ONLINE SUPPLEMENT

Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study

eTable I. Detailed description of heart rate variability (HRV) methodology; the Atherosclerosis Risk in Communities (ARIC) Study.

	Heart Rate Variability Parameters	
	Time-Domain	**Frequency-Domain**
Data Collection[1]	• Participants rested supine, comfortably for ≥ 20 minutes. • ARIC B-mode ultrasound and arterial distensibility studies. • 3 ECG leads placed on epigastrium. • Dedicated computer and software continuously collected ECG data. • Visit 1: 2-minute recordings collected; Visit 4: 6-minute recordings collected.	
Data Processing[2,3]	• Software converted R-interval data to beat-to-beat heart rate data. • Computer algorithm imputed beat-to-beat heart data and performed smoothing.	• Coders electronically marked all R-peaks (procedure performed in duplicate). • Abnormal beats flagged; two subsequent intervals excluded.
Data Analysis[2,3]	• Linear interpolation used on neighboring data points. • Neighboring data points used to fit a quadratic least squares model to obtain residuals. • Fast Fourier Transformation applied to residuals to compute power spectral density (PSD). • From PSD curve, low and high frequency spectral powers were calculated using a rectangular method.	• Software calculated R-R interval duration on the basis of difference between coordinates. • Software calculated mean of duplicate R-R interval measurements.

eTable II: Clinical implications of HRV assessment; the Atherosclerosis Risk in Communities (ARIC) Study.

HRV Parameter*	Units	Description	ANS Function
Time-domain			
SD_{NN}	ms	Standard deviation of all NN RR intervals	Overall ANS variability
RMSSD	ms	Root mean square of successive differences in NN RR intervals	PNS
$Mean_{NN}$†	ms	Mean of all NN intervals	-
Frequency-domain			
LF	ms^2	Low frequency power	SNS & PNS
HF	ms^2	High frequency power	PNS
LF:HF	-	Ratio low:high frequency power	Balance between SNS & PNS

Abbreviations: Normal-to-normal, NN; interval between R waves of successive heartbeats, RR interval; autonomic nervous system, ANS; parasympathetic nervous system, PNS; sympathetic nervous system, SNS; milliseconds, ms; milliseconds squared, ms^2.

***All ECG recordings obtained under standardized conditions to minimize external stimuli on autonomic function.**

†Used primarily to calculate other HRV parameters.

eTable III: HRV quintile ranges for visit 1; the Atherosclerosis Risk in Communities (ARIC) Study.

	HRV Parameter					
	Time-domain*			Frequency-domain†		
	SD_{NN}	RMSSD	$Mean_{NN}$	LF	HF	LF:HF
Quintile 1	0.5-23.4	0.0 - 15.1	471.4 - 791.2	0.0 - 5.5	0.0 - 2.9	0.02 - 0.88
Quintile 2	23.5-30.4	15.2 - 21.0	791.3 - 862.2	5.6 - 12.2	3.0 - 6.3	0.89 - 1.53
Quintile 3	30.5-38.0	21.1 - 27.8	862.3 - 927.8	12.3 - 23.0	6.4 - 11.7	1.54 - 2.40
Quintile 4	38.1-49.5	27.9 - 39.0	927.9 - 1007.8	23.1 - 45.9	11.8 - 23.2	2.41 - 4.00
Quintile 5	49.6-394	39.1 - 652.4	1007.9 - 1587.2	46.0 - 1440.0	23.3 - 1700.0	4.01 - 33.84

Abbreviations: Standard deviation of all NN intervals, SD_{NN}; root mean square of successive differences in NN RR intervals, RMSSD; mean of all NN intervals, $Mean_{NN}$; low frequency power, LF; high frequency power, HF; ratio low:high frequency power, LF/HF.

***Time-domain units: milliseconds, ms.**

†Frequency-domain units: milliseconds squared, ms^2 (except LF:HF, a ratio).

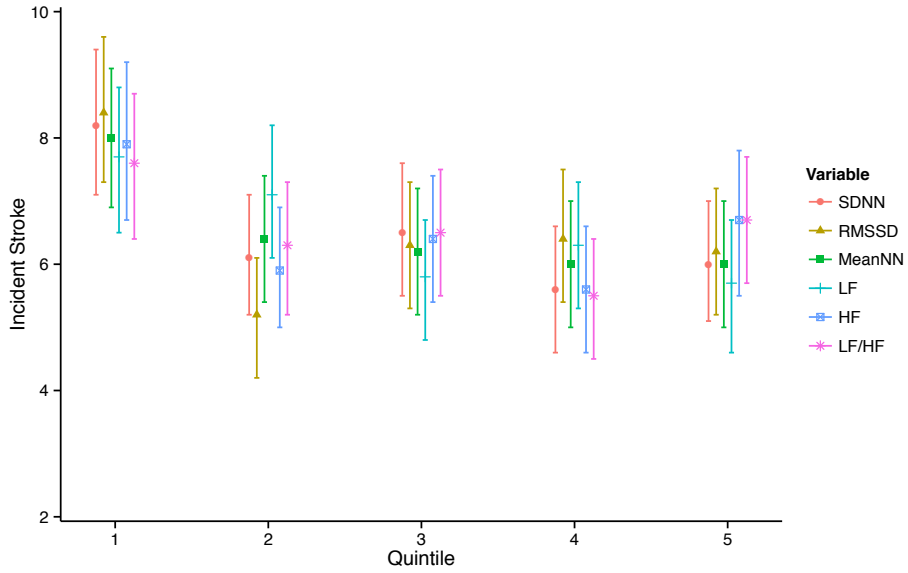
eTable IV: Time-domain (top) and frequency-domain (bottom) heart rate variability at visit 4 and stroke risk for people without (*n* = 6951) and with (*n* = 1090) prevalent diabetes; total strokes *n* = 372.

Time Domain						
	SD_{NN}		**$Mean_{NN}$**		**RMSSD**	
	No diabetes	**Diabetes**	**No diabetes**	**Diabetes**	**No diabetes**	**Diabetes**
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Quintile 1	0.8 (0.5, 1.2)	1.8 (0.8, 3.8)	1.2 (0.8, 1.7)	1.5 (0.7, 3.1)	1.0 (0.6, 1.5)	2.1 (1.0, 4.4)
Quintile 2	0.8 (0.6, 1.2)	1.7 (0.8, 3.6)	1.4 (1.0, 2.1)	1.7 (0.8, 3.6)	0.8 (0.5, 1.2)	2.1 (1.0, 4.5)
Quintile 3	0.7 (0.5, 1.1)	1.9 (0.9, 4.0)	1.2 (0.8, 1.7)	1.3 (0.6, 3.0)	1.0 (0.7, 1.4)	1.4 (0.6, 3.0)
Quintile 4	0.8 (0.5, 1.1)	1.4 (0.6, 3.3)	0.9 (0.6, 1.4)	0.6 (0.2, 1.7)	1.1 (0.8, 1.7)	1.6 (0.7, 3.4)
Quintile 5	Ref	Ref	Ref	Ref	Ref	Ref
$p_{interaction}$	0.31		0.62		0.14	
Frequency Domain						
	Low frequency		**High frequency**		**Low frequency/High frequency**	
	No diabetes	**Diabetes**	**No diabetes**	**Diabetes**	**No diabetes**	**Diabetes**
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Quintile 1	1.2 (0.8, 1.8)	1.7 (0.9, 3.3)	1.0 (0.7, 1.5)	1.4 (0.7, 2.8)	1.2 (0.8, 1.8)	1.5 (0.8, 2.9)
Quintile 2	1.1 (0.7, 1.7)	1.1 (0.5, 2.3)	1.0 (0.6, 1.4)	1.4 (0.7, 2.8)	1.2 (0.8, 1.9)	0.8 (0.3, 1.7)
Quintile 3	1.3 (0.9, 1.9)	1.7 (0.8, 3.6)	1.1 (0.8, 1.7)	1.6 (0.8, 3.1)	1.1 (0.7, 1.7)	1.4 (0.7, 2.7)
Quintile 4	1.0 (0.7, 1.6)	1.0 (0.5, 2.2)	0.8 (0.6, 1.3)	1.0 (0.5, 2.2)	1.3 (0.9, 1.9)	1.1 (0.5, 2.2)
Quintile 5	Ref	Ref	Ref	Ref	Ref	Ref
$p_{interaction}$	0.80		0.99		0.25	

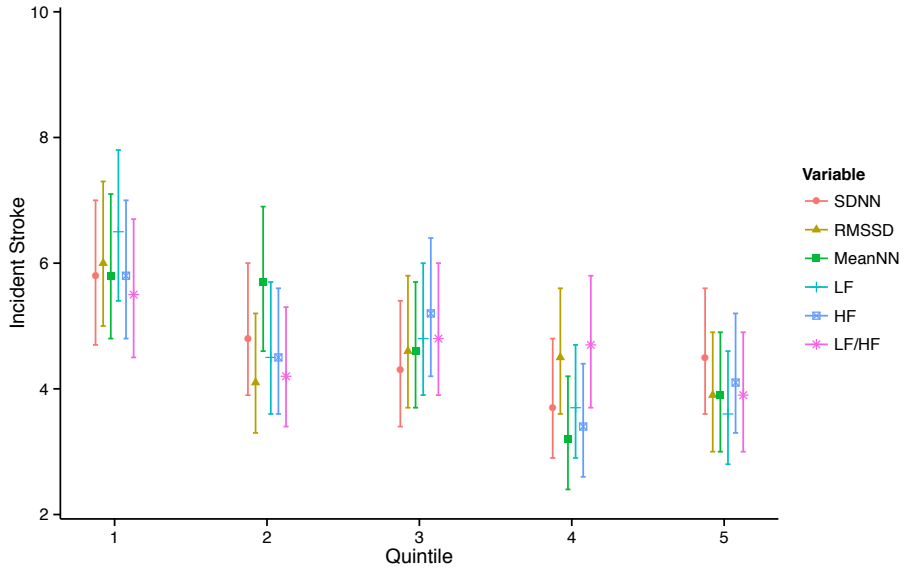
HR = Hazard Ratio; CI = Confidence Interval; Ref = Reference quintile.
Visit 4 HRV measurements used 6-minute ECG recordings.
All results from Model 2: adjusted for age, sex, race, education, smoking, alcohol consumption, physical activity, body mass index, systolic and diastolic blood pressure, blood lipids, prevalent diabetes, antihypertensive use, and heart rate (except for $Mean_{NN}$).
Hazard ratios can be interpreted as the comparison between quintiles 1, 2, 3, and 4 with quintile 5 (reference).

Figure. Unadjusted cumulative incidence of stroke (%, 95% CI) by HRV quintiles at: (A) visit 1, and (B) visit 4 in The Atherosclerosis Risk in Communities Study (ARIC).

(A) Visit 1



(B) Visit 4



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