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Atherosclerosis newsletter

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Nutrition and lifestyle are important determinants of cardiovascular risk. Despite little or no changes in the genome, atherosclerotic cardiovascular event rates increase rapidly upon industrialisation and urbanisation of societies. Traditionally, these changes are explained by hypercaloric nutrition and lack of physical activity. Additional factors include environmental factors such as air pollution and traffic noise. These adverse effects generate cardiovascular risk factors directly and indirectly, for example by epigenetic regulation or by changes in the gut microbiota. Volumes 311 and 312 of *Atherosclerosis* contain several reviews and original articles addressing the importance of lifestyle and nutrition for the risk of atherosclerotic cardiovascular disease and its associated factors.

Should we target increased physical activity or less sedentary behavior in the battle against cardiovascular disease risk development?

Physical inactivity is a well-established risk factor for cardiovascular disease (CVD) incidence and mortality. In the last decade, there is also emerging evidence of the role of sedentary behaviors (sitting) as a risk factor for CVD. Therefore, there is increasing interest in understanding the independent and joint effects of physical activity and sedentary behavior on CVD risk. Higher levels of moderate-to-vigorous physical activity and less time spent in sedentary behavior are associated with a decreased risk of CVD. There is also preliminary evidence that higher levels of light-intensity physical activity are associated with lower all-cause mortality rates; however, the cardio-protective effects of light-intensity physical activity are yet to be determined. The results from several studies have demonstrated that the effect of sedentary behavior on CVD risk is more pronounced among individuals who are physically inactive, compared to those who are more active. Further, high levels (60–75 min per day) of moderate-to-vigorous physical activity appear to eliminate the increased risk of CVD associated with excessive sedentary behavior. Replacing sedentary behavior with any intensity of physical activity will produce health benefits; however, the greatest benefits occur when replacing sedentary behavior with moderate-to-vigorous intensity physical activity. Here, Katzmarzyk et al. review the joint associations of physical activity and sedentary behavior with CVD, in an attempt to optimize behavioral-based strategies designed to reduce CVD risk.

The position of functional foods and supplements with a serum LDL-C lowering effect in the spectrum ranging from universal to care-related CVD risk management

A wealth of data demonstrates a causal link between serum low-density lipoprotein cholesterol (LDL-C) concentrations and cardiovascular disease (CVD). Any decrease in serum LDL-C concentrations is associated with a decreased CVD risk, and this benefit is similar to a comparable LDL-C reduction after drug treatment and dietary intervention. Moreover, life-long reduction in serum LDL-C levels has a large impact on CVD risk, and a long-term dietary enrichment with functional foods or supplements with a proven LDL lowering efficacy is a feasible and efficient approach to decrease future CVD risk.

Functional foods with an LDL-C lowering effect can improve health and/or reduce the risk of disease. However, it has not been mentioned specifically whether this concerns mainly universal prevention or whether it can also be applied to the hierarchy towards care related prevention. In this review, Baumgartner et al. describe the effects of a list of interesting functional food ingredients with proven benefit in LDL-C lowering. Particular attention is paid to the emerging evidence that the addition of these functional ingredients and supplements is advisable as universal and selective prevention in the general population. Moreover, functional ingredients and supplements are helpful in care related prevention, i.e. in patients with elevated LDL-C concentrations who are statin-intolerant or are not able to achieve their LDL-C target levels. The authors also highlight practical aspects regarding the use of functional foods with an LDL-C lowering effect, such as the increasing importance of shared decision making of medical doctors and dieticians with patients to ensure proper empowerment and better adherence to dietary approaches. Costs issues related to the use of these functional foods are also addressed.

How strong is the evidence that gut microbiota composition can be influenced by lifestyle interventions in a cardio-protective way?

Alterations in composition and function of the gut microbiota have been demonstrated in diseases involving the cardiovascular system, particularly coronary heart disease and atherosclerosis. The data are still limited but the typical altered genera include *Roseburia* and *Faecalibacterium*. Plausible mechanisms by which microbiota may mediate cardio-protective effects have been postulated, including the production of metabolites like trimethylamine (TMA), as well as immunomodulatory functions. This raises the question of whether it is possible to modify the gut microbiota by lifestyle interventions and thereby improve cardiovascular health. Nevertheless, lifestyle intervention studies that have involved modifications of dietary intake and/or physical activity, and investigations of changes in the gut microbiota and subsequent modifications of the cardioprotective markers, are still scarce, and the results have been inconclusive. Current evidence points to benefits of consuming high-fibre foods, nuts and an overall

healthy dietary pattern to achieve beneficial effects on both gut microbiota and serum cardiovascular markers, primarily lipids. The relationship between physical exercise and gut microbiota is probably complex and may be dependent on the intensity of exercise. Gerdes et al. review the available evidence on lifestyle, specifically diet, physical activity and smoking as modifiers of the gut microbiota, and subsequently as modifiers of serum cardiovascular health markers. They attempt to elucidate the plausible mechanisms and further critically appraise the caveats and gaps in the research.

Omega-3 fatty acids and risk of cardiovascular disease in Inuit: First prospective cohort study

"Kalaalimernit" is the traditional food of the Greenlandic Inuit. The diet is based on local foods, mainly fish and marine mammals, with a high content of very long-chain (VLC) n-3 polyunsaturated fatty acids (PUFAs) (carbon chain length ≥20). No prospective study has ever assessed whether marine n-3 PUFAs protect Inuit against cardiovascular disease, as claimed. This is highly relevant, if one considers that cardiovascular disease (CVD) incidence rates are rising concurrently with a westernization of their diet. Senftleber et al. aimed to assess the association between blood cell membrane phospholipid content of eicosapentaenoic acid and docosahexaenoic acid (EPA + DHA) on CVD risk in Inuit.

Data from a cohort of adult Greenlanders with follow-up in national registers were included in the analysis. The main outcome was fatal and non-fatal CVD incidence among participants without previous CVD. The continuous effect of EPA + DHA was calculated as incidence rate ratios (IRRs) using Poisson regression with age as time scale, adjusting for age, sex, genetic admixture, lifestyle and dietary risk factors.

Out of 3095 eligible participants, 2924 were included. During a median follow-up of 9.7 years, 216 had their first CVD event. No association between EPA + DHA and CVD risk was seen. No association was seen with risk of ischemic heart disease (IHD) and stroke as separate outcomes or for intake of EPA and DHA.

These results suggest that there is no association between a very large increment in long-chain n-3 polyunsaturated fatty acids and cardiovascular risk. A larger sample size and/or longer follow-up is needed to detect smaller effects and associations with IHD and/or stroke.

Early life predictors of development of blood pressure from childhood to adulthood: Evidence from a 30-year longitudinal birth cohort study

Raised blood pressure or hypertension in early life is a marker for early cardiovascular disease risk, and a risk factor for diabetes and target-organ damage. The early life predictors of changes in blood pressure of offspring between childhood and young adulthood have not been well defined yet. Das et al. aimed to determine the life course association of offspring's blood pressure with prenatal and early

infancy lifestyle, and other factors, taking advantage of a large community-based, longitudinal study of a birth cohort in Australia – the Mater-University of Queensland Study of Pregnancy (MUSP).

Systolic and diastolic blood pressure (SBP, DBP) was measured for 3793, 3782, 2628 and 1780 offspring of the Australian longitudinal cohort study at 5, 14, 21 and 30 years of their age, respectively. Individual PP and mean arterial pressure (MAP) was equated, and generalized estimating equations with time (age) and predictor interaction modelling were performed.

Blood pressures of the offspring increased significantly between 5 and 30 years. Early life factors such as pre-pregnancy overweight/obesity, and hypertensive disorder in pregnancy were significantly positively associated, and duration of gestation and pre-pregnancy thinness of the mothers negatively associated with this life course increase in the offspring's blood pressure. Rapid increase in body weight from birth to 5 years had a strong association with increasing blood pressure components throughout their life course.

Several maternal pre-pregnancy and pregnancy factors along with the early life growth characteristics of the offspring are important predictors of increase in blood pressure from their childhood to adulthood. Thus, primary prevention of hypertension may need to start from early life, as early as from pregnancy.

AHRR hypomethylation as an epigenetic marker of smoking history predicts risk of myocardial infarction in former smokers

Smoking is a major cause of cardiovascular disease (CVD), and it is estimated that one out of four deaths from CVD is attributed to smoking. The epigenetic trait DNA methylation occurs when a methyl group is added to the DNA, often resulting in modification of the gene function. Lifestyle factors such as smoking and alcohol consumption can affect DNA methylation, and these methylation changes can persist for many months/years after changes of the original stimuli. An epigenome-wide association study comparing active, former, and never smokers identified a CpG site (cg05575921) in the aryl hydrocarbon receptor repressor (*AHRR*), which has the highest level of DNA methylation change in response to tobacco smoking. *AHRR* hypomethylation at cg05575921 is associated with active and former smoking status at baseline, and cumulative amount of tobacco smoked. Langsted et al. tested the hypothesis that *AHRR* cg05575921 hypomethylation, as an epigenetic marker of smoking history, predicts the risk of myocardial infarction in former smokers.

They included in the study 10,510 individuals with methylation extent measurements and information on smoking status from the Copenhagen City Heart Study (CCHS), a prospective, cohort study of the general population. The endpoint myocardial infarction was retrieved from the national Danish Patient Registry and the national Danish Causes of Death Registry.

For individuals in the 1st quartile of *AHRR* cg05575921 methylation, 99% were ever smokers at baseline (active and former smokers combined) compared to 42% in the 4th quartile. For former smokers, the cumulative incidence of myocardial infarction was higher in the lowest methylation degree compared to the highest one. Compared to never smokers, the multivariable adjusted subhazard ratio for myocardial infarction was 1.09 for former smokers with the highest methylation level, 1.38 for active smokers with the highest methylation level, 1.39 for former smokers with the lowest methylation level, and 1.61 for active smokers with the lowest methylation level.

AHRR cg05575921 hypomethylation as an epigenetic marker of smoking history predicts risk of myocardial infarction, particularly in former smokers. *AHRR* hypomethylation, regardless of smoking status, is associated with increased risk of myocardial infarction.