

Non-conventional risk and prognostic factors in coronary heart disease : Studies on heart rate variability, alcohol consumption, inflammation and depression

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Abstract

Background and aims. Although, there has been a drop in age-specific coronary heart disease (CHD) incidence, and its prognosis has improved considerably in most parts of the industrialized world, CHD is still by far the leading cause of death in industrialized countries. The established, conventional risk factors, i.e. hypertension, hypercholesterolemia, smoking, diabetes mellitus, obesity, and physical inactivity, are only partly responsible for the development of CHD. Recently, many relatively novel risk and prognostic factors had been proposed. Heart rate variability (HRV), alcohol consumption, inflammation and depression are among the most important novel factors. In this thesis we investigated their interrelations and their relation to CHD. **Methods.** We used the corresponding data of three large population based studies, that of the Healthier Female Heart (HFH) Study, the Stockholm Female Coronary Risk (FemCorRisk) Study, and the Stockholm Heart Epidemiology Program (SHEEP). Cross-sectional relationships between the non-conventional risk factors were investigated in the HFH study (paper I-III). The HFH study included consecutive women patients who were hospitalized for acute myocardial infarction, and/or underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. We examined these patients in a stable phase, one year and five months after their index event. Ambulatory 24-hour ECG recordings were analyzed, and HRV was calculated. Self-reported consumption of individual alcoholic beverage types was assessed using a standardized questionnaire. Circulating levels of inflammatory markers were determined. Depression, vital exhaustion, and self-rated health were assessed by questionnaires. We examined the association between alcohol consumption and progression of coronary artery atherosclerosis (paper IV) using serial quantitative coronary angiography (QCA) in the FemCorRisk Study, which included middle-aged women patients who were hospitalized with acute myocardial infarction or unstable angina pectoris. We also assessed the long-term prognostic importance of HRV on mortality in these women (paper V), i.e. in a patient population, which was largely neglected in previous research. We examined if depression increases the risk for first myocardial infarction in the case-control SHEEP study. Depression was defined as history of hospitalization for the clinical diagnosis based on the data of the computerized Swedish hospital discharge registry (paper VI). **Results and Conclusions.** HRV. We found that wine intake was associated with increased HRV independently of potential confounding factors and intake of other beverages in women with CHD. In contrast, consumption of beer, spirits or the total amount of alcohol did not relate to any of the HRV parameters (paper I). Concentration of IL-6 showed an inverse relation to HRV even after adjustment for potential confounding factors (paper II). HRV parameters predicted all-cause and cardiovascular mortality in a 9-year follow-up even after controlling for established prognostic factors (paper V). Alcohol consumption. Our finding that wine intake is associated with HRV suggests that HRV may be an important linking factor between CHD and wine drinking (paper I). We also demonstrated that moderate alcohol consumption is inversely associated with progression of coronary atherosclerosis regardless of the beverage type (paper IV). Inflammation. The inverse association between HRV and IL-6 suggests that increased inflammatory activity might represent a new auxiliary mechanism linking autonomic dysfunction, as reflected by decreased HRV, to poor prognosis in CHD (paper II). Our results do not suggest that inflammation is a major mediator between depression and CHD (paper III, VI). However, self-rated health and vital exhaustion, constructs also referring to one's subjective well-being, showed an inverse relation to

circulating levels of inflammatory markers (paper III). Depression. In the SHEEP study we found that hospitalization for depression, especially if repeated, was a considerable risk factor for AMI, and was also associated with poor short-term prognosis after the coronary event. Socio-economic position, lifestyle factors, lipid profile, coagulation, inflammatory and other factors could only partly explain our findings (paper VI).

List of papers:

I. Janszky I, Ericson M, Blom M, Georgiades A, Magnusson JO, Alinagizadeh H, Ahnve S (2005). "Wine drinking is associated with increased heart rate variability in women with coronary heart disease." *Heart* 91(3): 314-8.

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II. Janszky I, Ericson M, Lekander M, Blom M, Buhlin K, Georgiades A, Ahnve S (2004). "Inflammatory markers and heart rate variability in women with coronary heart disease. " *J Intern Med* 256(5): 421-8.

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III. Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S (2005). "Self-rated health and vital exhaustion, but not depression is related to inflammation in women with coronary heart disease." *Brain, Behavior and Immunity*. [Accepted]

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IV. Janszky I, Mukamal KJ, Orth-Gomer K, Romelsjo A, Schenck-Gustafsson K, Svane B, Kirkeeide RL, Mittleman MA (2004). "Alcohol consumption and coronary atherosclerosis progression - the Stockholm Female Coronary Risk Angiographic Study. " *Atherosclerosis* 176(2): 311-9.

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V. Janszky I, Ericson M, Mittleman MA, Wamala S, Al-Khalili F, Schenck-Gustafsson K, Orth-Gomer K (2004). "Heart rate variability in long-term risk assessment in middle-aged women with coronary heart disease: The Stockholm Female Coronary Risk Study. " *J Intern Med* 255(1): 13-21.

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VI. Janszky I, Ahlbom A, Hallqvist J, Ahnve S (2005). "Severe depression is associated with an increased risk for myocardial

infarction, not explained by lifestyle, lipids, coagulation and inflammation - the SHEEP study." [Submitted]

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Significant associations between increased heart rate and metabolic risk factors, inflammation and residence in the village are found. Keywords. ESSE-RF study, heart rate, prevalence, associations, risk factors. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet*. 2008;372:817-21. doi: 10.1016/S0140-6736(08)61171-X. 12. Mareev V.Yu., Danielyan M.Yu, Belenkov Yu.N. Effect of therapy on prognosis and survival of patients with chronic heart failure. *Russkij Medicinskij Zhurnal*. 1999;2:9. (In Russ.) Conventional risk factors for coronary heart disease were not assessed consistently or adequately. Only three of the forty-eight papers gave consideration to the time course of depression during follow-up and prior to study entry. Potentially confounding variables such as anxiety, personality traits and other psychiatric disorders were not taken into consideration in the majority of papers. The poverty of information about depression apart from a baseline rating with considerable variation in rating methods precludes any firm conclusion about a dose-effect relationship that would support a causal role of depression in CHD. 4. DISCUSSION. A case study in depression and coronary heart disease. *BMC Medical Research Methodology*, 6, 4. doi:10.1186/1471-2288-6-4. There are exciting findings in the field of depression and coronary heart disease. Whether diagnosed or simply self-reported, depression continues to mark very high risk for a recurrent acute coronary syndrome or for death in patients with

coronary heart disease. Many intriguing mechanisms have been posited to be implicated in the association between depression and heart disease, and randomized controlled trials of depression treatment are beginning to delineate the types of depression management strategies that may benefit the many coronary heart disease patients with depression. Non-conventional risk and prognostic factors in coronary heart disease : Studies on heart rate variability, alcohol consumption, inflammation and depression. University dissertation from Stockholm : Karolinska Institutet, Department of Public Health Sciences. Recently, many relatively novel risk and prognostic factors had been proposed. Heart rate variability (HRV), alcohol consumption, inflammation and depression are among the most important novel factors. We examined if depression increases the risk for first myocardial infarction in the case-control SHEEP study. Depression was defined as history of hospitalization for the clinical diagnosis based on the data of the computerized Swedish hospital discharge registry (paper VI). coronary heart disease and cardiovascular risk factors (study of the ESSE-RF in the Kemerovo region). Complex problems of cardiovascular diseases 2017; 4: 21-6. To analyze the relation of alcohol consumption level with cardiovascular diseases and risk factors in the population of Kemerovskaya Oblast. Material and methods. The study was performed under the framework of multicenter epidemiological trial ESSE-RF in Kemerovskaya Oblast, with 1628 participants with the age 25-64 y. o. The data was analyzed concerning the prevalence, volume and type of alcohol beverages by the respondents, as the prevalence of a range of cardiovascular diseases and risk factors.