# The association of heart rate variability at baseline and the pro-inflammatory state five years later

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#### Background

Low-grade inflammation has recently been confirmed as a major risk factor for cardiovascular disease (CVD). It is characterized by increased levels of CRP, fibrinogen, TNF-a, IL-6 and IL-6R. Reduced heart rate variability (HRV), which reflects lowered cardiac parasympathetic control, is another recently established risk factor for CVD. It has been hypothesized that there may be a direct and causal connection between these, at first sight rather different, risk factors for CVD. excluded subjects taking medication affecting immune functioning.

#### Methods

462 participants registered by the Netherlands Twin Registry (NTR) were selected because they had taken part in both a 24-hour ambulatory study and a BioBank study, which took place approximately 5 years later. In the first study, a 24-hour electrocardiogram (ECG) signal was used to extract 3 HRV measures: SDNN, RMSSD and RSA. In the second study a fasting blood sample was collected in the morning and values of 5 immune parameters were determined: CRP, fibrinogen, TNF-α, IL-6 and IL-6R. In our HRV analyses we excluded subjects taking medication affecting the autonomic nervous system. In the analyses of the immune parameters we additionally excluded subjects taking medication affecting immune functioning.

#### Results

Associations between the different pro-inflammatory markers were most apparent between the two acute phase reactants, CRP and fibrinogen (r = .472, P < .01). Of the cytokines, IL-6 appeared to be moderately associated with all other inflammatory markers (with r ranging from .22 to .39) while the association of TNF- $\alpha$  was only restricted to its cytokine counterpart.

	CRP	Fibrinogen	TNF-α	IL-6
CRP	-			
Fibrinogen	.47**	-		
TNF-α	.04	.03	-	
IL-6	.31**	.39**	.24**	-
IL-6R	.06	.18**	.07	.22**

\* \* Correlation significant at the .01 level (2-tailed) \* Correlation significant at the .05 level (2-tailed)

The three different HRV measures were highly correlated, which indicates the same construct is measured. In addition, body posture and/or activity did not impact the strength of this association (  $.70 < r_{lying}$ .89;  $.75 < r_{sitting} < .89$ ;  $.71 < r_{active} < .80$ ).

	Lying		Sitting		Active	
	RMSSD	SDNN	RMSSD	SDNN	RMSSD	SDNN
SDNN	RMSSD .89** .85**		<i>RMSSD</i> .89** .85**		<i>RMSSD</i> .80** .76**	
RSA	.85**	.70**	.85**	.75**	.76**	.71**







Moderate but consistent associations between HRV and the proinflammatory state over time were seen between HRV and the plasma levels of the acute phase reactants (CRP and fibrinogen) and IL-6.

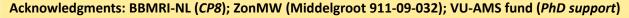
	CRP	Fibrinogen	TNF-α	IL-6	IL-6R
	RMSSD				
Lying	13*	16**	02	10*	.06
Sitting	13*	14**	03	13*	10
Activity	09	17**	05	13*	06
	SDNN				
Lying	17**	17**	03	12*	01
Sitting	14**	16**	01	13*	07
Activity	16**	20**	05	16**	10
	RSA				
Lying	11*	10*	04	13*	02
Sitting	13*	13**	01	16**	11
Activity	098	16**	02	19**	06

## Conclusion

Low HRV, reflecting decreases in parasympathetic cardiac activity, predicts a higher pro-inflammatory state over a 5 year follow-up period. This is in keeping with the recent hypothesis that parasympathetic activity can inhibit cytokine production (Tracey, 2009).

#### References:

Stacey, K . J. (2009). Reflex control of immunity. Nature Reviews Immunology, 9, 418-428





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