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Galectin-3 and risk of ischaemic stroke: Reasons for Geographic and Racial Differences in Stroke cohort

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Abstract

Background and purpose: Galectin-3 is a biomarker of atherosclerotic and cardiovascular disease, and may be a useful marker for ischaemic stroke risk.

Methods: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort enrolled and examined 30 239 US participants between 2003 and 2007 (41% black, 59% white and 55% in the southeastern stroke belt). Baseline galectin-3 was measured in 526 subjects with incident ischaemic stroke over 5.4 years and in a cohort random sample (CRS) of 947 participants. Cox proportional hazards models were used to calculate hazard ratios (HRs) of ischaemic stroke by quartiles of galectin-3.

Results: In the CRS, galectin-3 was significantly higher with older age, black race, female sex, body mass index, hypertension, diabetes mellitus and kidney disease, and also in those who developed incident stroke. Participants with galectin-3 levels in the fourth versus first quartile had a 2.3-fold increased stroke risk [95% confidence interval (CI) 1.6, 3.4] in an unadjusted model. An

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Supporting Information

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interaction with age was found ($P = 0.06$), and therefore age-stratified analyses were performed. Amongst those younger than age 64, baseline galectin-3 in the second–fourth quartiles was associated with increased stroke risk (HR 3.0, 95% CI 1.6, 5.5) compared to the first quartile in an age-, race- and sex-adjusted model. The HR was 2.0 (95% CI 1.0, 4.0) with multivariable adjustment. There was no association amongst older participants.

Conclusions: Galectin-3 was associated with incident ischaemic stroke in younger but not older individuals. Confirmation of this finding, and elucidation of its implications for stroke pathophysiology and prevention, is needed.

Keywords

aging; biomarkers; cerebrovascular disease/stroke; epidemiology; galectin-3; inflammation; ischaemic stroke; risk factors

Introduction

Galectin-3, a β-galactoside-binding protein, has regulatory roles in fibrosis, inflammation, tissue repair and cell proliferation [1]. The American Heart Association/American College of Cardiology Foundation guidelines recommend the use of serum galectin-3 for additive risk stratification for hospitalization, death and prognosis in patients with established heart failure as a Class IIb indication [2]. Recent studies also suggested associations of galectin-3 with other forms of cardiovascular disease such as myocardial infarction [3] and atherosclerotic plaque stability [4].

Despite the recent attention outlined above, and a few studies on outcomes after ischaemic and hemorrhagic stroke [5,6], there has been limited investigation of the role of galectin-3 in determining the risk of stroke and cerebrovascular disease. The association of galectin-3 with the risk of ischaemic stroke was therefore examined, and the question of whether there were racial differences in this association was investigated, in a large population-based cohort of black and white Americans.

Methods

Subjects

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a prospective longitudinal cohort study of 30 239 community-dwelling black and white participants ≥45 years of age [7]. As previously reported, subjects were recruited between January 2003 and October 2007 by telephone [7]. The telephone response rate was 33% and the cooperation rate was 49%, which was consistent with prior studies [8]. Of those enrolled, 45% were men, 55% women; 58% were white, 42% black; 56% were residents of the stroke belt. Written informed consent, blood pressure, anthropomorphic measurements, blood samples, electrocardiography (ECG) and medication inventory were obtained at an in-home examination. Study methods were reviewed and approved by the Institutional Review Boards at each participating institution.

Measurement and definitions

Hypertension was defined as systolic blood pressure 140 mmHg, diastolic pressure >90 mmHg or self-reported hypertension treated with antihypertensive medications. Diabetes mellitus was defined by fasting glucose >126 mg/dl, non-fasting glucose >200 mg/dl or self-report with the use of antidiabetic medications. Left ventricular hypertrophy (LVH) was classified by ECG. Atrial fibrillation was defined as self-report or presence on ECG. Coronary heart disease was defined as self-reported myocardial infarction, bypass, percutaneous coronary intervention or myocardial infarction on ECG. Pre-baseline stroke was defined by self-report. Heart failure was defined as presence of orthopnea or paroxysmal nocturnal dyspnea.

Stroke ascertainment

A first ischaemic stroke through 1 September 2011 was ascertained. Participants were contacted every 6 months by telephone to collect health information. Medical records were obtained for patients with ischaemic stroke during the specified time period. All records were reviewed and validated by two or more physicians. Stroke was defined as focal neurological symptoms lasting >24 h or non-focal symptoms with positive imaging for ischaemic stroke. Ischaemic strokes were classified into subtypes of cardio-embolic, large vessel disease, small vessel disease, other and unknown, based on the TOAST criteria [9].

Case–cohort study

For this analysis a case–cohort study design was used, as previously published [10,11]. Cases were 569 participants with no baseline stroke who had an incident ischaemic stroke during follow-up. Controls were selected from a cohort random sample (CRS), which was composed of 1100 participants selected from the entire REGARDS cohort [11]. Age-, sex- and race-based stratified random sampling was performed (50% black, 50% white, 50% women, 50% men, age groups 20% 45–54, 20% 55–64, 25% 65–74, 25% 75–84 and 10% ≥85). The same exclusion criteria were used as were used for cases, and those with baseline stroke were excluded.

Laboratory methods

Fasting blood samples were drawn at the baseline home visit for each subject using previously published standardized methods [10]. Plasma galectin-3 was measured in the case–cohort sample using an ultra-sensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA). The laboratory analytical coefficient of variation range was 5.6%–7.4%. The lower detection limit was 1.8 ng/ml. Of the 1453 participants, two (0.1%) had values below the lower limit. A value halfway between 0 and the lower limit was assigned to these, i.e. 0.9 ng/ml. The upper detection limit was 35 ng/ml. There were two (0.1%) participants with values above the upper limit. For these values 10% higher than the upper limit, i.e. 38.5 ng/ml, was assigned.

There were 111 participants with missing galectin-3 (8% of cases and 7% of the CRS), mostly due to missing samples. This left 526 stroke cases (including 20 who were members of the CRS) and 947 in the CRS.

Statistical methods

All analyses were performed using SAS 9.3 (Cary, NC, USA). Associations of galectin-3 with stroke risk factors were analyzed by displaying means or proportions of risk factors by quartiles of galectin-3 in the CRS. Differences in risk factors by galectin-3 category were tested by chi-squared tests or ANOVA, accounting for the stratified sampling design. Risk factors that were significantly associated with galectin-3 in a univariate model were then evaluated in a multivariable linear regression model to determine independent correlates. Of particular interest in this analysis was whether galectin-3 was higher in blacks than whites.

Evaluation of galectin-3 and stroke risk was undertaken using Cox proportional hazards models with four levels of adjustment. Galectin-3 was divided into quartiles (Q1, gal-3 ≤ 8; Q2, 8 < gal-3 ≤ 10.4; Q3, 10.4 < gal-3 ≤ 13; Q4, gal-3 > 13, all in ng/ml), with the bottom quartile serving as the reference group. All models accounted for the stratified selection of the CRS by adjusting for sampling weights. The first model included age, sex and race. The second model added Framingham stroke risk factors (diabetes, systolic blood pressure, use of any antihypertensive medications, LVH by ECG, history of heart disease, atrial fibrillation). The third model added income and education. Differences in association by age, sex and race were investigated by introducing interaction terms for galectin-3 and these factors, with statistical significance for the interaction defined as $P < 0.10$. The role of galectin-3 in mediating the relationship between race and stroke was examined by first fitting a proportional hazards model for stroke with age, race, sex and an age by race interaction term as the independent variables, and then determining the amount of attenuation in the hazard ratios for race when galectin-3 was added to the model. Because of the known age by race interaction in stroke risk [12], the race hazard ratios were stratified by age. In secondary analyses, the relationship between galectin-3 level and stroke was investigated separately for four stroke subtypes, whilst maintaining the stratification by median age. The ‘other’ subtype was not included in our analysis since the numbers were too small ($n = 34$).

Results

The demographic characteristics of patients and controls are provided in Table S1. Unweighted and weighted sample sizes are provided in Tables 1 and S1. In the CRS, the mean ± standard deviation of plasma galectin-3 was 10.9 ± 0.2 ng/ml. Tables 1 and 2 show that baseline galectin-3 was significantly higher with older age, female sex, hypertension, diabetes, impaired kidney function, baseline heart disease and higher body mass index, whilst it was lower with higher income, education and physical activity. Independent of other factors, mean galectin-3 was 1.0 ng/ml higher in blacks than whites [95% confidence interval (CI) 0.48, 1.56; $P < 0.001$].

The hazard ratio (HR) for stroke increased with increasing quartiles of galectin-3; before adjustment, subjects in the fourth versus first quartile had a 2.3-fold increased stroke risk (95% CI 1.6, 3.4) in the overall population (Table 3). Adjustment for age attenuated this HR to 1.3 (0.9, 1.9), whilst separate adjustment for race and sex had minimal influence (Table 3). This confounding by age directed us to test for an interaction of galectin-3 with age. The age 9 galectin-3 interaction term P value was 0.06, so a further analysis for stroke risk

stratified by the median age (64 years) was performed. Table 4 shows these results by quartiles; there was no association of galectin-3 with stroke in those older than 64. Amongst younger participants, any level of galectin-3 above the first quartile was associated with increased stroke risk. Since there were wide confidence intervals by quartile and these HRs were similar, quartiles 2–4 were collapsed in subsequent *post hoc* analyses, which are shown in Table 5. Amongst those younger than 64 years, with galectin-3 levels in the second–fourth quartiles, the HR of stroke was 2.4 (1.4, 4.1) and increased to 3.0 (1.6, 5.5) after adjustment for age, sex and race (Table 5). Adjustment for traditional stroke risk factors attenuated the HR to 1.9 (95% CI 1.0, 3.8), with additional adjustment for income and education bringing it to 2.0 (95% CI 1.0, 4.0). There were no differences in associations of galectin-3 with stroke by race or sex in younger participants. The hazard ratios for race at specified ages (45, 55, 65, 75) were unchanged when galectin-3 was added to the model, indicating no mediation of the relationship between race and stroke by galectin-3 (data not shown). Furthermore, amongst those younger than 64, considering subtypes of ischaemic stroke, the strongest relationships were seen for cardio-embolic stroke and stroke of unknown etiology. Amongst those older than age 64, galectin-3 remained unrelated to risk of each stroke subtype (Table S2).

Discussion

In this population-based study, higher plasma galectin-3 was associated with ischaemic stroke risk in younger but not older persons. This relationship in younger persons was stronger for cardio-embolic and unknown stroke subtypes, although sample sizes were very small for this part of our analysis. Galectin-3 concentration increased with increasing age, independent of other factors, and it was also associated with several other variables including hypertension, diabetes, impaired kidney function and heart disease.

The reason for a different association of galectin-3 with stroke by age is unclear. Galectin-3 levels may rise early with inflammation, before those processes result in development of clinically apparent stroke risk factors such as hypertension and diabetes. These clinically apparent risk factors are more prevalent with increasing age, and might mask the relationship between galectin-3 and stroke in older age. This may also explain the attenuation of the hazard seen in the relationship of galectin-3 with ischaemic stroke (Table 4) when Framingham risk factors for stroke are added in model C. The influence of genetic factors also needs to be considered, particularly since genetic predisposition is of more importance in younger stroke patients [13]. A genome-wide association study revealed that 25.6% of the variance in galectin-3 levels came from the LGALS3 gene on chromosome 14, and 3.8% of the variance was contributed by ABO blood group [14]. Whilst alleles of the LGALS3 gene have been found to be associated with elevated C-reactive protein levels [15], there is no clear evidence linking them to stroke risk. The ABO locus has been linked to stroke and vascular disease, but since it explained so little of the variance in galectin-3 it is unlikely to be relevant to the relationship between galectin-3 and stroke that was observed in younger people. Lastly, there might be a plateau effect for galectin-3 with increasing age, resulting in a loss of discriminatory power of galectin-3 as a biomarker in individuals with age >64 years.

Galectin-3 was higher in blacks than whites in our study. This is consistent with the findings of a recent study by McEvoy *et al.* [16] from the ARIC cohort. However, in our mediation analysis, galectin-3 was not a mediator of the association of race with stroke risk. Additionally, there was no threshold value for galectin-3 above which risk sharply increased.

Only one other large prospective study of initially stroke-free individuals which reported an association of galectin-3 with stroke is known to us. This study investigated a general-population cohort from Finland of 8444 individuals [17] and found that galectin-3 was weakly associated with an incident ischaemic stroke HR of 1.16 (1.04, 1.30) over a 15-year follow-up. This relationship was attenuated in multivariable adjusted models, HR 1.07 (0.95, 1.19). Most of the other population-based cardiovascular studies that investigated the prognostic value of galectin-3 did not include stroke as a separate end-point [18–20]. The only other study besides REGARDS that demonstrated an association of galectin-3 with the risk of stroke evaluated patients who underwent carotid endarterectomy [21]. Additionally, few studies have investigated the impact of galectin-3 levels on outcomes after cerebrovascular accidents – higher levels acutely were associated with worse outcomes in intracranial hemorrhage [6] as well as subarachnoid hemorrhage [22]. A recent study suggested no impact of galectin-3 levels on occurrence of acute neurological decline, 3-month mortality or 3-month clinical outcome after ischaemic stroke, but the sample size was very small with 26 stroke patients and 10 controls [5]. Overall, the limited literature on galectin-3 suggests that there may be a link to stroke incidence and outcomes, but there are contradictory findings as well, and more investigation is warranted.

Mechanistically, there are several reasons why elevated galectin-3 could correlate with higher risk and worse outcome in ischaemic stroke. First, its association with conditions such as heart failure and coronary artery disease [3] suggests that it might be a marker of a general propensity to vascular diseases, including those affecting the cerebral circulation. Galectin-3 levels are also positively associated with CHA_2DS_2VASc scores in patients with atrial fibrillation, which puts them at a higher risk of embolic ischaemic strokes [23]. Experimental evidence indicates the importance of galectin-3 in atherosclerotic plaque stability and remodeling [4]. Additionally, galectin-3 is expressed by microglia following various brain injuries, including ischaemic stroke, and might be important for the inflammation, gliosis and tissue remodeling that follows stroke [24]. It is interesting, however, to note that inhibiting galectin-3 after cerebral ischaemia in animal models has deleterious consequences, which is contrary to the findings from clinical studies [25]. It is possible that galectin-3 has varying influences on stroke risk and outcome depending on the site of its expression and chronological context in relation to the ischaemic event. Finally, galectin-3 also relates to thrombotic potential, which might explain part of its association with stroke [26,27].

The strengths of our study include the racial and geographic diversity of the cohort, high retention rates, and the prospective nature of our study design. A few limitations must be noted. Galectin-3 was only measured once; serial measurements could improve prognostic accuracy. The imprecision of risk estimates in quartiles 2–4 in younger subjects, and *post hoc* collapsing of these quartiles for presentation of results, means that the results must be considered preliminary and replication is needed. Defining heart failure through the presence

of orthopnea or paroxysmal nocturnal dyspnea could have led to us missing some cases, whilst erroneously classifying some patients with normal heart function as having heart failure. Finally, our results are not generalizable to ethnicities other than blacks and whites.

Summary

In a large prospective longitudinal cohort study of blacks and whites, galectin-3 was associated with incident stroke in younger but not older individuals. Whether galectin-3 is an innocent bystander or is involved in the pathogenesis of stroke requires further study. Confirmatory studies, especially in younger populations, are needed to replicate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Salvagno GL, Pavan C. Prognostic biomarkers in acute coronary syndrome. Ann Transl Med 2016; 4: 258. [PubMed: 27500159]
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147–e239. [PubMed: 23747642]
3. Meijers WC, van der Velde AR, Pascual-Figal DA, deBoer RA. Galectin-3 and post-myocardial infarction cardiac remodeling. Eur J Pharmacol 2015; 763(Pt A): 115–121. [PubMed: 26101067]
4. Papaspyridonos M, McNeill E, de Bono JP, et al. Galectin-3 is an amplifier of inflammation in atherosclerotic plaque progression through macrophage activation and monocyte chemoattraction. Arterioscler Thromb Vasc Biol 2008; 28: 433–440. [PubMed: 18096829]
5. Bustamante A, Diaz-Fernandez B, Penalba A, Garcia-Berrocoso T, Montaner J. Galectin-3 is not an outcome biomarker in ischemic stroke. Letter concerning the study 'Role of galectin-3 in plasma as a predictive biomarker of outcome after acute intracerebral hemorrhage'. J Neurol Sci 2016; 371: 67–68. [PubMed: 27871452]
6. Yan XJ, Yu GF, Jie YQ, Fan XF, Huang Q, Dai WM. Role of galectin-3 in plasma as a predictive biomarker of outcome after acute intracerebral hemorrhage. J Neurol Sci 2016; 368: 121–127. [PubMed: 27538613]
7. Howard VJ, Cushman M, Pulley L, et al. The Reasons for Geographic and Racial Differences in Stroke study: objectives and design. Neuroepidemiology 2005; 25: 135–143. [PubMed: 15990444]
8. Toledano MB, Smith RB, Brook JP, Douglass M, Elliott P. How to establish and follow up a large prospective cohort study in the 21st century – lessons from UK COSMOS. PLoS One 2015; 10: e0131521. [PubMed: 26147611]

9. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24: 35–41. [PubMed: 7678184]
10. Gillett SR, Boyle RH, Zakai NA, McClure LA, Jenny NS, Cushman M. Validating laboratory results in a national observational cohort study without field centers: the Reasons for Geographic and Racial Differences in Stroke cohort. Clin Biochem 2014; 47: 243–246. [PubMed: 25130959]
11. Cushman M, Judd SE, Howard VJ, et al. N-terminal pro-B-type natriuretic peptide and stroke risk: the Reasons for Geographic and Racial Differences in Stroke cohort. Stroke 2014; 45: 1646–1650. [PubMed: 24757103]
12. Howard G, Kissela BM, Kleindorfer DO, et al. Differences in the role of black race and stroke risk factors for first vs. recurrent stroke. Neurology 2016; 86: 637–642. [PubMed: 26791153]
13. Terni E, Giannini N, Brondi M, Montano V, Bonuccelli U, Mancuso M. Genetics of ischaemic stroke in young adults. BBA Clin 2015; 3: 96–106. [PubMed: 26672892]
14. de Boer RA, Verweij N, van Veldhuisen DJ, et al. A genome-wide association study of circulating galectin-3. PLoS ONE 2012; 7: e47385. [PubMed: 23056639]
15. Trompet S, Jukema W, Mooijaart SP, et al. Genetic variation in galectin-3 gene associates with cognitive function at old age. Neurobiol Aging 2012; 33: 2232. e1–e9.
16. McEvoy JW, Chen Y, Halushka MK, et al. Galectin-3 and risk of heart failure and death in blacks and whites. J Am Heart Assoc 2016; 5: e003079. [PubMed: 27178204]
17. Jagodzinski A, Havulinna AS, Appelbaum S, et al. Predictive value of galectin-3 for incident cardiovascular disease and heart failure in the population-based FIN-RISK 1997 cohort. Int J Cardiol 2015; 192: 33–39. [PubMed: 25985013]
18. Jansen H, Koenig W, Jaensch A, et al. Prognostic utility of galectin-3 for recurrent cardiovascular events during long-term follow-up in patients with stable coronary heart disease: results of the KAROLA study. Clin Chem 2016; 62: 1372–1379. [PubMed: 27540030]
19. Gullestad L, Ueland T, Kjekshus J, et al. The predictive value of galectin-3 for mortality and cardiovascular events in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Am Heart J 2012; 164: 878–883. [PubMed: 23194488]
20. de Boer RA, van Veldhuisen DJ, Gansevoort RT, et al. The fibrosis marker galectin-3 and outcome in the general population. J Intern Med 2012; 272: 55–64. [PubMed: 22026577]
21. Edsfeldt A, Bengtsson E, Asciutto G, et al. High plasma levels of galectin-3 are associated with increased risk for stroke after carotid endarterectomy. Cerebrovas Dis 2016; 41: 199–203.
22. Liu H, Liu Y, Zhao J, Liu H, He S. Prognostic value of plasma galectin-3 levels after aneurysmal subarachnoid hemorrhage. Brain Behav 2016; 6: e00543. [PubMed: 27781149]
23. Chen D, Procter N, Goh V, et al. New onset atrial fibrillation is associated with elevated galectin-3 levels. Int J Cardiol 2016; 223: 48–49. [PubMed: 27529590]
24. Burguillos MA, Svensson M, Schulte T, et al. Microglia-secreted galectin-3 acts as a Toll-like receptor 4 ligand and contributes to microglial activation. Cell Rep 2015; 10: 1626–1638. [PubMed: 25753426]
25. Lalancette-Hebert M, Swarup V, Beaulieu JM, et al. Galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury. J Neurosci 2012; 32: 10383–10395. [PubMed: 22836271]
26. DeRoo RP, Wrobleski SK, et al. The role of galectin-3 and galectin-3 binding protein in venous thrombosis. Blood 2015; 125: 1813–1821. [PubMed: 25428218]
27. Oluwaseun OE, Heckbert SR, Aguilar D, et al. Galectin-3 and venous thromboembolism incidence: the Atherosclerosis Risk in Communities study. Res Pract Thromb Haemost 2017; 10.1002/rth2.12038. [Epub ahead of print].

Table 1

Demographic variables by galectin-3 quartile (Q) in the cohort random sample *

	Galectin-3 quartile				
	Q1	**Q2**	**Q3**	**Q4**	***P* value**
Sample size					
Unweighted	220	237	222	268	
Weighted	6636	6502	6326	6401	
Age (mean, years)	61.0	64.5	65.5	68.0	<0.001
Race (% white)	70	59	56	52	0.003
Sex (% male)	58	42	42	36	<0.001
Physical activity frequency (%)					
None	23	35	34	41	0.01
1–3 times per week	41	33	41	32	
4+ times per week	36	32	25	28	
BMI (mean, kg/m^2)	27.8	29.2	30.6	29.6	<0.001
History of heart disease (% yes)	11	14	16	24	0.007
Hypertension (% yes)	46	59	63	75	<0.001
SBP (mean, mmHg)	125	127	128	129	0.002
Diabetes (% yes)	7	22	26	30	<0.001
LVH by ECG (% yes)	5	9	7	10	0.24
Atrial fibrillation	6	12	10	8	0.36
Income (%) <$20 000	11	15	15	22	<0.001
Education (%) <high school	6	11	11	18	0.001

BMI, body mass index; ECG, electrocardiography; LVH, left ventricular hypertrophy; SBP, systolic blood pressure, mmHg.

* Analyses weighted to reflect distributions in the analytic cohort.

Table 2

Multivariable linear regression model for correlates of galectin-3 in the cohort random sample

	Difference in galectin-3, ng/ml	95% CI for difference	*P* value
Age, per 1 SD (12 years)	0.64	0.25, 1.04	0.001
Race, black versus white	1.02	0.48, 1.56	<0.001
Sex, male versus female	−0.97	−1.49, −0.44	<0.001
Region			
Belt versus buckle	0.58	−0.15, 1.31	0.12
Other versus buckle	−0.03	−0.73, 0.67	0.93
Physical activity frequency (%)			
1–3 times per week versus none	−1.01	−1.62, −0.40	0.001
4+ times per week versus none	−0.25	−0.46, −0.03	0.02
History of heart disease, yes versus no	1.08	0.37, 1.80	0.003
Diabetes, yes versus no	0.95	0.31, 1.59	0.004
Chronic kidney disease, yes versus no	2.04	0.84, 3.25	<0.001
eGFR, per 1 SD (21 ml/min/1.73 m^2)	−0.79	−1.21, −0.37	<0.001

CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table 3

Association of galectin-3 with stroke, adjusted for sex, race and age

Model	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
Unadjusted	Referent	1.6 (1.1, 2.3)	1.9 (1.3, 2.8)	2.3 (1.6, 3.4)	<0.001
Sex only	Referent	1.7 (1.2, 2.6)	2.1 (1.4, 3.1)	2.6 (1.7, 3.8)	<0.001
Race only	Referent	1.6 (1.1, 2.3)	1.8 (1.3, 2.7)	2.2 (1.5, 3.2)	<0.001
Age only	Referent	1.2 (0.8, 1.7)	1.3 (0.9, 1.8)	1.3 (0.9, 1.9)	0.54

Table 4

Galectin-3 and the hazard ratio of ischaemic stroke, stratified by median age

Model	*N*	Q1	Q2	Q3	Q4	*P* value overall
1. Age < 64						
A	489	Referent	2.1 (1.1, 4.0), *P* = 0.03	3.0 (1.6, 5.8), *P* < 0.001	2.0 (1.0, 4.2), *P* = 0.06	0.008
B	489	Referent	2.7 (1.3, 5.4), *P* = 0.006	4.0 (1.9, 8.5), *P* < 0.001	2.4 (1.1, 5.3), *P* = 0.03	0.004
C	443	Referent	1.6 (0.8, 3.5), *P* = 0.19	2.7 (1.1, 6.3), *P* = 0.02	1.6 (0.7, 4.0), *P* = 0.30	0.16
D	443	Referent	1.6 (0.7, 3.5), *P* = 0.28	2.8 (1.1, 6.8), *P* = 0.03	1.7 (0.7, 4.6), *P* = 0.27	0.17
2. Age 64+						
A	984	Referent	1.0 (0.6, 1.6), *P* = 0.87	1.0 (0.6, 1.7), *P* = 0.91	1.3 (0.8, 2.1), *P* = 0.29	0.49
B	984	Referent	0.8 (0.5, 1.3), *P* = 0.37	0.8 (0.5, 1.3), *P* = 0.37	1.0 (0.6, 1.5), *P* = 0.85	0.67
C	919	Referent	0.7 (0.4, 1.2), *P* = 0.22	0.9 (0.5, 1.4), *P* = 0.55	0.9 (0.5, 1.4), *P* = 0.56	0.67
D	919	Referent	0.7 (0.4, 1.2), *P* = 0.16	0.8 (0.5, 1.3), *P* = 0.38	0.8 (0.5, 1.4), *P* = 0.49	0.58

Models: A, unadjusted; B, adjusted for age, sex, race, age × race; C, model B + Framingham stroke risk factors (diabetes, systolic blood pressure, use of any antihypertensive medications, left ventricular hypertrophy, history of coronary artery disease, atrial fibrillation); D, model C + income, education. *N*, total number of participants in the analysis; Q, quartile.

Table 5

Associations of galectin-3 with ischaemic stroke risk, stratified by age

Model	*N*	Q1	Q2-Q4
Age < 64			
A	489	Referent	2.4 (1.4, 4.1), $P = 0.002$
B	489	Referent	3.0 (1.6, 5.5), $P < 0.001$
C	443	Referent	1.9 (1.0, 3.8), $P = 0.05$
D	443	Referent	2.0 (1.0, 4.0), $P = 0.06$
Age 64+			
A	984	Referent	1.1 (0.7, 1.7), $P = 0.66$
B	984	Referent	0.9 (0.6, 1.3), $P = 0.46$
C	919	Referent	0.8 (0.5, 1.3), $P = 0.36$
D	919	Referent	0.8 (0.5, 1.2), $P = 0.26$

Models: A, unadjusted; B, adjusted for age, sex, race, age × race; C, model B + Framingham stroke risk factors (diabetes, systolic blood pressure, use of any antihypertensive medications, left ventricular hypertrophy, history of coronary artery disease, atrial fibrillation); D, model C + income, education. *N*, total number of participants in the analysis; Q, quartile.