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ORIGINAL ARTICLE

Use of reperfusion therapy and time delay in patients with ischaemic stroke by immigration status: A register-based cohort study in Denmark

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Abstract

Background and purpose: Reperfusion therapy is the mainstay of treatment for acute ischaemic stroke (AIS); however, little is known about the use of reperfusion therapy and time delay amongst immigrants.

Methods: This is a Danish nationwide register-based cohort study of patients with AIS aged ≥18 years (n = 49,817) recruited from 2009 to 2018. Use of reperfusion therapy (intravenous thrombolysis and/or mechanical thrombectomy) and time delay between immigrants and Danish-born residents were compared using multivariable logistics and quantile regression.

Results: Overall, 10,649 (39.8%) Danish-born residents and 452 (39.0%) immigrants with AIS were treated with reperfusion therapy in patients arriving <4.5 h following stroke onset. Compared with Danish-born residents, immigrants had lower odds of receiving reperfusion therapy after adjustment for prehospital delay, age, sex, stroke severity, sociodemographic factors and comorbidities (adjusted odds ratio 0.67; 95% confidence interval 0.49–0.92, p = 0.01). The lowest odds were observed amongst immigrants originating from Poland and non-Western countries. Similarly, immigrants had a longer prehospital delay than Danish-born residents in the fully adjusted model in patients arriving <4.5 h after stroke onset (15 min; 95% confidence interval 4–26 min, p = 0.03). No evidence was found that system delay and clinical outcome differed between immigrants and Danish-born residents in patients eligible for reperfusion therapy after adjustment for sociodemographic factors and comorbidities.

Conclusion: Immigration status was significantly associated with lower chances of receiving reperfusion therapy and there may be differences in patient delay between immigrants and Danish-born residents in patients arriving to a stroke unit <4.5 h after stroke onset.

KEYWORDS
immigration, ischaemic stroke, prehospital delay, reperfusion therapy, system delay

See commentary by P. J. Nederkoorn on page 1863

INTRODUCTION

In 2016, stroke caused approximately 5.5 million deaths worldwide and it is considered one of the leading causes of death and disability amongst adults [1,2]. Reperfusion therapy (thrombolysis and/or thrombectomy) is the mainstay of treatment for acute ischaemic stroke. Intravenous (IV) thrombolysis is time critical with earlier treatment (<4.5 h of stroke onset) being associated with good stroke outcome irrespective of age or stroke severity [3,4]. Several studies conducted in the USA have documented under-utilization of reperfusion therapy in Black and Hispanic patients with acute stroke compared with Whites [5–10]. In Europe, a single-centre study conducted in the Netherlands also reported lower utilization of IV thrombolysis in non-White stroke patients than in White patients [11].

Under-utilization of reperfusion therapy amongst ethnic minorities may be explained by a delayed presentation to hospital. Thus, a south London stroke study reported a longer prehospital delay amongst Blacks than amongst Whites after acute stroke [12]. Explanations for this delay amongst minorities have been attributed to patient factors (such as lack of symptom awareness and treatment availability, language barriers and socioeconomic conditions) and system factors (such as geographical stroke centre location and availability of clinical resources) [12–14]. However, the current literature has several shortcomings. Overall, studies lack data on various time delay components including patient-dependent delay, prehospital delay and inhospital system delay amongst immigrants compared with local-born populations. Duration of residence was not included as a determinant of access to reperfusion therapy and time delay. Furthermore, factors like marital status and education were unavailable in most of these studies [7–9,13,14].

In the present study, nationwide data from patients admitted with acute ischaemic stroke in Denmark were used. First, it was hypothesized that immigrants have lower utilization of reperfusion therapy than Danish-born residents taking into account patient- and system-related factors. Secondly, an investigation was made of whether disparities exist between immigrants and Danish-born residents with respect to time from symptom onset to initiation of treatment at a stroke unit.

METHODS

Data sources and study population

Danish healthcare is publicly funded, allowing free access to emergency medical services (EMS) and free hospital care for all residents including immigrants. This nationwide register-based cohort study utilized data from the Danish Stroke Registry (DSR), the Danish Prehospital Database and Statistics Denmark. The study was approved by the Danish Data Protection Agency, reference number 514-0457/20-3000, and adheres to the principles of the Declaration of Helsinki. No further approval is required when conducting register-based research in Denmark.

The DSR, which became operational in 2003, is a nationwide clinical register which contributed information on stroke types, risk factors, comorbidities and timestamps from stroke (symptom) onset time to start of treatment. Detailed information about the DSR has been published elsewhere [15]. The DSR has been found to have a sensitivity and a positive predictive value of stroke diagnoses exceeding 90% [16]. Data on prehospital timestamps from the Prehospital Database, which is a nationwide clinical quality database established in 2015 [17,18], were retrieved. Prehospital data were available from 2016 to 2018. Statistics Denmark provided individual data on socioeconomic variables such as family income, highest attained education, occupation, immigration status (country of origin) and date of immigration [19–23]. In Denmark, each resident is assigned a unique 10-digit personal identification number, which enables individual-level linkage between the registers.

The present study comprised a population of men and women with acute ischaemic stroke aged from 18 to 95 years between 1 January 2009 and 31 December 2018. Excluded were patients with undocumented or incorrect registration of either stroke onset time or stroke unit arrival time and patients admitted more than 24 h after their stroke onset. In the subanalysis of reperfusion therapy, patients with documented contraindications to reperfusion therapy were excluded.

Immigrants

An immigrant group was constructed based on the definition that they were born or originated outside Denmark [22,23]. In addition, immigrants were classified as originating from Western or non-Western countries according to the categorizations of Statistics Denmark. Western countries included all 28 European Union countries and Andorra, Iceland, Liechtenstein, Monaco, Norway, San Marino, Switzerland, Vatican State, Canada, USA, Australia and New Zealand [23]. The non-Western group were all other countries. These categories were used as they have been associated with various challenges in accessing healthcare in Denmark [24]. Also people originating from Turkey, Poland and Pakistan are presented as separate categories because of their large proportion amongst the population of immigrants in Denmark. Danish-born residents were used as a reference. Descendants were excluded due to low numbers.

Outcomes

The primary outcome was use of reperfusion therapy. Reperfusion therapy was defined as IV thrombolysis and/or mechanical thrombectomy. The primary outcome was restricted to individuals arriving <4.5 h after stroke onset. Secondary outcomes included patient- and system-dependent time delays focusing on onset-to-call time, onset-to-door time and door-to-needle time for reperfusion therapy

as continuous outcomes. Onset-to-call time, onset-to-door time and door-to-needle time were defined as patient-dependent delay, prehospital delay and inhospital delay, respectively. Prehospital delay (onset-to-door time) was categorized into patients arriving <4.5 h after stroke onset and those arriving ≥4.5–24 h after stroke onset. Additionally, clinical outcome (functional outcome) was included and the analysis was restricted to patients arriving within 4.5 h following stroke onset. Further details regarding the outcome are provided in Appendix S1.

Covariates

Patient- and system-related factors were used as the covariates to study associations between immigration status and use of reperfusion therapy. Patient factors included age at stroke, sex, stroke severity, marital status, duration of residence, education, occupation, income, smoking, diabetes, hypertension, atrial fibrillation, myocardial infarction, and previous stroke or transient ischaemic attack (TIA), whereas the system factor was a prehospital delay.

Similarly, the aforementioned covariates were used to investigate associations between immigration status with respect to time delay and functional outcome after stroke. Stroke severity was determined at admission and classified as very severe, severe, moderate or mild stroke according to the Scandinavian Stroke Scale (SSS) score. The SSS is widely used in Scandinavian countries and was designed for ease of use by clinicians. The scale has been validated and comprises nine items: level of consciousness, eye movement, arm motor power, hand motor power, leg motor power, orientation, speech, facial palsy and gait. The maximum total score is 58, which is a normal individual. Like the National Institutes of Health Stroke Scale, the SSS has a comparable performance in predicting death or dependence after stroke [25]. A score of 0–30 points was categorized as 'severe stroke' and >30 as 'less severe stroke' in the use of reperfusion therapy, time delay and functional outcome analyses. Duration of residence was first handled as a continuous variable and in further analysis this variable was grouped into the following levels: <10 years of residence, 10–20 years of residence, >20 years of residence in Denmark, and Danish-born residents. Education was classified as low (primary and lower secondary education), medium (upper secondary, post-secondary non-tertiary and short-cycle tertiary education) or high (bachelor, master and doctoral education) according to the International Standard Classification of Education. Marital status was grouped as cohabiting, living alone or other. Income was categorized as low, middle or high. Additionally, occupation was classified as employed, pensioner or unemployed.

Statistical analyses

Categorical and continuous data were summarized by frequency and percentage and by median and interquartile range, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to study associations between immigration status and use of reperfusion therapy and were adjusted for potential confounders in multivariable logistic regression analysis. System-related factors (onset-to-door time) and patient factors (age, sex, stroke severity, income, occupation, education, marital status, duration of residence, previous stroke or TIA, smoking, myocardial infarction, atrial fibrillation, diabetes and hypertension) were adjusted and their contribution to the differences in use of reperfusion therapy was examined. In addition, multivariable quantile regression was used to study associations between immigration status with respect to time delay (onset-to-call time, onset-to-door time and door-to-needle time). Quantile regression is an extension of standard linear regression, which estimates the conditional median of the outcome variable and can be used in the case of skewed data. The method has previously been used in estimating time-to-treatment delay [26]. Coefficients for time delay were stated in minutes and with 95% CIs. Furthermore, subgroup analyses in which immigrants were compared with Danish-born residents based on sex, stroke severity, marital status, education level and duration of residence with respect to use of reperfusion therapy and time delay were performed [27]. Moreover, the association between immigration status and poststroke functional outcome was investigated in patients arriving within 4.5 h following stroke onset. The models were adjusted using the same group of covariates.

All analyses were performed in R statistical software (version 4.0.2 and 3.3.3).

RESULTS

Patient characteristics

During the 2009–2018 period, 49,817 ischaemic stroke cases arrived within 24 h after symptom onset, of whom 2083 were immigrants and 47,734 were Danish-born residents (Figure 1). Compared with Danish-born residents, immigrants were younger at the time of their stroke diagnosis (69 vs. 73 years), more likely to have a low income (36.2% vs. 29.4%), more likely to be unemployed (24.9% vs. 10.3%) and more likely to be cohabiting (61.7% vs. 58.6%) (Table 1). Turkish immigrants were the most likely of all ethnic groups to have a low educational level (Table S1). Pakistanis were the most likely of all ethnic groups to have hypertension and diabetes. Hypertension was the most prevalent comorbidity in the entire study population. The majority of the patients had mild stroke.

Use of reperfusion therapy

Overall, 10,649 (39.8%) Danish-born residents and 452 (39.0%) immigrants with ischaemic stroke were treated with reperfusion therapy ($p = 0.29$) amongst patients arriving within 4.5 h after stroke onset. The unadjusted ORs of reperfusion therapy did not differ between immigrants and Danish-born residents (OR 0.86; 95% CI

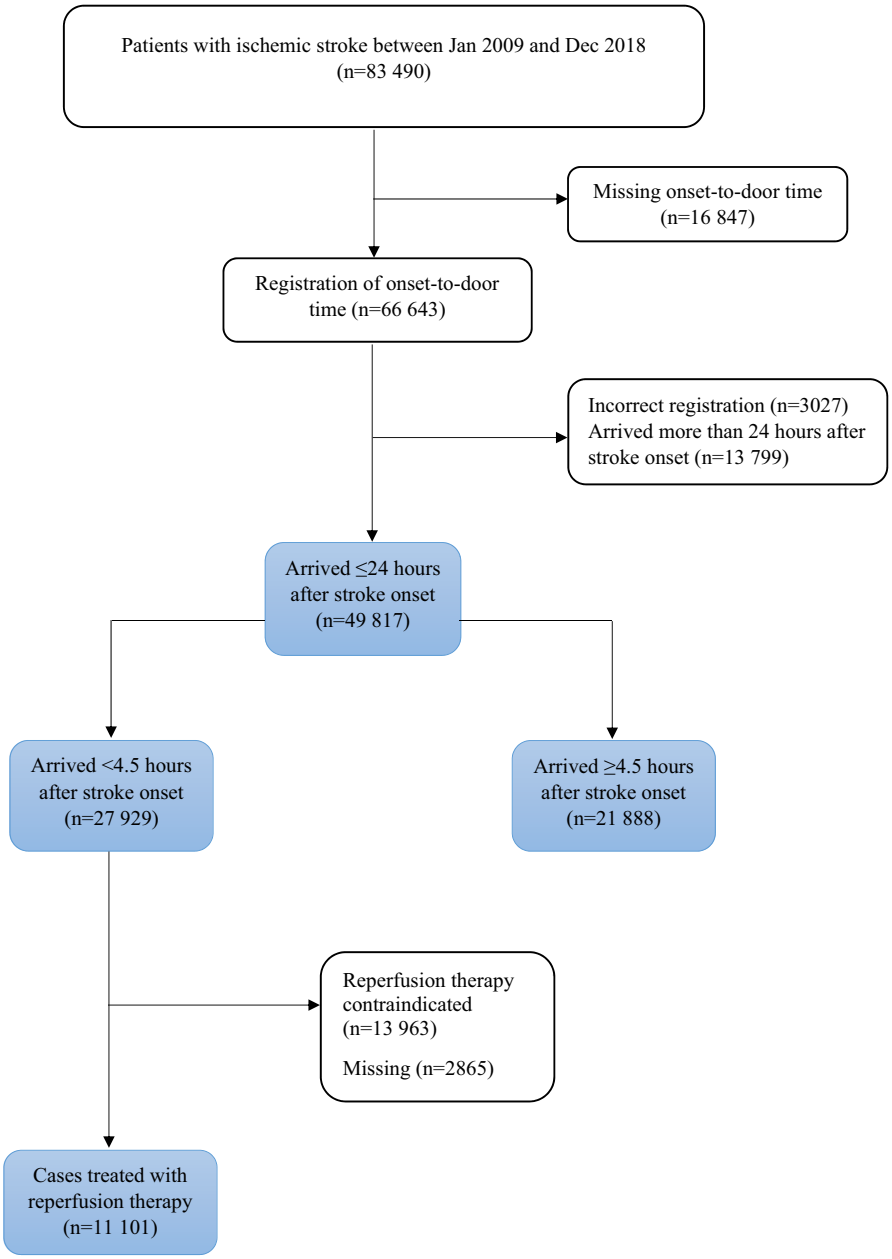

FIGURE 1 Flowchart of the study population

0.73–1.02, $p = 0.08$; Table 2). All ORs of reperfusion therapy were significantly <1 in immigrants than in Danish-born residents when onset-to-door time, stroke severity, sociodemographic factors and comorbidities were adjusted independently. In the multivariable model adjusted for prehospital delay, age, sex, stroke severity, duration of residence, sociodemographic factors and comorbidities, the OR of reperfusion therapy was significantly lower amongst immigrants than amongst Danish-born residents (adjusted OR [AOR] 0.67; 95% CI 0.49–0.92, $p = 0.01$) in patients arriving within 4.5 h after stroke onset. Compared with Danish-born residents, the difference in odds was more pronounced amongst Polish immigrants (AOR 0.30; 95% CI 0.11–0.86, $p = 0.02$) and immigrants originating from non-Western countries (AOR 0.61; 95% CI 0.40–0.92, $p = 0.01$) in the fully adjusted model. Similarly, living alone and less severe stroke were significantly associated with lower odds of receiving reperfusion therapy amongst immigrants than amongst Danish-born residents (AOR 0.86; 95% CI 0.76–0.98, $p = 0.04$; and AOR 0.92; 95% CI 0.85–0.99, $p = 0.04$, respectively) (Figure 2). No evidence was found of sex differences in the use of reperfusion therapy amongst immigrant women compared with immigrant men (AOR 1.21; 95% CI 0.71–2.05, interaction $p = 0.47$) and in Danish-born women compared with Danish-born men (AOR 1.24; 95% CI 0.93–1.67, interaction $p = 0.14$).

Patient and system time delays

Positive and negative numbers indicate longer and shorter time delays, respectively. Overall, the median prehospital system delays through the EMS did not differ between immigrants and

TABLE 1 Characteristics of the study population who arrived within 24 h after stroke onset by immigration status

	Danish-born (*n* = 47,734)	Immigrants (*n* = 2083)
Women, *n* (%)	26,839 (56.2)	1142 (54.8)
Median age at stroke, years (IQR)	73 (63–81)	69 (59–78)
Median age at immigration, years (IQR)	NA	35 (25–46)
Median duration of residence, years (IQR)	NA	25 (17–33)
Education[a], *n* (%)		
Low	20,057 (42.0)	525 (25.2)
Medium	5850 (12.3)	628 (30.1)
High	6351 (13.3)	345 (16.6)
Missing	15,476 (32.4)	585 (28.1)
Family income[b], *n* (%)		
Low	13,998 (29.4)	754 (36.2)
Middle	15,823 (33.1)	660 (31.7)
High	17,913 (37.5)	669 (32.1)
Occupation, *n* (%)		
Employed	14,936 (31.3)	565 (27.1)
Pensioner	27,853 (58.4)	999 (48.0)
Unemployed	4945 (10.3)	519 (24.9)
Marital status, *n* (%)		
Cohabiting	27,958 (58.6)	1285 (61.7)
Living alone	17,763 (37.2)	699 (33.6)
Other	1291 (2.7)	54 (2.6)
Missing	722 (1.5)	45 (2.1)
Comorbidities, *n* (%)		
Current smoking	13,380 (28.0)	581 (27.9)
Hypertension	26,608 (55.7)	1129 (54.2)
Diabetes	6906 (14.5)	487 (23.4)
Myocardial infarction	4268 (8.9)	206 (9.9)
Atrial fibrillation	8927 (18.7)	371 (17.8)
Previous stroke or TIA	11,570 (24.2)	463 (22.2)
Stroke severity[c], *n* (%)		
Very severe	3254 (6.8)	147 (7.1)
Severe	4485 (9.4)	225 (10.8)
Moderate	9238 (19.4)	396 (19.0)
Mild	29,652 (62.1)	1241 (59.6)
Missing	1105 (2.3)	74 (3.5)

Abbreviations: IQR, interquartile range; NA, not applicable; TIA, transient ischaemic attack.

[a]According to the International Standard Classification of Education.

[b]Tertiles.

[c]Based on the Scandinavian Stroke Scale score.

Danish-born residents in patients arriving within 24 h following stroke onset (see overlapping CIs in Tables S2 and S3). Similarly, unadjusted coefficients of prehospital delay (onset-to-door time) did not differ between immigrants and Danish-born residents in patients arriving <4.5 h and in those arriving ≥4.5–24 h after stroke onset (Table 3). However, it was found that immigrants had a significant prehospital delay, corresponding to a 15-min longer onset-to-door time than Danish-born residents after adjustment for age, sex, stroke severity, duration of residence, sociodemographic factors and comorbidities (15 min; 95% CI 4–26 min, $p = 0.03$) amongst patients arriving within 4.5 h following stroke onset. In particular, a longer prehospital delay was seen in immigrants originating from non-Western countries (18 min; 95% CI 2–34 min, $p = 0.04$). Moreover, low educational level, living alone and less severe stroke were associated with a longer prehospital delay amongst immigrants than amongst Danish-born residents in patients arriving within 4.5 h following stroke onset (Figure 3). In contrast, no difference was observed in inhospital system delay (door-to-needle time) or onset-to-call time between immigrants and Danish-born residents in patients arriving within 4.5 h after stroke onset (Tables S4).

Further analyses showed no difference in functional outcome between immigrants and Danish-born residents after adjustment for sociodemographic factors and comorbidities in patients arriving within 4.5 h after stroke onset (Table 4).

DISCUSSION

In this study, no difference was found in the rates of reperfusion therapy between immigrants and Danish-born residents. However, after adjustment for all relevant confounders, it was observed that immigrants had 33% lower chances of receiving reperfusion therapy than Danish-born residents. The lower chances of receiving reperfusion therapy were most evident in immigrants originating from Poland and non-Western countries. No sex differences in the utilization of reperfusion therapy amongst immigrants and Danish-born residents were found. Moreover, immigrants had a longer prehospital delay than Danish-born residents after controlling for baseline characteristics, sociodemographic factors and comorbidities amongst patients arriving within 4.5 h after stroke onset. In contrast, no evidence was found that prehospital delay differed between immigrants and Danish-born residents amongst patients arriving beyond 4.5 h but within 24 h after stroke onset. In addition, no difference in system delay or clinical outcome was found between immigrants and Danish-born residents in patients arriving within 4.5 h after stroke onset.

The majority of earlier studies investigating racial and ethnic disparities in acute stroke care were conducted in the USA [5–10]. A south London stroke study and a study from a single hospital in the Netherlands are amongst the few studies conducted in Europe [11,12]. Generally, these studies reported that Black ethnicity more often than White was associated with significant prehospital and inhospital delays, and lower chances of receiving reperfusion therapy. In our study, Black ethnicity was not studied due to the limited number of ethnic Black immigrants. Consistent with our findings, one

TABLE 2 Odds ratio of receiving reperfusion therapy amongst patients arriving <4.5 h after stroke onset by country of origin

	Patients with ischaemic stroke receiving reperfusion therapy between 2009 and 2018							
	Reperfusion therapy	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Danish-born	10,649 (39.8)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Immigrants	452 (39.0)	0.86 (0.73–1.02)	0.82 (0.69–0.97)	0.80 (0.67–0.94)	0.83 (0.70–0.98)	0.79 (0.65–0.94)	0.62 (0.48–0.81)	0.67 (0.49–0.92)
Western	274 (39.4)	0.89 (0.72–1.11)	0.85 (0.68–1.05)	0.94 (0.75–1.16)	0.96 (0.77–1.19)	0.90 (0.71–1.14)	0.65 (0.44–0.94)	0.67 (0.45–1.01)
Non-Western	178 (38.5)	0.81 (0.63–1.06)	0.78 (0.59–1.02)	0.63 (0.48–0.82)	0.68 (0.52–0.88)	0.64 (0.48–0.86)	0.60 (0.43–0.84)	0.61 (0.40–0.92)
Turkish	31 (38.7)	1.25 (0.83–1.88)	1.04 (0.66–1.63)	1.00 (0.66–1.51)	1.08 (0.71–1.62)	0.96 (0.61–1.53)	1.12 (0.69–1.81)	1.06 (0.58–1.93)
Polish	16 (41.0)	0.79 (0.44–1.44)	1.00 (0.50–1.98)	0.68 (0.37–1.25)	0.73 (0.40–1.33)	0.79 (0.43–1.46)	0.33 (0.13–0.84)	0.30 (0.11–0.86)
Pakistani	16 (30.8)	0.69 (0.40–1.20)	0.68 (0.37–1.27)	0.57 (0.32–0.99)	0.64 (0.40–1.12)	0.57 (0.32–1.02)	0.55 (0.27–1.13)	0.51 (0.23–1.17)

Note: OR indicates odds ratio with 95% confidence interval. Reperfusion therapy encompasses thrombolysis and/or thrombectomy.

Model 1: Adjusted for onset-to-door time. Model 2: Adjusted for age, sex and stroke severity. Model 3: Adjusted for age, sex, smoking, myocardial infarction, atrial fibrillation, diabetes and hypertension. Model 4: Adjusted for age, sex, income, occupation, education and marital status. Model 5: Adjusted for age, sex and duration of residence. Model 6: Fully adjusted for age, sex, onset-to-door time, stroke severity, income, occupation, education, marital status, duration of residence, previous stroke or transient ischaemic attack, smoking, myocardial infarction, atrial fibrillation, diabetes and hypertension.

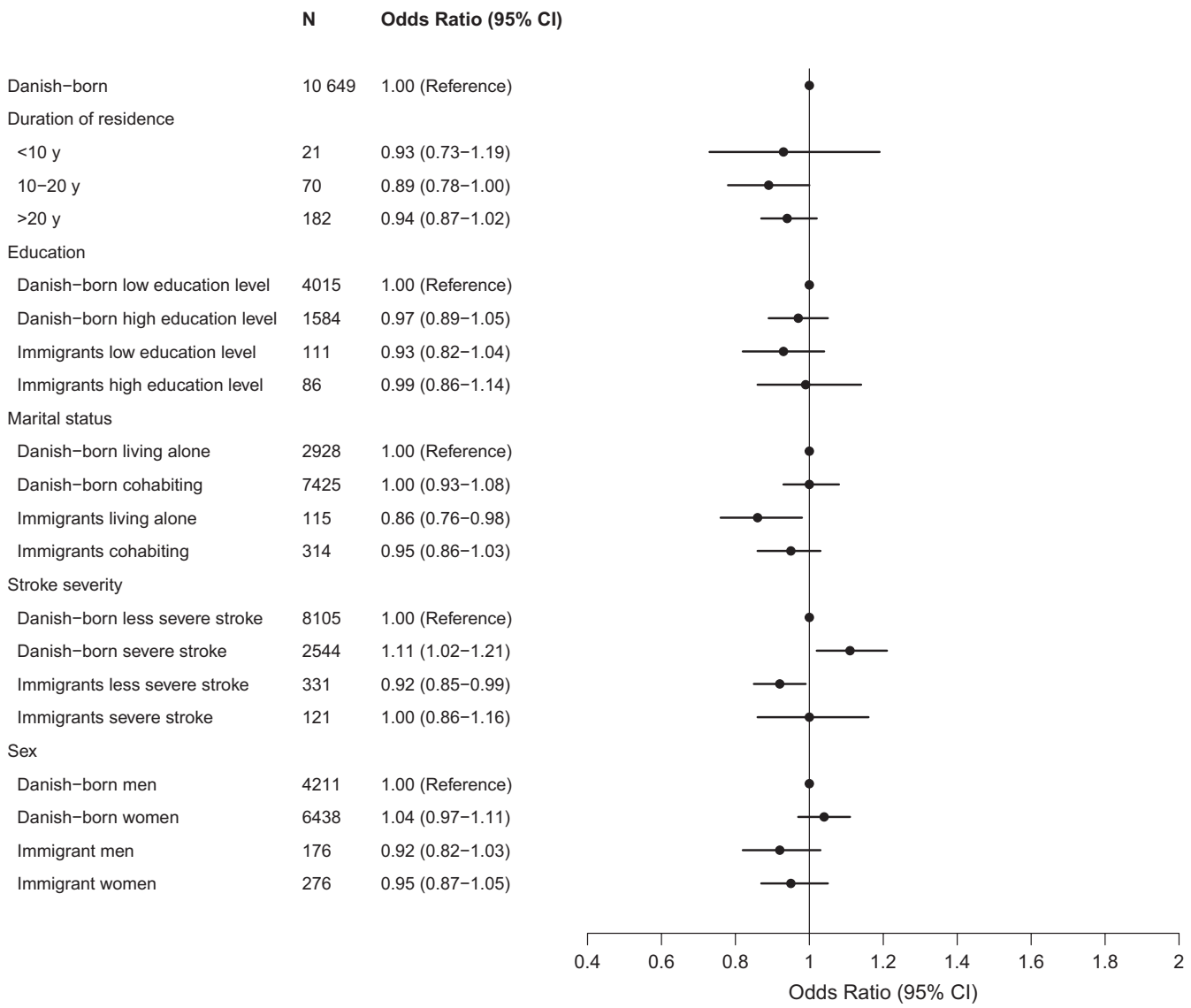

FIGURE 2 Forest plot showing factors associated with access to reperfusion therapy in patients arriving <4.5 h after stroke onset. Included were patients with ischaemic stroke receiving reperfusion therapy from 2009 to 2018. OR indicates odds ratio and CI confidence interval. Odds ratios were extracted from the fully adjusted model for the relationship between predictors and use of reperfusion therapy. Stroke severity was measured by the Scandinavian Stroke Scale score: 0–30 points was classified as 'severe stroke' and >30 as 'less severe stroke'

study in the USA found no sex disparities in the utilization of thrombolysis amongst minorities [14].

Differences in utilization of reperfusion therapy may depend on several factors such as prehospital delay (onset-to-door time), stroke severity, sociodemographic factors and comorbidities. First, our data showed a significantly lower chance of reperfusion therapy amongst immigrants than amongst Danish-born residents after controlling for prehospital delay. Early arrival at hospital is one of the important factors in accessing reperfusion therapy within a window period of 4.5 h after stroke onset. Secondly, it was found that less severe stroke in immigrants than in Danish-born residents was associated with longer prehospital delay and lower chances of reperfusion therapy. The observed finding is probably due to either strong sociocultural norms shaping the motivation for immigrants' health-seeking behaviours or simply a lack of knowledge about what minor stroke symptoms may reflect. A minor stroke may be perceived as less serious or patients may fail to recognize it as a stroke, which may be the case amongst immigrants, particularly those originating from non-Western countries. Compared with Danish-born residents, there were reduced chances of reperfusion therapy amongst immigrants when sociodemographic factors were adjusted independently. Likewise, our estimates show that living alone was significantly associated with longer prehospital delay and lower chances of reperfusion therapy amongst immigrants than amongst Danish-born residents. A possible explanation for this might be that, if a person lives alone, she or he is less likely to be witnessed by others in the case of an acute stroke event, resulting in lower chances of receiving reperfusion therapy. Polish immigrants were more likely to be living alone and this might

TABLE 3 Quantile regression analysis showing prehospital delay in minutes by country of origin

	Patients arriving <4.5 h after stroke onset			Patients arriving ≥4.5–24 h after stroke onset			Patients arriving ≤24 h after stroke onset		
	Onset-to-door time (min)			Onset-to-door time (min)			Onset-to-door time (min)		
		Unadjusted	Fully adjusted[a]		Unadjusted	Fully adjusted[a]		Unadjusted	Fully adjusted[a]
	n (%)	Coefficient (95% CI)	Coefficient (95% CI)	*n* (%)	Coefficient (95% CI)	Coefficient (95% CI)	Total *n*	Coefficients (95% CI)	Coefficients (95% CI)
Danish-born	26,771 (56.1)	Reference	Reference	20,963 (43.9)	Reference	Reference	47,734	Reference	Reference
Immigrants	1158 (55.6)	−10 (−17 to −3)	15 (4 to 26)	925 (44.4)	−11 (−50 to 28)	−16 (−47 to 15)	2083	−2 (−18 to 14)	−16 (−47 to 15)
Western	696 (55.9)	−12 (−21 to −3)	11 (−1 to 23)	549 (44.1)	−40 (−90 to 10)	−20 (−60 to 20)	1245	−5 (−26 to 16)	−20 (−60 to 20)
Non-Western	462 (55.1)	−3 (−14 to 8)	18 (2 to 34)	376 (44.9)	28 (−33 to 89)	−9 (−49 to 31)	838	8 (−18 to 34)	−9 (−48 to 30)
Turkish	80 (56.3)	−1 (−28 to 26)	25 (−3 to 53)	62 (43.7)	−12 (−159 to 135)	22 (−65 to 109)	142	3 (−59 to 65)	21 (−65 to 109)
Polish	39 (50.0)	5 (−34 to 44)	16 (−22 to 54)	39 (50.0)	−105 (−291 to 81)	100 (−6 to 206)	78	43 (−41 to 127)	100 (−5 to 205)
Pakistani	52 (52.5)	7 (−26 to 40)	12 (−21 to 45)	47 (47.5)	66 (−103 to 235)	−13 (−122 to 96)	99	26 (−48 to 100)	−13 (−123 to 97)

Note: Positive and negative values indicate longer and shorter time delays, respectively. Prehospital delay (onset-to-door time) constitutes patient delay and system delay (admission through the emergency medical services) amongst patients with ischaemic stroke. CI indicates confidence interval and TIA transient ischaemic attack. Coefficients are in minutes, which is a median difference in relation to the reference population.

[a]The fully adjusted model comprised age, sex, stroke severity, previous stroke or TIA, smoking, myocardial infarction, atrial fibrillation, diabetes, hypertension, income, occupation, education, marital status and duration of residence.

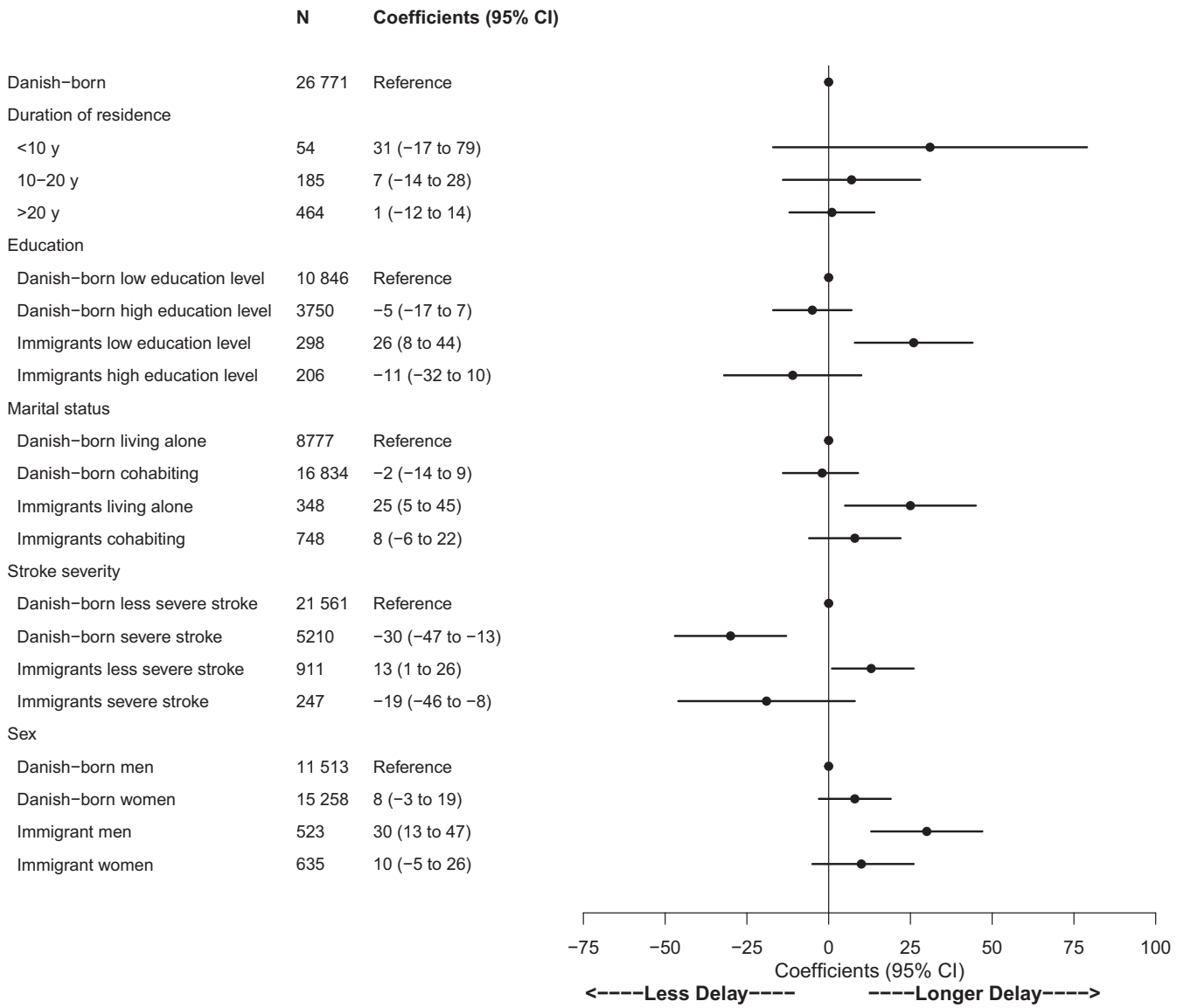

FIGURE 3 Forest plot showing factors associated with prehospital delay (in minutes) amongst patients arriving <4.5 h after stroke onset. Data on prehospital delay (onset-to-door time) were available from 2009 to 2018. Prehospital delay constitutes patient delay and system delay (admission via the emergency medical services) amongst patients with ischaemic stroke. Variables were extracted from the fully adjusted model. CI is the confidence interval. Positive and negative values indicate longer and shorter time delays, which is a median difference in relation to the reference population. Stroke severity was measured by the Scandinavian Stroke Scale score; 0–30 points was classified as 'severe stroke' and >30 as 'less severe stroke'

contribute to explaining why they had lower chances of receiving reperfusion therapy than any other immigrant group.

Another important finding was that a 15-min difference in prehospital delay was identified amongst immigrants and Danish-born residents in the fully adjusted model. This difference in prehospital delay may partly explain the lower chances of reperfusion therapy in immigrants and it may be related to delays in patients not admitted through the EMS pathway. Moreover, it was found that low educational attainment amongst immigrants was associated with a longer prehospital delay compared with Danish-born residents of a similar education level. The level of education in immigrants may be an important factor to consider when designing stroke preventive policies and interventions as it might influence the decision to contact the EMS or hospital after an acute stroke event. All hospitals in Denmark treating patients with acute stroke are required by law to provide free emergency medical care, including reperfusion therapy to any patient. Therefore, it is unlikely that the difference detected in reperfusion therapy is contributed by insurance status. Although adjustments were made for a wide range of clinical and sociodemographic factors, other unmeasured confounders such as a physician's implicit bias about immigrants, knowledge of stroke symptoms, language barriers, cultural norms, body mass index and alcohol use may explain the lower chances of reperfusion therapy seen in immigrants. For example, language barriers in non-Danish speaking patients have indeed been found to hinder provision of care at some Danish hospitals [24]. Despite not observing a difference in clinical outcome

TABLE 4 Functional outcome amongst patients arriving within 4.5 h after stroke onset by country of origin

	Patients with ischaemic stroke between 2009 and 2018		
	Functional outcome	Unadjusted	Fully adjusted[b]
	n	OR (95% CI)	OR (95% CI)
Good functional outcome[a]			
Danish-born	4189	1.00 (Reference)	1.00 (Reference)
Immigrants	158	0.73 (0.51–1.06)	0.55 (0.20–1.48)
Western	88	0.74 (0.46–1.18)	0.73 (0.18–2.88)
Non-Western	70	0.73 (0.41–1.31)	0.41 (0.10–1.59)
Poor functional outcome[a]			
Danish-born	1437	1.00 (Reference)	1.00 (Reference)
Immigrants	69	1.35 (0.93–1.95)	1.79 (0.67–4.79)
Western	47	1.35 (0.84–2.15)	1.35 (0.34–5.30)
Non-Western	22	1.36 (0.76–2.42)	2.40 (0.62–6.10)

Note: OR indicates odds ratio. Functional outcome was evaluated 3 months following stroke onset. Functional outcome was assessed by the modified Rankin Scale score; a score of 0 or 1 was categorized as 'good functional outcome' and 4, 5 and 6 as 'poor functional outcome'.

[a]Measurements were recorded only for persons receiving reperfusion therapy.

[b]The fully adjusted model comprised age, stroke severity, duration of residence, onset-to-door time, income, occupation, education, marital status, previous stroke or transient ischaemic attack, smoking, myocardial infarction, atrial fibrillation, diabetes, hypertension and reperfusion therapy.

between immigrants and Danish-born residents in patients eligible for reperfusion therapy, a study in the USA has previously reported that every 15-min increase in door-to-needle times was significantly associated with poor stroke outcome [28]. Hence, the 15-min difference in prehospital delay warrants consideration.

Strengths and limitations

The strength of this study is that it utilized a nationwide sample to document all phases of prehospital and inhospital time delays by immigration status and included a wide range of factors associated with the use of reperfusion therapy and timely admission amongst immigrants compared with Danish-born residents. Data on onset-to-door/stroke unit time were available during the entire study period between 2009 and 2018. These findings raise intriguing questions regarding the awareness of stroke signs and symptoms and the availability of acute treatment amongst immigrants in Denmark. Some potential limitations should be noted for this study. Owing to the observational nature of our study, only associations and not causation can be explored. It is possible that some of our estimates might be influenced by random variation due to the small sample size. Although the study was nationwide and population-based, the limited number of stroke patients with immigrant background reflects that the immigrant population in Denmark in general is younger than the Danish-born population and some immigrants may choose to go back to their country of origin as they get older (and experience a higher stroke risk). Caution is therefore needed when interpreting in particular the country-specific analyses. Furthermore, reasons for reperfusion therapy contraindications have yet to be recorded in detail in the DSR. Our findings may be limited by excluding approximately 20% of the stroke population due to missing information on onset-to-door time.

CONCLUSION

In this study, immigration status was significantly associated with lower chances of receiving reperfusion therapy in patients arriving within 4.5 h after stroke onset. No difference was found in system-related time delays and clinical outcome between immigrants and Danish-born residents in patients eligible for reperfusion therapy; however, there may be differences in patient delay amongst individuals arriving at a stroke unit within 4.5 h after stroke onset. Our findings inform clinicians and policy makers about the need for a concerted effort to raise awareness of stroke symptoms and the availability of acute treatment, particularly amongst immigrants.

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

George Frederick Mkoma: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (equal); methodology (lead); project administration (lead); resources (equal); software (lead); validation (equal); visualization (lead); writing—original draft (lead); writing—review and editing (lead). M. Norredam: Conceptualization (lead); data curation (supporting); formal analysis (supporting); funding acquisition (lead); methodology (supporting); project administration (equal); resources (equal); supervision (lead); writing—review and editing (supporting). Helle Klingenberg Iversen: Conceptualization (lead); project administration (supporting); supervision (supporting); writing—review and editing (supporting). Grethe Andersen: Conceptualization (lead); project administration (supporting); supervision (supporting); writing—review and editing (supporting). Søren Paaske Johnsen: Conceptualization (lead); data curation (equal); formal analysis (equal); funding acquisition (supporting); methodology (equal); project administration (equal); resources (equal); supervision (lead); validation (lead); writing—review and editing (supporting).

ETHICAL APPROVAL

This study was approved by the Danish Data Protection Agency, reference number 514-0457/20-3000, and adheres to the principles of the Declaration of Helsinki. No further approval is required when conducting register-based research in Denmark.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are stored at Statistics Denmark and have not been made publicly available in accordance with Danish data protection policy. However, the authors welcome initiatives for cooperation, and data access may be granted upon application.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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