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**Title:** Heart rate variability and its relation to long-term smoking

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**Body:** Introduction. Heart rate variability (HRV) has been used in clinical studies to determine alterations in heart function. The deleterious effects of smoking on the cardiovascular system have also been reported extensively. We tested the hypothesis that long term active exposure to tobacco smoke triggers an irreversible change in the adaptability of the cardiovascular system, and that this effect may be reflected in alterations of HRV. Methods. We analyzed series of inter beat intervals using a nonlinear method, leading to a parameter known as the maximal Lyapunov exponent (coefficient  $\lambda$ ), which can be interpreted as a measure of unpredictability of the heart beat. By using multivariable regression models, we were able to explore the association between HRV and tobacco smoke exposure. The datasets were part of the SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults) cohort study, which contains 24h ECG data for 1586 participants and information about tobacco smoke exposure and further covariates such as biometric and disease related variables. Results. The covariate pack-years was significantly associated with lower  $\lambda$  coefficients in men and women, indicating higher predictability of heart rate among smokers. The effect remained the same when we analyzed ex-smokers and current smokers separately. The number of years of having quit smoking does not correlate with an increase of  $\lambda$  among ex-smokers. Conclusion. Smoking is associated with a significant increase in heart rate predictability, irrespectively of the current smoking status and the years of having quit smoking. Therefore, direct long term exposure to tobacco smoke may irreversibly affect the adaptability of the cardiovascular system.