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Atherosclerosis newsletter

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"Call for Original Research Papers on Lp(a)"

With the advent of specific Lp(a)-lowering therapies, the Lp(a) field is experiencing a sense of excitement and optimism. Therefore, *Atherosclerosis* as the journal of the European Atherosclerosis Society (EAS) is **calling for the submission of Original Research Papers** on various topics in Lp(a), which contribute **novel findings** to the field. These manuscripts will undergo a regular review process and in case of acceptance will go online within the usual time of processing.

The submitted Original Research Articles will be handled by Marlys L. Koschinsky as Guest Editor and Florian Kronenberg as Co-Editor of *Atherosclerosis*. They will decide on the peer reviewers of the submitted articles. If a manuscript is accepted for publication, these Original Research Articles will appear printed together in a combined issue of the journal containing roughly a dozen in-depth review articles on Lp(a), which aims to provide the most comprehensive, insightful, and current overview of the Lp(a) field. The topics and authors for these review articles have already been decided and secured for this project. The publication is planned for the first quarter of 2022 and is expected to receive a high visibility.

For preparation of the Original Research manuscripts please see the **"Guide for authors"** at https://www.elsevier.com/journals/atherosclerosis/0021-9150/guide-for-authors.

The possibility for submission of the first draft of Original Research Papers for the mentioned issue of *Atherosclerosis* will end on October 31, 2021. This call is only open for Original Research Articles and no review articles are allowed. Please select "Special issue: Lp(a)" as article type at submission.

To submit your paper go to: Editorial Manager®

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The effect of treatable risk factors on the onset of atherosclerotic cardiovascular diseases (ASCVD) is strongly modulated by non-treatable factors. Volumes 328, 329 and 330 contain several papers that investigate the impact of sex, paternal or maternal inheritance of mutations, psychosocial factors and inflammation on the ASCVD risk association of smoking, hyperlipidemia, hypertension, or hyperuricemia

Smoking and sex differences in first manifestation of cardiovascular disease

In 2019, tobacco accounted for 8.71 million deaths. Of tobacco attributable deaths, 36.7% were due to cardiovascular (CV) disease. In this context, the effects of low intensity smoking are still largely understudied. Vasiljevic et al. investigated the relation among sex, age, cigarette smoking and ST segment elevation myocardial infarction (STEMI) as initial manifestation of CV disease.

Data of 50,713 acute coronary syndrome patients with no prior manifestation of CV disease from the ISACS-Archives registry were analysed and the rates of STEMI in current smokers *versus* non-smokers were compared.

In the young middle age group, there was evidence of a more harmful effect in women compared with men. This association persisted even in women who smoked 1 to 10 packs per year. In the older group, rates of STEMI were similar for women and men. STEMI was associated with a twofold higher 30-day mortality rate in young middle age women compared with men of the same age.

The results suggest that low intensity smoking provides inadequate protection in young-middle age women as they still have a substantially higher rate of STEMI and related mortality compared with men even smoking less than 10 packs per year.

Detailed association between serum uric acid levels and the incidence of chronic kidney disease stratified by sex in middle-aged adults

Chronic kidney disease (CKD) is a global health burden. CKD incidence, and disability and death due to CKD have been increasing. Previous studies have shown a J- or U-shaped association between serum uric acid (SUA) and cardiovascular mortality. With regard to the association of SUA with the kidney, high SUA levels may serve as an independent risk factor for CKD. Although high SUA levels may be involved in CKD incidence in middle-aged individuals, there is little evidence regarding the association between SUA and CKD incidence in this population. Nakayama et al. assessed the risk of CKD incidence in a refined SUA category in middle-aged adults stratified by sex.

Data from 138,511 participants <65 years old without CKD at baseline, acquired from the Japan Medical Data Center (JMDC) database, were analyzed. The Cox model was used to assess the adjusted hazard ratio (HR).

During the mean follow-up of 4.68 years, 12,589 participants developed CKD. The fully adjusted HRs for CKD incidence in men with SUA <4.0, 10.0–10.9 and ≥ 11.0 mg/dL compared to men with SUA 4.0–4.9 mg/dL were 1.13, 1.98, and 3.74, respectively. The fully adjusted HRs for CKD incidence in women with SUA <4.0, 8.0–8.9, and ≥9.0 mg/dL compared to women with SUA 4.0–4.9 mg/dL were 1.08, 2.39, and 3.20, respectively.

Both high and low SUA levels were identified as risk factors for CKD incidence in middle-aged men and women. The association of SUA levels with the increase in the risk of CKD incidence differed by sex, and the range of SUA levels associated with an increase in the risk of CKD incidence varied by sex.

Interaction between testosterone and obesity on hypertension: A population-based cross-sectional study

Hypertension is a leading risk factor for cardiovascular diseases and premature deaths, which is also the major cause of deaths in China. It has numerous risk factors, including genetic and environmental factors. In addition to obesity, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus, accumulated evidence suggests that low testosterone concentrations may be an independent risk factor for hypertension in males. Wei et al. aimed to evaluate the effects of serum testosterone, obesity and their interaction on blood pressure (BP) parameters and hypertension among Chinese rural adults.

A total of 6199 adults were recruited from the Henan Rural Cohort Study. Serum testosterone was measured by liquid chromatography-tandem mass spectrometry. Logistic regression and linear regression were used to evaluate the association between testosterone, hypertension and BP parameters (including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and mean arterial pressure (MAP)). A generalized linear model was performed to identify the interactive effects of testosterone and obesity on hypertension.

High levels of serum testosterone were associated with a lower prevalence of hypertension in males. After stratification by obesity, observed associations were only found in non-obese males. Each one-unit increase in ln-testosterone was associated with a 1.23 mmHg decrease in SBP, 0.97 mmHg decrease in DBP, and 1.05 mmHg decrease in MAP among males. Moreover, interactive effects between testosterone and obesity on hypertension and BP parameters were found, indicating that protective effects of serum testosterone on hypertension and BP parameters were counteracted and accompanied by increased values of obesity-related indicators in males, and additional testosterone

increased BP parameters and prevalence of hypertension at high levels of waist-to-hip ratio and waist-to-height ratio in females.

Elevated levels of serum testosterone were associated with decreased BP parameters and prevalent hypertension in males, and obesity modifying effects of serum testosterone on BP parameters and hypertension.

Paternal inheritance predicts earlier cardiovascular event onset in patients with familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic disease, with an autosomal codominant inheritance, predisposing to premature atherosclerotic cardiovascular disease (ASCVD). Paternal or maternal inheritance of the FH-causing mutation may affect the FH phenotype in offspring, but the effect of the genetic transmission on cardiovascular disease risk remains to be established. Paquette et al. compared the incidence of cardiovascular events between patients with maternal *vs*. paternal inheritance of familial hypercholesterolemia.

The authors prospectively studied 725 genetically-confirmed FH patients, including 268 with maternal inheritance and 321 with paternal inheritance of the mutation. ASCVD was defined as angina, myocardial infarction, coronary angioplasty, coronary bypass surgery, claudication, peripheral angioplasty, peripheral arterial surgery, transient ischemic attack, stroke, carotid endarterectomy and CV death. Cox-proportional hazard models and Kaplan-Meier analysis were used to compare the two groups.

Before 50 years of age, paternal inheritance of FH was associated with a 1.5-fold increased risk for ASCVD, as compared to maternal inheritance. This association remained significant after adjusting for confounding factors. The age of first ASCVD event was also significantly lower in the paternal inheritance group than in the maternal inheritance group (46 years) suggesting that paternal inheritance of the FH-causing mutation is associated with an earlier cardiovascular event onset compared to maternal inheritance. The mechanisms behind these findings remain to be established.

Psychosocial factors and subsequent risk of hospitalizations with peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study

Psychosocial factors are associated with increased risk of cardiovascular disease (CVD). There are plausible mechanisms by which psychosocial factors can increase the risk of CVD (e.g. autonomic nervous system dysfunction, hypothalamic-pituitary-adrenal axis dysregulation, inflammation). Behavioral mechanisms such as smoking, high-fat diet, poor adherence to medical treatment, and lack of physical exercise are likely to play a role as well. Despite a large body of evidence linking psychosocial factors with CVD, data regarding the association of psychosocial factors with the risk of peripheral

artery disease (PAD) are sparse. Honda et al. aimed to compare associations of psychosocial factors with the risk of PAD and two other major atherosclerotic CVD: coronary heart disease (CHD) and ischemic stroke, in the Atherosclerosis Risk in Communities (ARIC) study.

In 11,104 participants without a clinical history of PAD and CHD/stroke at baseline (1990–1992), four psychosocial domains were evaluated: depressive/fatigue symptoms by the Maastricht Questionnaire, social support by the Interpersonal Evaluation List, social networks by the Lubben Scale, and trait anger by the Spielberger Scale. PAD was defined as hospitalizations with diagnosis or related procedures. CHD included adjudicated coronary heart disease and stroke included ischemic stroke.

The authors observed 397 PAD and 1940 CHD/stroke events during a median follow-up of 23.1 years. Higher depressive/fatigue symptoms and less social support were significantly associated with incident PAD. When these factors were simultaneously modeled, only depressive/fatigue symptoms remained significant. Incident CHD/stroke was not associated with either depressive/fatigue symptoms or social support. Social networks and trait anger were not independently associated with PAD or CHD/stroke.

These results support the importance of depressive/fatigue symptoms in vascular health and suggest the need of including PAD when studying the impact of psychosocial factors on CVD.

Brain-heart connections in stress and cardiovascular disease: Implications for the cardiac patient

The influence of psychological stress on the physiology of the cardiovascular system, and on the etiology and outcomes of cardiovascular disease (CVD) has been the object of intense investigation. As a whole, current knowledge points to a “brain-heart axis” that is especially important in individuals with pre-existing CVD. Acute psychological stress provocation in the laboratory has been useful to clarify the effects of psychological stress on cardiovascular physiology, immune function, vascular reactivity, myocardial ischemia, neurobiology and cardiovascular outcomes. An emerging paradigm is that dynamic perturbations of physiological and molecular pathways during stress or negative emotions are important in influencing cardiovascular outcomes, and that some patient subgroups, such as women, patients with an early-onset myocardial infarction, and patients with adverse psychosocial exposures, may be at especially high risk for these effects. Vaccarino et al. summarize recent knowledge on mind-body connections in CVD among cardiac patients and highlight important pathways of risk, which could become the object of future intervention efforts. As a whole, this research suggests that an integrated study of mind and body is necessary to fully understand the determinants and consequences of CVD.

Association of triglyceride-rich lipoprotein-cholesterol with recurrent cardiovascular events in statin-treated patients according to different inflammatory status

Triglyceride-rich lipoprotein-cholesterol (TRL-C) is the cholesterol content of triglyceride-rich lipoprotein (TRLs), also referred to as remnant cholesterol. There is considerable evidence suggesting that elevated plasma TRL-C levels are causally related to residual cardiovascular risk beyond LDL-C, and therefore a potential therapeutic target. However, the prognostic value of TRL-C is still not clear yet, since some other studies presented negative or contradictory results. Inflammation also plays an important role in the pathogenesis and prognosis of atherosclerotic cardiovascular disease. Recent studies suggest that elevated TRL-C levels are causally related to low-grade inflammation. However, whether inflammation can affect TRL-C-associated cardiovascular risk is unknown. Liu et al. examined the association between TRL-C and risk of recurrent cardiovascular events (RCVEs), and whether this relationship is modulated by systemic inflammation in statin-treated patients with coronary artery disease (CAD) and nearly normal triglyceride.

6723 CAD patients were consecutively enrolled, following a first CVE with triglyceride <2.3 mmol/L. Baseline lipid profile and high-sensitivity C-reactive protein (hsCRP) levels were determined. All patients were searched for RCVEs. The risk of RCVEs was assessed across quartiles (Q) of baseline TRL-C and further stratified by the median of hsCRP.

Over a mean follow-up of 58.91 ± 17.79 months, 538 RCVEs were recorded. After adjustment for potential confounders, Q4 of TRL-C was significantly associated with the risk of RCVEs, which remained unchanged after hsCRP stratification. When subjects were grouped according to both TRL-C and hsCRP levels, patients with Q4 of TRL-C and hsCRP had the highest increase of the risk of RCVEs compared with the reference group. Furthermore, adding TRL-C to the original predicting model led to a slight but significant improvement.

This analysis shows that elevated TRL-C is associated with an increased RCVEs risk in statin-treated patients with CAD independent of systemic inflammation, suggesting that it might be a useful marker for risk stratification and a treatment target in this patient population.