Statistical analysis plan for ADDITION PRO study

Title: Long-term weekly heart rate variability associations with cardiovascular disease in prediabetes – a prospective cohort-study from the ADDITION-PRO

Jonas R. Schaarup[1], Lasse Bjerg[2], Christian S. Hansen[3], Annelli Sandbæk[1,2], Dorte Vistisen[3,4], Daniel R. Witte[1,2]

[1]Department of Public Health, Aarhus University, Denmark; [2] Steno Diabetes Center Aarhus, Aarhus University Hospital, Denmark; [3] Steno Diabetes Center Copenhagen, Copenhagen, Denmark; [4]Department of Public Health, University of Copenhagen, Copenhagen, Denmark

ORCID identifier(s)

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Corresponding author

Jonas R. Schaarup

Work address: Steno Diabetes Center Aarhus, Palle Juul-Jensens Boulevard 11, Aarhus N, 8200, DK

E-mail: jfrscha@ph.au.dk

Phone number: +45 29936899

Description

Inclusion criteria for the participants was having a least 48 hour measured heart rate and no prior CVD events before inclusion.

Frequencies (percentages) and medians (lower and upper quartiles) will be calculated to describe categorical and continuous variables, respectively. These descriptive statistics will be presented in the table. Table 1 gives an overview of the study population general characteristics (demographic, lifestyle, bio markers). Prevalence and incidence rate of cardiovascular events (myocardial infarction, stroke, and heart failure), will be shown in table 2. Flow of participation will be shown in figure 1.

We will use cox proportional hazard model to investigate the association between heart rate variability indices and hard cardiovascular diseases outcomes (including myocardial infarction, stroke, and heart failure) as well as mortality. We will fit two models. Model 1 will include adjustments of age and sex. In addition to these, Model 2 will include alcohol consumption, smoking behavior, diet, physical activity, education, systolic blood pressure, body mass index, total cholesterol, and Hba1c. The hazard ratio by increase in HRV from the cox models will be presented in table 3. Because of biological differences in sex in the development CVD and women genuinely having a lower heart rate variability than men, we want to investigate the stratified association by sex.

To investigate for non-linearity (splines), we included defined knots based on quartiles in HRV distribution. The results from the spline models will by visualized in figure 2.

Both with multiple imputation and complete case analyses will be conducted in the R statistical computing environment (version X).

Tables and Figures

List of variables

Variables from ADDITION-PRO dataset

Age (years)
Sex (male)
Socioeconomic status
Smoking status
Physical activity (PAEE kj_kg_day)
Alcohol comsuption (units per week)
BMI (kg/m^2)
Waist circumference (cm)
Fat percentage (%)
Systolic blood pressure (mm hg)
Diastolic blood pressure (mm hg)
HbA1c (%)
LDL cholestorol (mmol/L)
HDL cholesterol (mmol/L)
Triglycerides (mmol/L)
Mean heart rate (bpm)
Median heart rate (bpm)
Heart rate variability indices

- Standard deviation of Normal to Normal intervals (ms)

- Root mean squared of successive RR intervals (ms)

- pNN50 (ms)

- SDSD (ms)

- High frequency (ms^2)

- Low frequency (ms^2)

- LF / HF ratio

- Ultra low frequency (ms^2)

- Ultra high frequency (ms^2)

Variables from ADDITION-PRO dataset

Medication use?

- Glucose lowering medication

- Cardioprotective medication

    - antihypentensive
    - lipid lowering

Variables from DST - *cardiovascular disease events*

Myocardial infarction

Stroke

Heart failure

Table 1 Population characteristics by diabetes status

	Study population in ADDITION-PRO
Age (years)	
Sex (male)	
Socioeconomic status	
Smoking status	
Physical activity (PAEE kj_kg_day)	
Alcohol comsuption (units per week)	
BMI (kg/m^2)	
Waist circumference (cm)	
Fat percentage (%)	
Systolic blood pressure (mm hg)	
Diastolic blood pressure (mm hg)	
HbA1c (%)	
LDL cholestorol (mmol/L)	
HDL cholesterol (mmol/L)	
Triglycerides (mmol/L)	
Mean heart rate (bpm)	
Median heart rate (bpm)	
Standard deviation of Normal to Normal intervals (ms)	
Root mean squared of successive RR intervals (ms)	
pNN50 (ms)	
SDSD (ms)	
High frequency (ms^2)	
Low frequency (ms^2)	

	Study population in ADDITION-PRO
Low frequency / high frequency (ratio)	
Ultra low frequency (ms^2)	
Ultra high frequency (ms^2)	

Table 2 CVD and mortality incident in study population

	Incidents CVD (cases per 1000 year)	Incidents mortality (cases per 1000 year)
All		
1st tertile HRV		
2nd tertile HRV		
3rd tertile HRV		

Table 3 Heart rate variability indices associated with CVD

	Model 1: HR (95% CI)		Model 2: HR (95% CI)	
	CVD events	All cause mortality	CVD events	All cause mortality
	n=x		n=x	
SDNN (per unit)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 1.xx)	0.xx (0.xx - 1.xx)
RMSSD (per unit)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 1.xx)	0.xx (0.xx - 1.xx=
High frequency (per unit)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 1.xx)	0.xx (0.xx - 1.xx)
Low frequency (per unit)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 1.xx)	0.xx (0.xx - 1.xx)
mean HR (per unit)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)	0.xx (0.xx - 0.xx)

Figure 1

Flow chart

Figure 2 (example)