

SUPPLEMENTAL MATERIAL

Supplemental Table I. Baseline Characteristics of those enrolled and those not in the study sample.

	IGF-1 Measurements Available	No IGF-1 Measurements Available	
	N=757	N=320	p-value
Age, mean ± SD	79±5	84±7	<0.001
Female, n (%)	470 (62)	201 (71)	0.004
Body Mass Index, mean ± SD	26.50 [23.51, 29.35] *	25.53 [22.83, 29.46] *	0.409
Waist-Hip Ratio, mean ± SD	0.93±0.09	0.91±0.09	0.088
Current Smoking, n (%)	62 (8)	25 (9)	0.693
Anti-hypertensive, n (%)	363 (51)	140 (54)	0.420
Prevalent AF, n (%)	81 (11)	39 (14)	0.149
IGF-1, mean ± SD	145±60		
Incident Stroke, n (%)	119 (16)		
Ischemic Stroke, n (%)	99 (13)		

N: Number; CVD: Cardiovascular disease; IGF-1: Insulin like growth factor1, SD: Standard Deviation, AF: Atrial Fibrillation.

*Median [Q1, Q3] .The comparison of means was performed on the natural log transformation of BMI.

Supplemental Table II. Stratified analysis by ischemic stroke subtypes.

Ischemic Stroke subtype	Large artery disease	Lacunar	Cardioembolic
Age and sex adjusted*	0.87 [0.61, 1.23] (0.42)	0.84 [0.46, 1.51] (0.54)	0.73 [0.52, 1.01] (0.06)
Multivariate †	0.92 [0.64, 1.31] (0.64)	0.83 [0.46, 1.51] (0.53)	0.73 [0.52, 1.02] (0.06)
Multivariate+Mediators‡	0.92 [0.64, 1.31] (0.91)	0.94 [0.51, 1.72] (0.82)	0.75 [0.54, 1.05] (0.09)

Hazard ratios, HR [95% CI], (p-values) are estimated for 1 SD (standard deviation) increase in IGF-1 levels in each category.

HR: Hazard ratio; CI: Confidence interval.

†: Adjusted for age, sex, systolic blood pressure, smoking, anti-hypertensive treatment, prevalent CVD.

‡: Additionally adjusted for Waist-hip ratio and diabetes mellitus.

Supplemental table III. Hazard ratio of cardioembolic ischemic stroke based on IGF-1 quintiles (N=757, Events=46)

	Quintile of Plasma IGF-1				
	I	II	III	IV	V
N	151	148	156	150	152
Age and sex adjusted*	2.91 [1.01, 8.41] (0.048)	2.45 [0.85, 7.09] (0.099)	2.40 [0.84, 6.82] (0.101)	1.23 [0.38, 4.03] (0.732)	1.00 (ref)
Multivariate †	2.82 [0.96, 8.28] (0.059)	2.36 [0.82, 6.86] (0.114)	2.41 [0.85, 6.87] (0.099)	1.15 [0.35, 3.79] (0.813)	1.00 (ref)
Multivariate+Mediators+AF ‡	1.67 [0.57, 4.94] (0.352)	1.93 [0.65, 5.73] (0.235)	2.32 [0.80, 6.70] (0.121)	1.08 [0.33, 3.59] (0.895)	1.00 (ref)

Results are HR [95% CI] with (p-values), comparing the top vs. bottom IGF-1 quintiles.

HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation; N: Number of observations.

†: Adjusted for age, sex, systolic blood pressure, smoking, anti-hypertensive treatment and prevalent CVD

‡: Additionally adjusted for waist-hip ratio, diabetes mellitus, and prevalent AF.

Supplemental table IV. Hazard ratio of non-cardioembolic ischemic stroke based on IGF-1 quintiles (N=757, Events=53)

	Quintile of Plasma IGF-1				
	I	II	III	IV	V
N	151	148	156	150	152
Age and sex adjusted*	2.26 [0.77, 6.65] (0.138)	1.82 [0.61, 5.47] (0.285)	2.46 [0.88, 6.92] (0.088)	3.00 [1.09, 8.26] (0.034)	1.00 (ref)
Multivariate †	1.99 [0.66, 5.96] (0.221)	1.67 [0.55, 5.04] (0.363)	2.52 [0.89, 7.10] (0.081)	3.15 [1.14, 8.74] (0.027)	1.00 (ref)
Multivariate+Mediators+AF ‡‡	1.89 [0.63, 5.69] (0.260)	1.44 [0.46, 4.45] (0.530)	2.53 [0.90, 7.12] (0.080)	3.40 [1.22, 9.46] (0.019)	1.00 (ref)

Results are HR [95% CI] with (p-values), comparing the top vs. bottom IGF-1 quintiles.

HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation; N: Number of observations.

†: Adjusted for age, sex, systolic blood pressure, smoking, anti-hypertensive treatment and prevalent CVD

‡: Additionally adjusted for waist-hip ratio, diabetes mellitus, and prevalent AF.

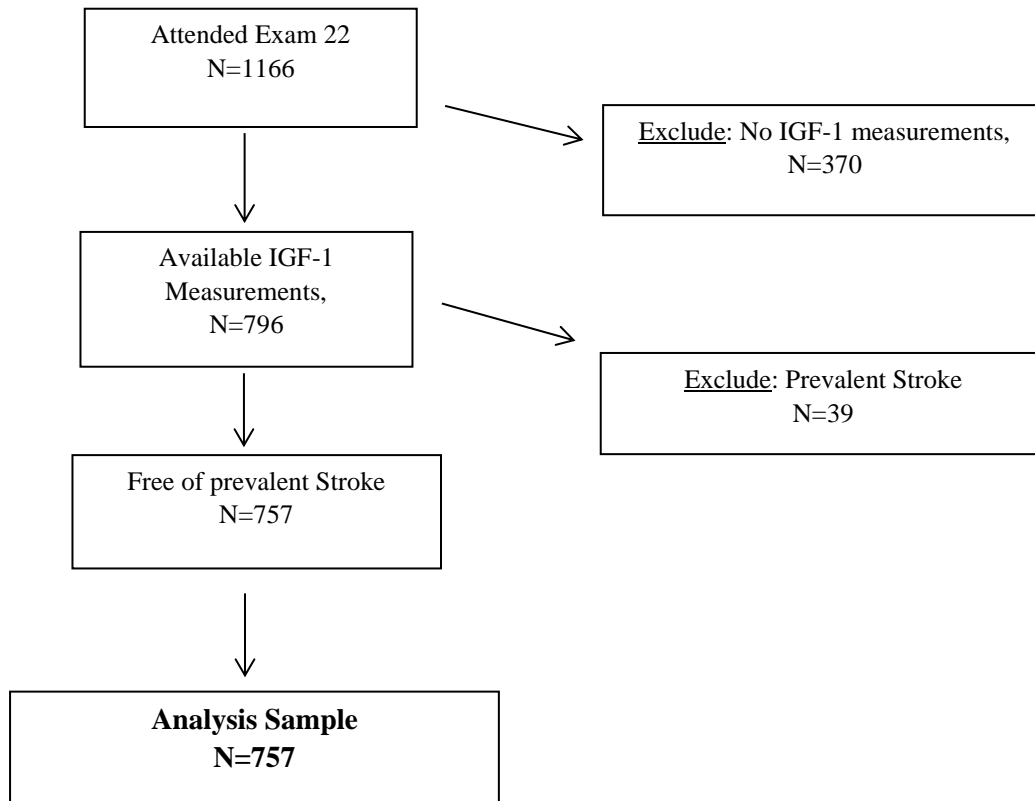


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Supplemental Figure I. Study sample flow chart.

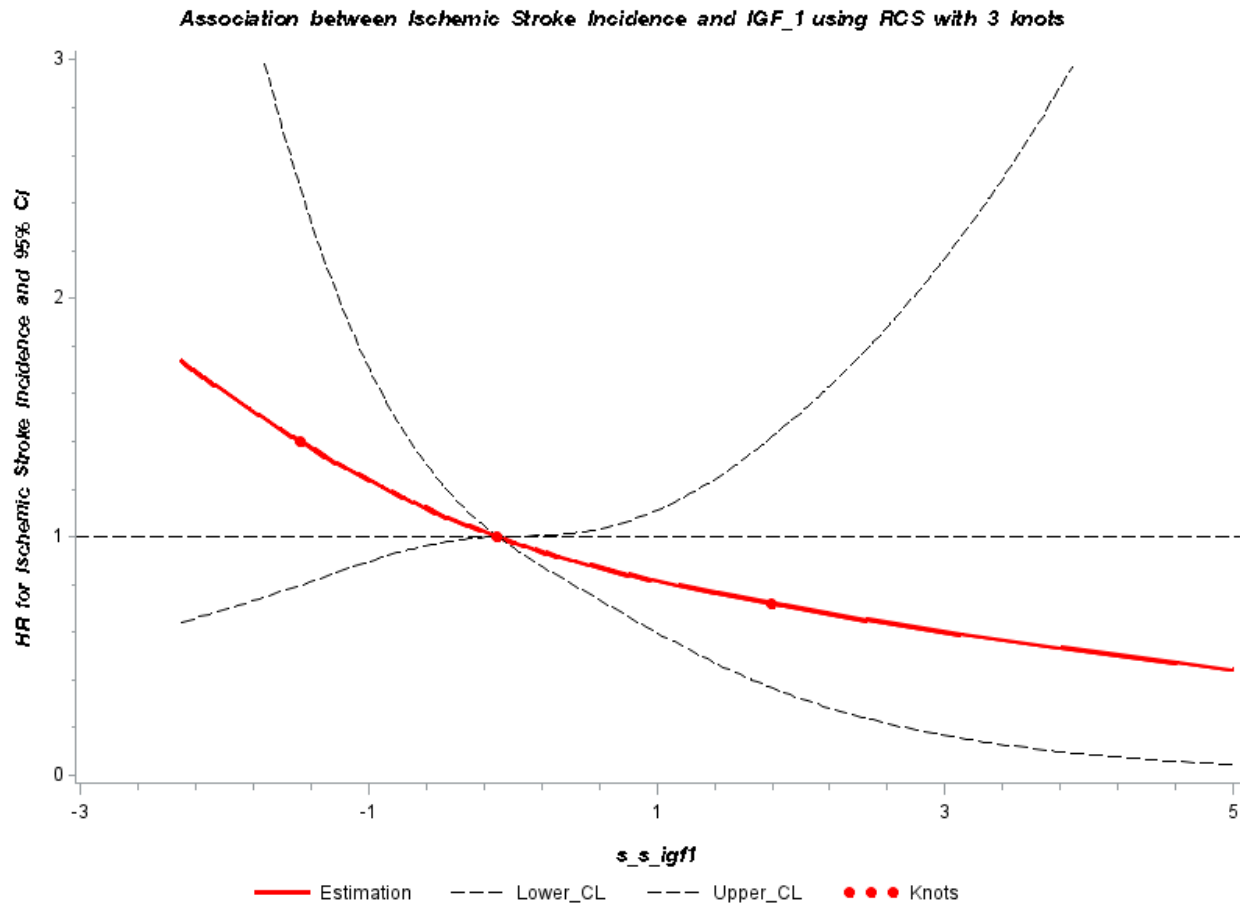


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Supplemental Figure II. Multivariable-adjusted relationship of serum IGF-1 levels with incident ischemic stroke evaluated by use of restricted cubic splines with 3 knots at fixed percentiles (5 th, 50 th and 95th) of distribution. Hazard ratios (red solid line) and 95% CIs (black dotted lines)

were estimated using restricted cubic spline Cox regression analysis. The multivariable model was adjusted for age, sex, systolic blood pressure, current smoking status, treatment for hypertension and prevalent CVD.

s_s_igf1: sex specific IGF-1; RCS: Restricted cubic spline; CL: confidence limit; HR: hazard ratio.