Mildly Attenuated Heart Rate Response During Exercise and Adverse Cardiovascular Outcome: Follow-up of 10,323 Healthy Men and Women after Treadmill Exercise

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Conflict of interest

- None

Chronotropic incompetence: inability of the heart to increase its rate

- Independent predictor of cardiovascular events and overall mortality
- Commonly defined as heart rate response of less than 85% of maximum heart rate
- The data on chronotropic threshold among healthy population is limited

Study Aims

- Describe the association between the heart rate response and subsequent cardiovascular disease in healthy men and women

- Identify the degree of chronotropic incompetence associated with long-term adverse cardiovascular events in this population.

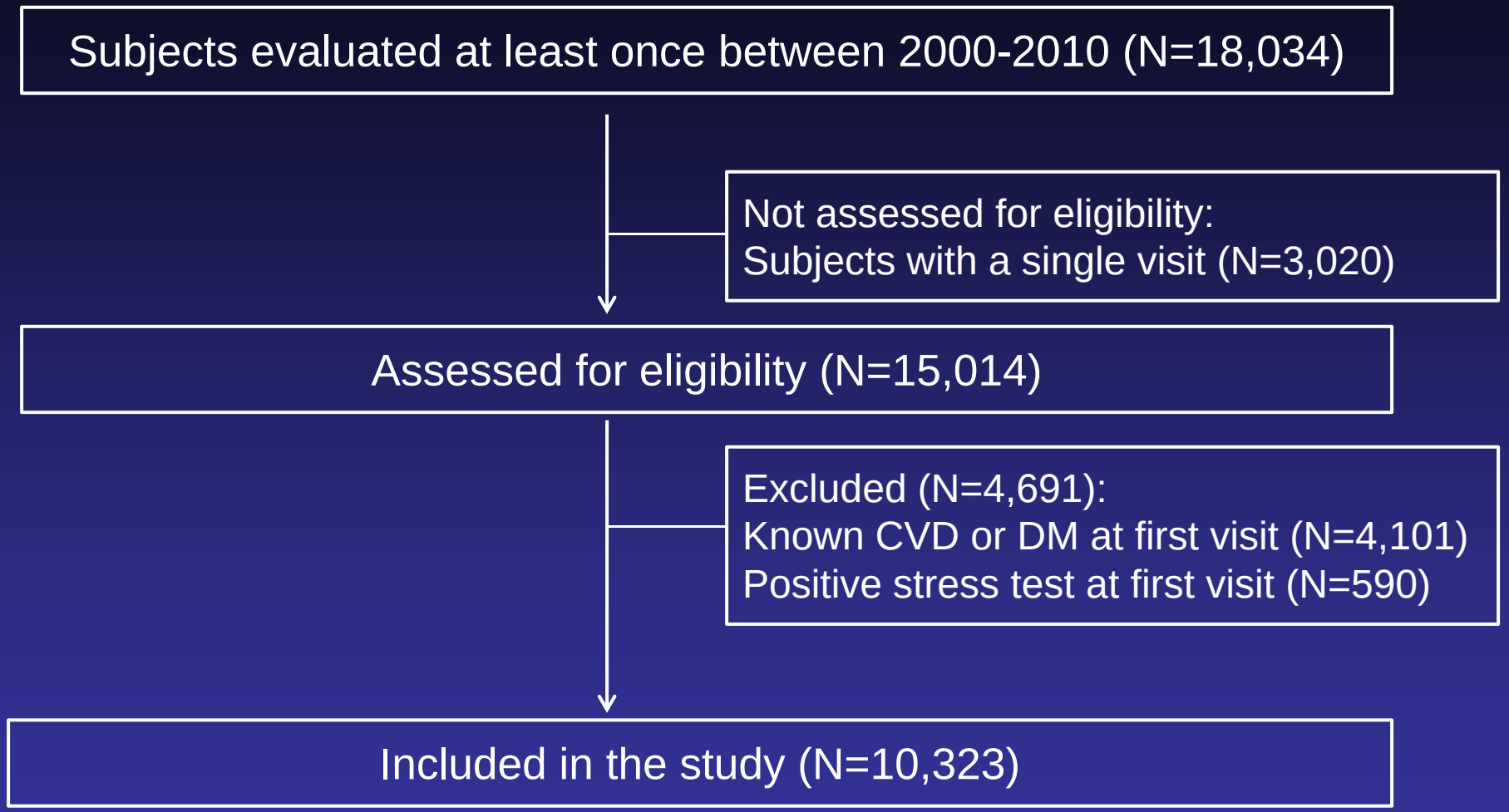
Study Hypothesis

- We hypothesized that even heart rate response variations within the normal range will also be associated with long-term cardiovascular outcomes

Study population: Screening of asymptomatic subjects

- 9,000 annual examinations, including:
  - Standard questionnaires
  - Physical examinations
  - Blood tests
  - Treadmill exercise stress test

Study population



Heart rate response definition

- Bruce protocol
- Age-predicted maximum heart rate (APMHR) = (220-age)
- Heart rate response = (maximal heart /APMHR) %
- Study population was divided to three tertiles:
  - **60.5% to 96.5%**
  - **96.6% to 98.8%**
  - **98.9% to 130.6%**

Study outcomes

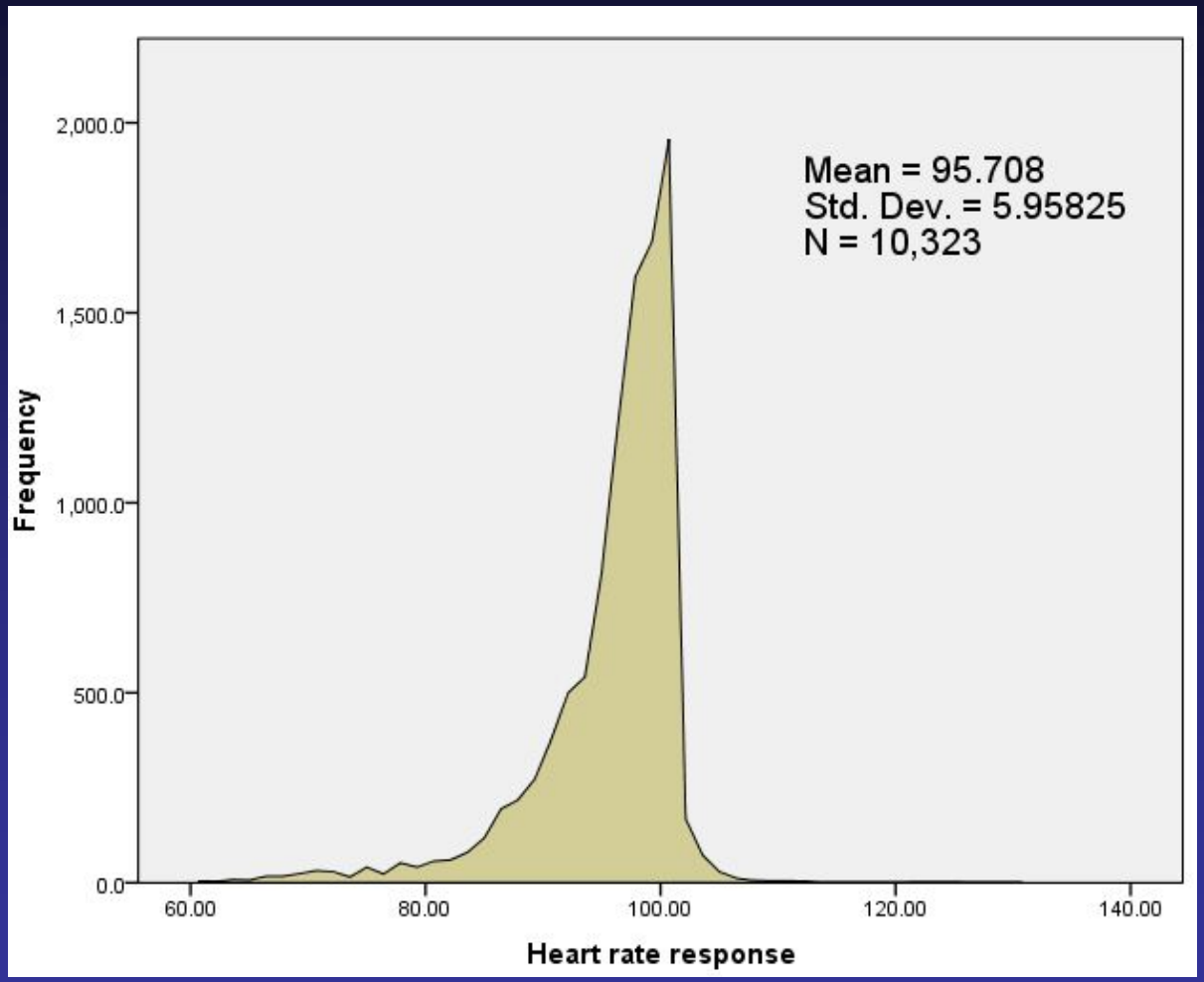
- Composite primary end point:
  - Acute coronary syndrome
  - Significant coronary heart disease
  - Cerebrovascular disease: CVA or TIA

- Secondary end point:
  - All-cause mortality

Young and healthy population

Age (years)	**50 ± 9**
Male (%)	**73**
BMI (kg/m^2)	**26 ± 3**
SBP at rest (mm Hg)	**120 ± 20**
Resting heart rate (bpm)	**76 ± 16**
LDL cholesterol	**126 ± 28**
Hypertension (%)	**14**
Current Smoker (%)	**16**
Physical Activity (%)	**63**

Heart rate response distribution

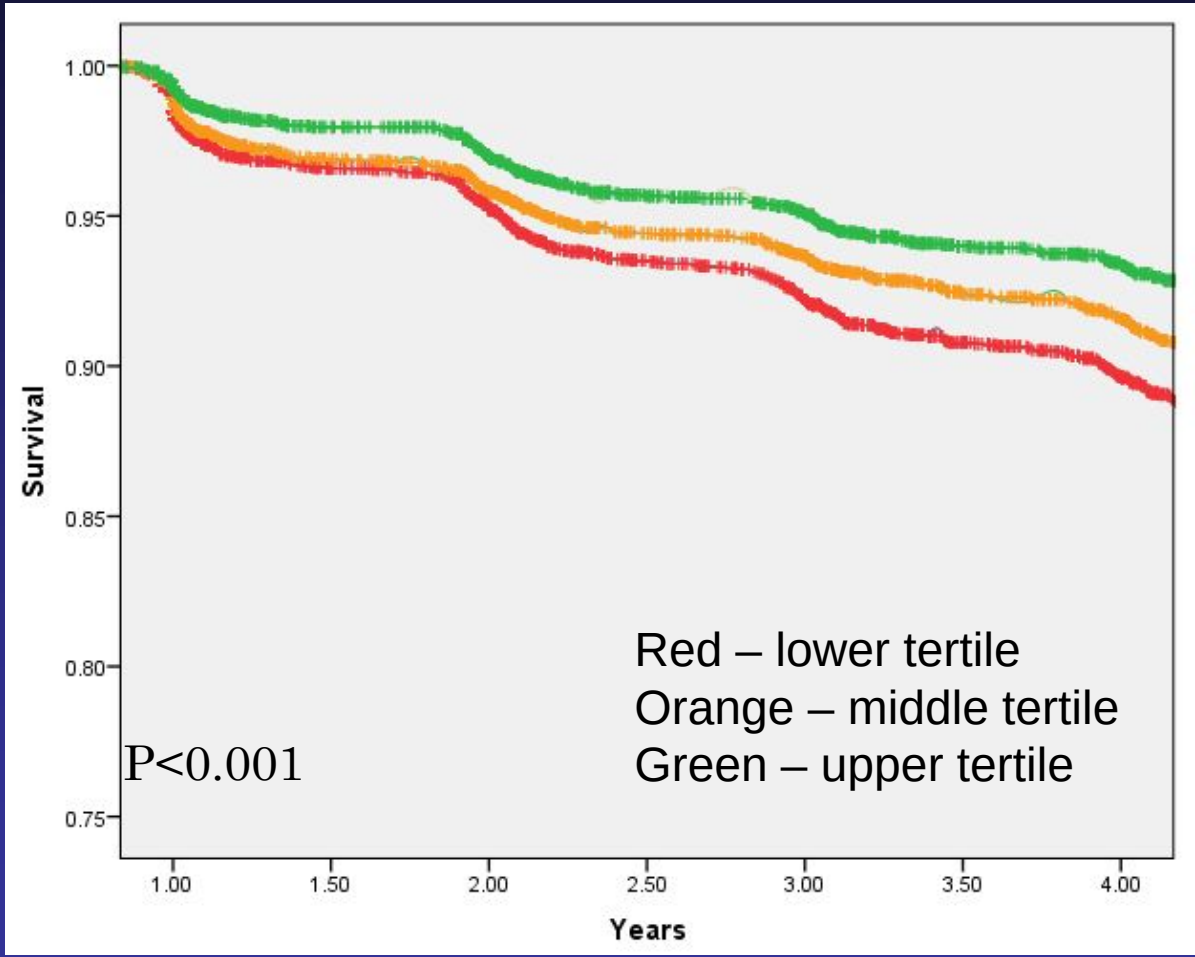


Baseline characteristic by tertiles

	Lower tertile	Middle tertile	Upper tertile
Age (years)	52 ± 10	49 ± 8	50 ± 8
Male (%)	67	76	78
BMI (kg/m^2)	27 ± 4	26 ± 3	25 ± 4
SBP at rest (mm Hg)	122 ± 22	121 ± 19	117 ± 18
Resting heart rate (bpm)	73 ± 16	77 ± 16	79 ± 17
LDL cholesterol	125 ± 28	127 ± 28	124 ± 29
Hypertension (%)	21	11	8
Current Smoker (%)	20	15	13
Physical Activity (%)	61	62	64

P < 0.001 for all parameters in the table

Subjects free from CVD endpoints



Unadjusted Odds Ratios

	Lower tertile	Middle tertile	Upper tertile (reference)
Composite end-point	1.61 (1.38 -1.86)	1.24 (1.06-1.46)	**1**
Cardiovascular	1.53 (1.30-1.80)	1.22 (1.03-1.45)	
Cerebrovascular	3.09 (1.66-5.75)	1.58 (0.81-3.14)	
All-cause mortality	1.72 (1.03-2.86)	0.95 (0.54-1.66)	

Fully-adjusted Cox proportional-hazards regression

Heart rate **response**	Hazard ratio	95% CI	P value
Upper tertile	**1 (Reference)**		
Middle tertile	**1.23**	**1.04-1.45**	**0.02**
Lower tertile	**1.34**	**1.14-1.59**	**0.001**

Adjusted for: Age, Gender, LDL cholesterol, Systolic blood pressure, smoking status, resting heart rate, physical activity, cardio-protective drugs and stress test final result.

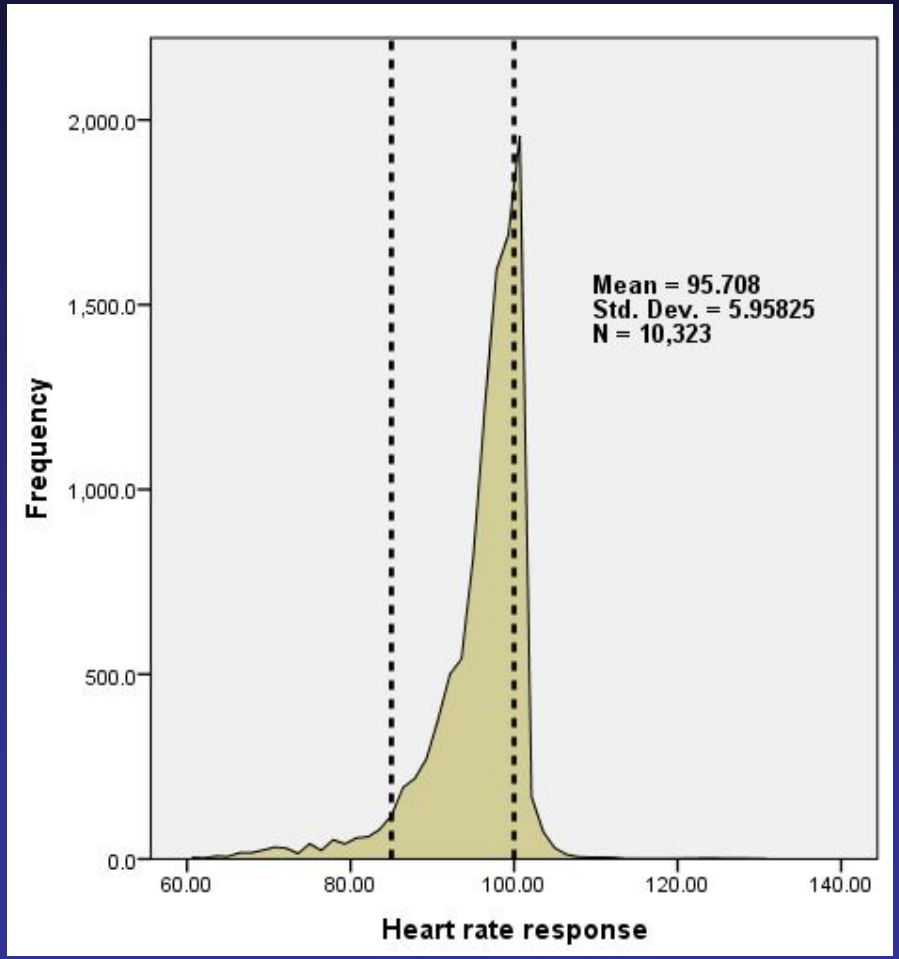
Heart rate response > 85%: A multivariate sub-analysis

9,754 subjects (95% of study population)

Heart rate response	Hazard ratio	95% CI	P value
Upper tertile	**1 (Reference)**		
Middle tertile	**1.19**	**1.00-1.41**	**0.05**
Lower tertile	**1.36**	**1.15-1.61**	**<0.001**

Adjusted for: Age, Gender, LDL cholesterol, Systolic blood pressure, resting heart rate, physical activity, cardio-protective drugs and stress test final result.

Sub-analysis of “Normal Range”: Heart rate response of 85%-100%



Heart rate response 85%-100%: Continuous variable sub-analysis

- 8,693 subjects (84% of study population)
- **Heart rate response decrease of 1% was associated with a 3% increase in CVD outcome (HR 1.03 CI 1.01-1.05, P<0.001).**

Conclusion

- In healthy adults undergoing routine exercise testing even mild reductions in heart rate response can be considered as markers of increased long-term CVD risk

Unadjusted Odds Ratios

Event	Unadjusted hazard ratio (95% CI)			Number of events		
	Lower tertile	Middle tertile	Upper tertile (reference)	Lower tertile	Middle tertile	**Upper tertile**
CVD	1.61 (1.38 -1.86)	1.24 (1.06-1.46)	1	428	338	**249**
Cardiovascular disease	1.53 (1.30-1.80)	1.22 (1.03-1.45)		385	315	**236**
Cerebrovascular disease	3.09 (1.66-5.75)	1.58 (0.81-3.14)		43	23	**13**
All-cause mortality	1.72 (1.03-2.86)	0.95 (0.54-1.66)		50	30	**22**