)	205 (1.38)	35 (1.38)	0.060
Transient ischemic attack	3485 (0.75)	2520 (0.86)	580 (0.55)	280 (0.62)	70 (0.47)	35 (1.38)	<0.001
Coronary heart disease	161570 (34.97)	114190 (38.89)	29505 (27.86)	13145 (29.15)	3940 (26.45)	790 (31.16)	<0.001
Family history of heart disease	15415 (3.34)	9805 (3.34)	3790 (3.58)	1105 (2.45)	610 (4.10)	105 (4.14)	<0.001
Previous cerebrovascular disease	78430 (16.98)	50030 (17.04)	18975 (17.92)	6795 (15.07)	2255 (15.14)	375 (14.79)	<0.001
Outcomes, (n%)							
LOS(>4DAYS)	166555 (36.05)	98020 (33.39)	45030 (42.52)	17270 (38.29)	5300 (35.58)	935 (36.88)	<0.001
In-Hospital-Mortality	13705 (2.97)	9440 (3.22)	2380 (2.25)	1340 (2.97)	465 (3.12)	80 (3.16)	<0.001
Routine Discharge	154855 (33.52)	97245 (33.12)	33990 (32.10)	17520 (38.85)	5095 (34.21)	1005 (39.64)	<0.001
Severe Stroke	395430 (85.59)	249755 (85.07)	90685 (85.63)	39765 (88.17)	12970 (87.08)	2255 (88.95)	<0.001
NIHSS,(n%)*							
0 (No stroke symptoms)	10525 (9.85)	7130 (6.68)	2115 (1.98)	940 (0.88)	290 (0.27)	50 (0.047)	<0.001
1–4 (Minor Stroke)	48440 (45.35)	32035 (29.99)	11075 (10.37)	3755 (3.52)	1380 (1.29)	195 (0.18)	<0.001
5–15 (Moderate to severe stroke)	36025 (33.73)	22385 (20.96)	9430 (8.83)	3015 (2.82)	1035 (0.97)	160 (0.15)	<0.001
16–20 (Moderate to severe stroke median)	5580 (5.22)	3560 (3.33)	1355 (1.27)	475 (0.44)	170 (0.16)	20 (0.019)	<0.001
21–42 (Severe stroke)	6235 (5.84)	4115 (3.85)	1420 (1.33)	475 (0.44)	200 (0.19)	25 (0.023)	<0.001
Missing (%)	355,215 (76.88)						

*(%) relative to the N of patients with full NIHSS data.
Cell sizes ≤ 10 were not reported to avoid patient reidentification, according to the Healthcare Cost and Utilization project guidelines.
Statistically significant differences ($P < 0.01$).

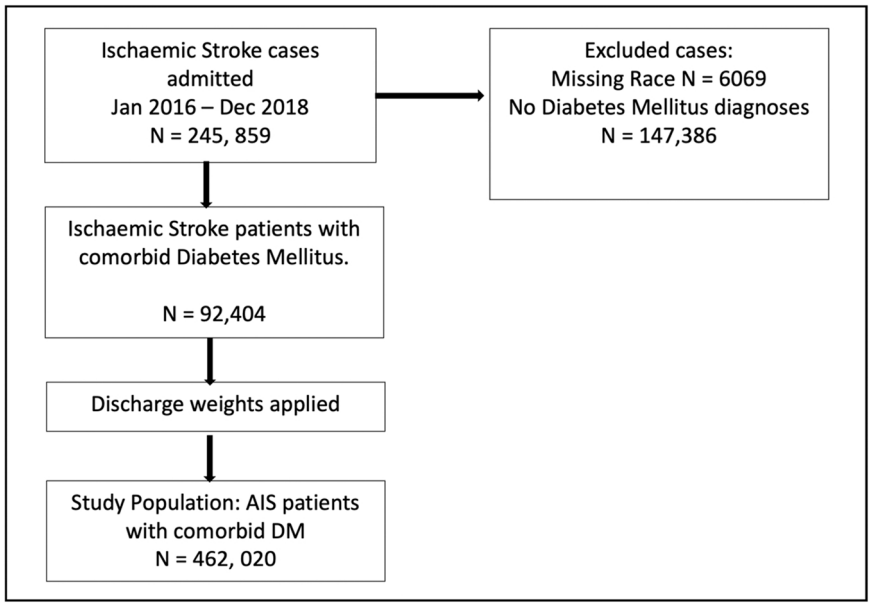


Fig. 1. Patient population Flow chart.

3. Results

3.1. Descriptive statistics

92,404 records with primary AIS diagnosis and secondary T2DM diagnosis and defined race variables were extracted, which were representative of 462,020 admissions (Fig. 1). The median (IQR) age was 72 (61−79) years; 48.91 % were women. The median LOS was 3 (2−6) days. There were 293,590 (64 %) White, 105,900 (23 %) African American, 45,100 (9.7 %) Hispanic, 14,895 (3 %) Asian/Pacific islanders, 2535 (0.5 %) Native American patients (Table 1, Table SIV). Racial minority groups were significantly: younger, more likely to have Medicaid insurance, longer in hospital, and more likely to be hypertensive than their White counterparts.

3.2. Association between revascularisation therapy and race/sex (Reference-White population/Men)

African American: OR = 0.76(0.62–0.93) and Hispanic (0.66 (0.50–0.89)) patients had lower odds of receiving EVT. Women had lower odds of EVT (0.87 (0.75–1.01)) (Table 2).

3.3. Association between race and in-hospital outcomes (Reference-White population)

African American patients had 28 % lower odds of in-hospital mortality (0.72 (0.61–0.86)) (Fig. 2), higher odds of LOS > 4 (1.46 (1.39–1.54)) and lower OR of routine discharge (0.78 (0.74–0.82)). Hispanic patients had higher OR of LOS> 4 (1.26 (1.17–1.36)). African American (1.17 (1.08–1.27), and Hispanic (1.12 (1.01–1.24) patients had higher odds of severe stroke.

3.4. Association between sex and in-hospital outcomes (Reference-Men)

Women overall had 15 % higher odds of in-hospital mortality (1.15 (1.01–1.32)), 8 % higher odds of prolonged hospitalisation (1.08 (1.03–1.12)), 20 % higher odds of a moderate/severe stroke (1.20 (1.11–1.29)) and 21 % lower odds of routine discharge (0.79 (0.75–0.83)) (Fig. 3).

3.5. Analysis of interaction between race and sex differences

Sex disparities in routine discharge were attenuated in African Americans (0.85 (0.78–0.93)) and Hispanics (0.90 (0.79–1.03)) (Figure SI). There were no other race differences in sex disparities for the other outcomes.

Table 2
Results of multivariable logistic regression analysing the relationship between sex, race, and the odds of receiving evidence-based stroke revascularisation therapy amongst ischaemic stroke patients with comorbid diabetes mellitus after NIHSS adjustment.

	Thrombolysis	Thrombectomy
	OR (99 % CI)	OR (99 % CI)
Men (reference)	**1**	**1**
Women	1.02 (0.93–1.11)	0.87 (0.75–1.01)
Whites (reference)	**1**	**1**
African Americans	0.89 (0.79–1.01)	**0.76 (0.62–0.93)**
Hispanics	0.99 (0.89–1.11)	**0.66 (0.50–0.89)**
Asian Americans	0.98 (0.84–1.14)	0.80 (0.59–1.10)
Native Americans	0.71 (0.43–1.15)	0.54 (0.19–1.55)

All models were adjusted for age, year, Elixhauser comorbidities and other comorbidities (Atrial fibrillation, dyslipidaemia, dementia, smoking, Parkinson disease, Rheumatic heart disease, coronary heart disease, all-cause bleeding, deep venous thrombosis/pulmonary embolism, infectious endocarditis, pneumonia, aspiration pneumonia, chronic lung disease, shock, sepsis, congenital heart disease, family history of cerebrovascular disease, family history of heart disease, previous cerebrovascular disease, NIHSS, hospital characteristics (location, insurance and teaching status). Race and sex were adjusted for as appropriate. Statistically significant results (P < 0.01) are displayed in bold.

3.6. Mediation Analysis

None of the main models were attenuated by the revascularization therapy (Table SVIII, SX).

4. Discussion

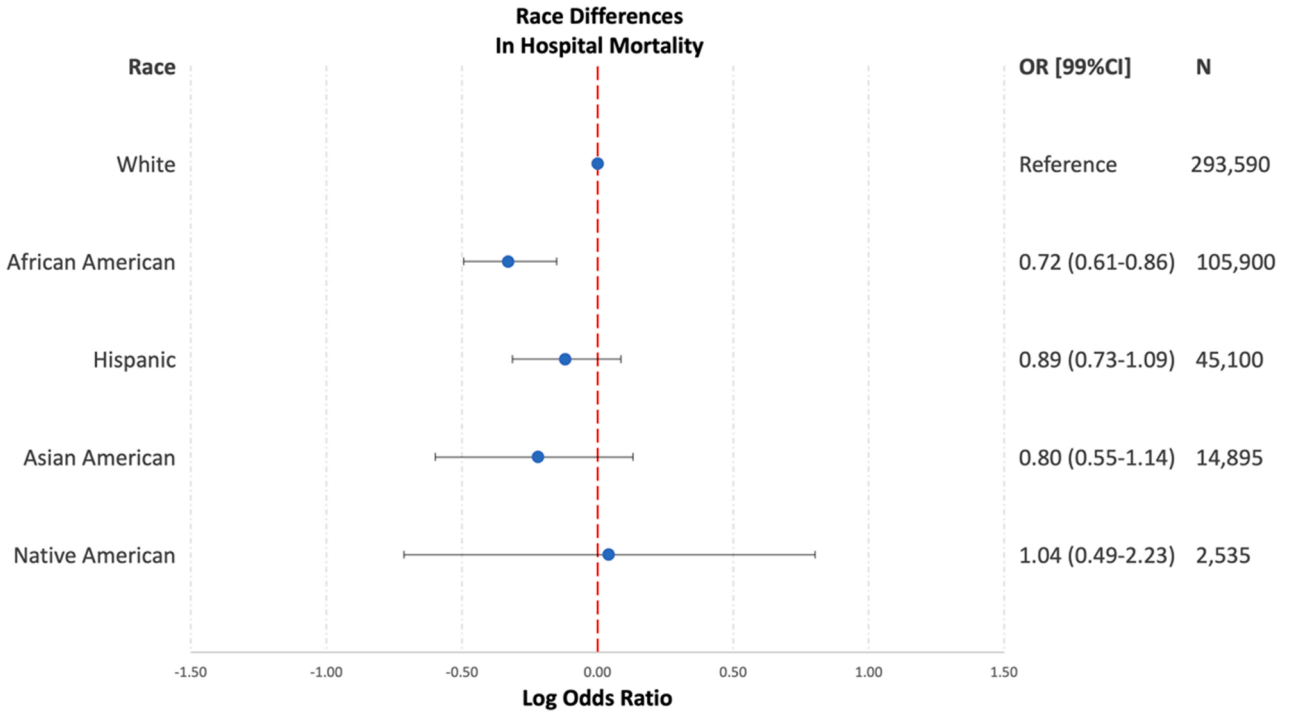
In this novel study we report important findings. Racial minorities were significantly less likely to receive revascularisation therapy compared to White patients. Across all racial groups, women had higher risk of adverse outcomes than men. African American patients with DM were significantly more likely to undergo prolonged hospitalisation, be discharged to locations other than home, present with more severe stroke phenotypes, but were less likely to die in hospital compared to the White population. AIS patients of other racial minority groups also had higher odds of adverse outcomes than their White counterparts.

We also found lower odds of in-hospital mortality in racial minorities compared to the White population [24]. These patients may be discharged more readily to community hospitals and their progression after transfer would not have been analysed in the current study [25]. As these patients have higher odds of more severe stroke and prolonged hospitalisation, transfer to another institution may confound our in-hospital mortality outcomes. Inadequate access to health care, poorer diabetes management and worse control of risk factors may also contribute to these findings [3]. Increased stroke severity in racial minority groups could be a driver for the increased LOS and decreased routine discharge. There were also significant sex disparities in in-hospital outcomes across all racial groups. Women had higher odds of adverse in-hospital outcomes, including in-hospital mortality. Despite adjustment, older age, and more severe stroke notable in women, could contribute to these disparities.

We found no differences in IVT administration between minority and White patients after adjustment. Our study did not consider other factors which may influence eligibility for IVT, prior studies however confirm that IVT administration in eligible patients was lower in African American populations [24,26]. Whilst evidence shows that the benefit of IVT extends to patients with DM, physician concern of higher complication rates in these populations as well as patient refusal to consent to revascularisation, may contribute to disparities [27–29]. Further research including a similarly large cohort, eligibility for revascularization, and patient refusal is required to clarify these disparities. Racial minorities had lower odds of receiving EVT. As African Americans with DM are more prone to microvascular disease and may have a lower incidence of large artery occlusions, this may render them less likely eligible for EVT [4]. As they were significantly younger and less likely to have private insurance compared to White patients, this may also influence their access to EVT. We highlight for the first time the race disparities in EVT utilisation in an AIS population with comorbid DM.

Our study is powered by several strengths. Based on a nationally representative sample of 0.5 million patients, our results reflect contemporary stroke clinical practice and are generalizable to patients with similar demographic characteristics. Additionally, we were able to adjust for a wide range of important confounders, including NIHSS.

We acknowledge some limitations. We were unable to account for diabetes severity or treatment. The Asian/Pacific Islander and Native American subgroups were likely underrepresented in our sample, their outcomes, therefore, warrant further investigation. Given the nature of observational studies, we cannot exclude the possibility of residual confounding. In addition, given the administrative nature of the NIS, we were unable to account for IVT and EVT eligibility, as we lacked data on the TOAST (Trial of ORG 10172 Acute Stroke Treatment) classification, time of infarction, hospital presentation, comprehensive neurological



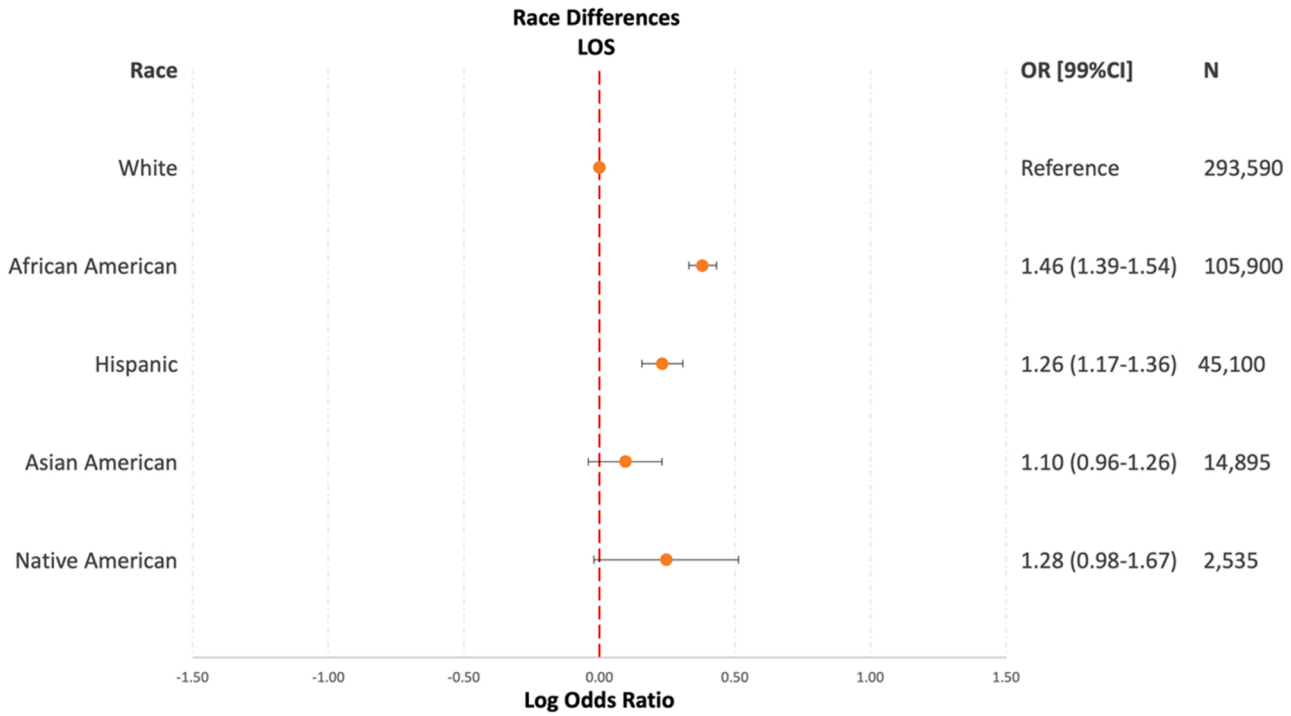


Fig. 2. Results of multivariable logistic regression analysing the relationship between race and ischaemic stroke in-hospital outcomes amongst patients with co-morbid diabetes mellitus after NIHSS and revascularisation therapy adjustment. All models were adjusted for age, year, Elixhauser comorbidities and other comorbidities (Atrial fibrillation, dyslipidaemia, dementia, smoking, Parkinson disease, Rheumatic heart disease, coronary heart disease, all-cause bleeding, deep venous thrombosis/pulmonary embolism, pericarditis, infectious endocarditis, pneumonia, aspiration pneumonia, chronic lung disease, shock, sepsis, congenital heart disease, family history of cerebrovascular disease, family history of heart disease, previous cerebrovascular disease, NIHSS, hospital characteristics (location, insurance and teaching status) and endovascular treatment (thrombolysis and thrombectomy). The horizontal axis is on logarithmic scale so that the OR are symmetrical around the null value of 0. LOS indicates length of stay; OR, odds ratio; Severe Stroke indicates NIHSS$>$ 5 and; NIHSS, National Institutes of Health Stroke Scale. Statistically significant result ($P < 0.01$).,.

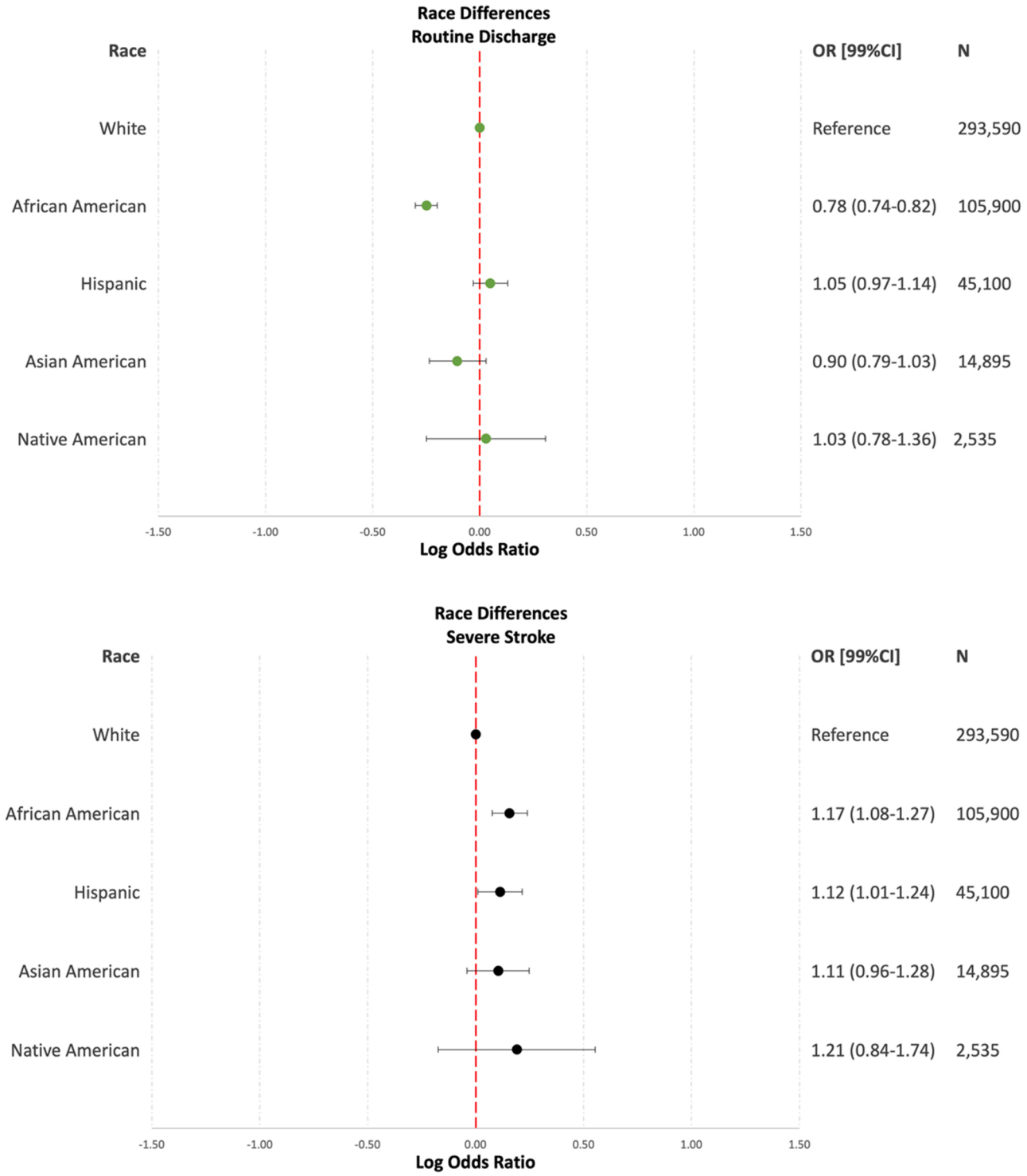


Fig. 2. (*continued*).

exam results or contraindications. The NIS provides no follow up data. Therefore, data were limited to the duration of index hospitalisation. Furthermore, readmissions within the same year are recoded as separate cases and therefore some patients may have been included more than once in the sample. The NIHSS is a potent predictor of stroke outcome. Therefore, despite strengthening our analyses by performing multiple imputation the high missingness of this variable ~~is a significant~~ remains a limitation of this study. However, it is important to note that as long as the fundamental assumption of MICE are met, this is a robust approach which has been show in simulation studies to produce unbiased results even with very large proportions of missing data [30]. We have also conducted a sensitivity analysis to investigate possible deviations from the missing-at-random assumption, which did not reveal any significant differences.

Conclusively, our study provides new insights into the racial and sex disparities of in-hospital outcomes amongst patients with AIS and co-morbid DM in contemporary practice. Whilst we show clear disparities both in treatment and in outcomes, our sequentially adjusted models suggest that the disparities in outcome are not entirely driven by the disparities in treatment. This indicates a multifactorial problem

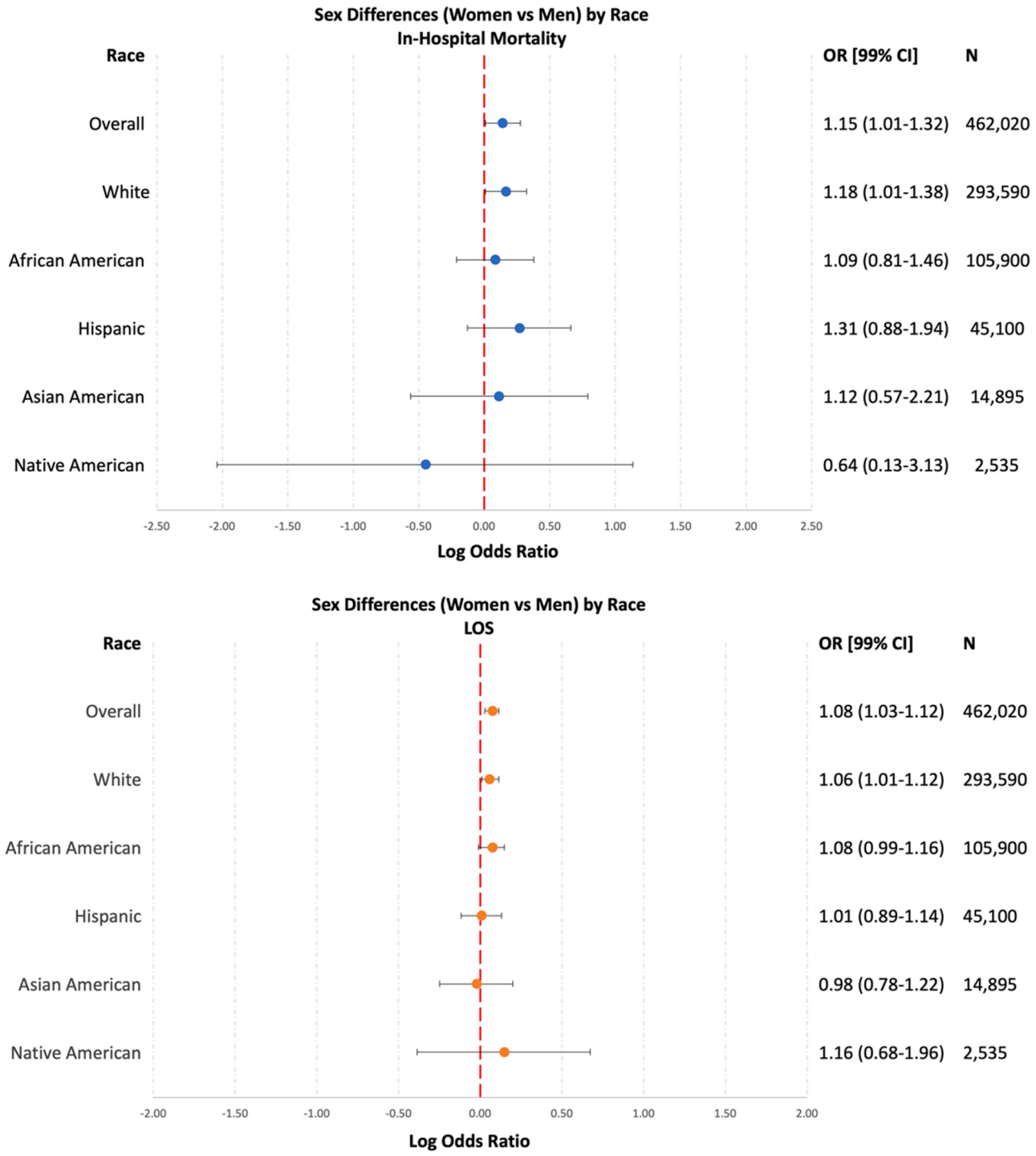


Fig. 3. Results of multivariable logistic regression analysing the relationship between sex and ischaemic stroke in-hospital outcomes amongst patients with comorbid diabetes mellitus after NIHSS and revascularisation therapy adjustment. All models were adjusted for age, year, Elixhauser comorbidities and other comorbidities (Atrial fibrillation, dyslipidaemia, dementia, smoking, Parkinson disease, Rheumatic heart disease, coronary heart disease, all-cause bleeding, deep venous thrombosis/pulmonary embolism, pericarditis, infectious endocarditis, pneumonia, aspiration pneumonia, chronic lung disease, shock, sepsis, congenital heart disease, family history of cerebrovascular disease, family history of heart disease, previous cerebrovascular disease, NIHSS, hospital characteristics (location, insurance and teaching status) and endovascular treatment (thrombolysis and thrombectomy). The horizontal axis is on logarithmic scale so that the OR are symmetrical around the null value of 0. LOS indicates length of stay; OR, odds ratio; Severe Stroke indicates NIHSS$>$ 5 and; NIHSS, National Institutes of Health Stroke Scale. Statistically significant result ($P < 0.01$).,.

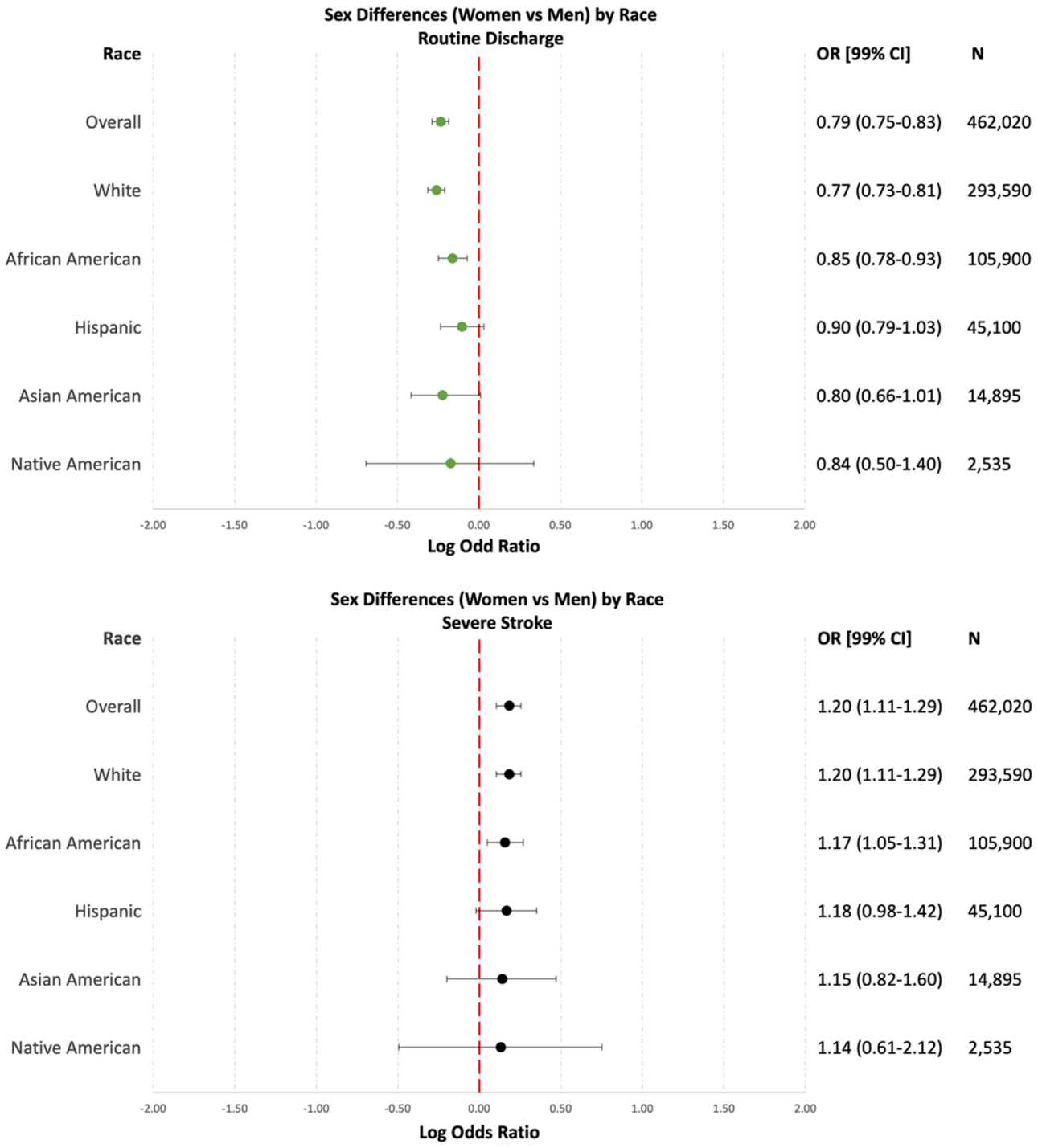


Fig. 3. (*continued*).

including potential unmeasured environmental factors such as lifestyle, societal factors, genetic origin variations and clinical management. The differences in modifiable risk factors should be addressed to eliminate these disparities. Targeted intervention is critical in attaining health equity.

Ethical approval

Not applicable.

Informed consent

Not applicable.

CRediT authorship contribution statement

T.A.P., A.P., and P.K.M. conceived of the presented idea. R.J.T. wrote the manuscript and analysed the data in consultation with T.A.P. and input from all authors. All authors contributed to the design and implementation of the research. All authors discussed the results and commented on the manuscript. T.A.P. and P.K.M. supervised the project.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2023.107747.

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