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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. All

To submit your paper go to: Editorial Manager®

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Several articles of Volume 328 of *Atherosclerosis* address the role of nature and nurture of risk factors and manifestation of atherosclerotic cardiovascular diseases.

Does variation in serum LDL-cholesterol response to dietary fatty acids help explain the controversy over fat quality and cardiovascular disease risk?

Controversy over fat quality and cardiovascular disease risk stems from a series of meta-analyses of prospective cohort and randomised intervention trials, which found little evidence for a significant relationship between the intake of saturated fat and disease endpoints. Possible explanations for these null findings include difficulties inherent in estimating true food intake, the confounding effects of macronutrient replacement and food composition, and marked inter-individual variation in the response of serum low-density lipoprotein (LDL)-cholesterol. In this review, Griffin et al. provide evidence to suggest that variation in LDL-responsiveness may harbour significant potential to confound the relationship between saturated fat and atherosclerotic cardiovascular disease risk, undermining the effectiveness of the dietary guideline to replace saturated fat with unsaturated fat. They conclude that the identification and application of a simple biomarker of this phenomenon would make it possible to tailor dietary guidelines to LDL responsive individuals, who gain a greater benefit to their cardiovascular health.

Carbohydrates: Separating fact from fiction

The role of carbohydrates in a healthy diet has been controversial. In this article, Blaak et al. reviewed the latest epidemiological and intervention studies on the effects of fiber, whole grain, and refined carbohydrates on weight, diabetes, lipids and major adverse cardiac events.

High intake of dietary fiber and whole grains is associated with positive effects on metabolic health while diet high in sugar and refined carbohydrates has negative effects on cardiometabolic health. Consistent evidence indicates that low fat and low carbohydrate diets at comparable energy levels have similar effects on body weight. Large epidemiological studies show an increase in mortality when carbohydrates are substituted for animal-derived fat or proteins while carbohydrates exchange with plant-based proteins leads to mortality reduction.

Given that most people worldwide currently consume less than 20 g of dietary fiber per day, with persistently high consumption of refined carbohydrates, current evidence emphasizes the need for additional measures to increase the amount and diversity of fiber intake to improve cardiometabolic and cardiovascular outcomes.

Is protein the forgotten ingredient: Effects of higher compared to lower protein diets on cardiometabolic risk factors. A systematic review and meta-analysis of randomised controlled trials

Dietary proteins are important sources of energy and essential amino acids, necessary for various processes, including tissue growth and maintenance. The effects of dietary protein on human health are determined by several factors, including quantity, quality (animal protein/plant protein) and source, animal (red and white meat, fish, eggs and dairy) or plant-based (nuts, legumes, grains).
Higher protein (HP) diets may lead to lower cardiometabolic risk, compared to lower protein (LP) diets. Vogtschmidt et al. aim to investigate the effects of HP *versus* LP diets on cardiometabolic risk factors in adults, using the current evidence from randomised controlled trials (RCTs).

Systematic searches were conducted in electronic databases up to November 2020. Random effects meta-analyses were conducted to pool the standardised mean differences and 95% confidence intervals. The main outcomes were weight loss, body mass index, waist circumference, fat mass, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein- and low-density lipoprotein-cholesterol, triacylglycerol, fasting glucose and insulin, and glycated haemoglobin.

Fifty-seven articles reporting on 54 RCTs were included, involving 4344 participants, with a mean study duration of 18 weeks. The results show that compared to LP diets, HP diets led to more weight loss, greater reductions in fat mass, systolic BP, total cholesterol, triacylglycerol and insulin. No significant differences were observed for the other outcomes.

APOE gene variants in primary dyslipidemia

Apolipoprotein E (apoE) is a major apolipoprotein involved in lipoprotein metabolism. It is a polymorphic protein and different isoforms are associated with variations in lipid and lipoprotein levels and thus cardiovascular risk. The isoform apoE4 is associated with an increase in low-density lipoprotein (LDL)-cholesterol levels and a higher cardiovascular risk compared to apoE3, while apoE2 is associated with a mild decrease in LDL-cholesterol levels. In the presence of other risk factors, apoE2 homozygotes could develop type III hyperlipoproteinemia (familial dysbetalipoproteinemia or FD), an atherogenic disorder characterized by an accumulation of remnants of triglyceride-rich lipoproteins. Several rare *APOE* gene variants were reported in different types of dyslipidemias including FD, familial combined hyperlipidemia (FCH), lipoprotein glomerulopathy and *bona fide* autosomal dominant hypercholesterolemia (ADH). ADH is characterized by elevated LDL-cholesterol levels leading to coronary heart disease, and due to molecular alterations in three main genes: *LDLR, APOB* and *PCSK9*. The identification of the *APOE*-p.Leu167del variant as the causative molecular element in two different ADH families, paved the way to consider *APOE* as a candidate gene for ADH. Due to non-Mendelian interacting factors, common genetic and environmental factors and perhaps epigenetics, clinical presentation of lipid disorders associated with *APOE* variants often strongly overlap. More studies are

needed to determine the spectrum of *APOE* implication in each of the diseases, notably ADH, to improve clinical and genetic diagnosis, prognosis and patient management. Khalil et al. reviewed these *APOE* variants and the molecular and clinical overlaps between dyslipidemias.

Apolipoprotein E genotype, lifestyle and coronary artery disease: Gene-environment interaction analyses in the UK Biobank population

Genetic variation in the *APOE* gene has been widely recognized to increase the risk of coronary artery disease (CAD), which has also been confirmed by genome-wide association studies. Preliminary evidence suggests that antioxidative lifestyle factors have an influence on CAD risk in the presence of the *APOE* genotype. Bos et al. assessed the effect modification of physical activity, oily fish and polyunsaturated fatty acid (PUFA) intake on risk of incident CAD in *APOE* genotype carriers.

The study comprised 345,659 white European participants from UK Biobank without a history of CAD. Information regarding physical activity, oily fish intake and PUFA intake was collected through questionnaires, and information on incident CAD through linkage with hospital admission records. Analyses were performed using Cox proportional hazard models adjusted for age and sex.

The results show that higher physical activity level and oily fish intake were associated with a lower incidence of CAD. However, these associations were similar across the different *APOE* genotypes. Notably, higher PUFA intake was associated with a lower CAD risk in *APOE ε4* genotype carriers, and not in *APOE ε3/ε3* genotype carriers, but without statistical evidence for effect modification.

While higher physical activity and high fish and PUFA intake were associated with a lower risk of incident CAD, no evidence for interaction of these lifestyle factors with *APOE* genotype was observed in UK Biobank participants. Interventions intended to reduce cardiovascular risk might therefore be similarly effective across the *APOE* genotype carriers.

Triglyceride-lowering *LPL* alleles combined with LDL-C-lowering alleles are associated with an additively improved lipoprotein profile

Mendelian randomization studies have shown that triglyceride (TG)-lowering lipoprotein lipase (LPL) alleles and low-density lipoprotein-cholesterol (LDL-C)-lowering alleles have independent beneficial associations on cardiovascular disease (CVD) risk. Ibi et al. aimed to provide further insight into this observation by applying Mendelian randomization analyses of genetically-influenced TG and LDL-C levels on plasma metabolomic profiles.

Over 100 lipoprotein metabolomic measures of the Netherlands Epidemiology of Obesity (NEO) study and Oxford Biobank (OBB) were quantified by nuclear magnetic resonance (NMR) spectroscopy. Weighted genetic scores for TG via five *LPL* alleles and LDL-C via 19 alleles were

calculated and dichotomized by the median, resulting in four genotype combinations of high/low TG and high/low LDL-C. Linear regression analyses were performed using a two × two design with the group with genetically-influenced high TG and LDL-C as a reference.

Compared to the individual groups with genetically-influenced lower TG or lower LDL-C only, the group with combined genetically-influenced lower TG and LDL-C showed an overall independent and additive pattern of changes in metabolomic measures. Over 100 measures were different (compared to the reference, with effect sizes and directionality being similar in NEO and OBB. Levels of all very-low density lipoprotein (VLDL) and LDL sub-particles were lower.

Our findings provide evidence that TG-lowering on top of LDL-C-lowering has additive beneficial effects on the lipoprotein profile compared to TG-lowering or LDL-C-lowering only, which is in accordance with reported additive genetic effects on CVD risk reduction.

Perinatal exposure to maternal smoking and adulthood smoking behaviors in predicting cardiovascular diseases: A prospective cohort study

Intrauterine adverse exposure may cause permanent developmental adaptations in the structure and function of the cardiovascular system, and subsequently increase the susceptibility to a variety of cardiometabolic diseases later in life. Growing evidence suggests that such perinatal risk factors may affect disease risk in concert with the adulthood risk factors; however, studies on their interactions on disease risk are sparse. Little is known about the associations between perinatal exposure to maternal smoking and cardiovascular disease (CVD) incidence in offspring, and whether such associations are modified by adulthood and genetically determined smoking behaviors. Song et al. performed prospective analyses on the association between perinatal exposure to maternal smoking and incident CVD, and assessed the interactions of perinatal maternal smoking with adulthood and genetically determined smoking behaviors on both multiplicative and additive scales, among participants from the UK Biobank.

A total of 414,588 participants without CVD at baseline were included between 2006 and 2010 and followed up through 2018. Cox-proportional hazard models were used to examine the association of perinatal maternal smoking with CVD, and both multiplicative and additive interaction analyses were performed to investigate the modification effects of smoking behaviors.

During a median follow-up of 8.93 years, 10,860 incident CVD events were observed, including 7006 myocardial infarction (MI) and 4147 stroke. Perinatal exposure to maternal smoking was associated with increased risks of CVD, MI and stroke. In addition, significant interactions were observed between perinatal exposure to maternal smoking and adulthood exposure to own smoking on CVD and MI on both the multiplicative and additive scales. The proportions due to additive interaction between perinatal and adulthood exposure to smoking were 14% for CVD and 16% for MI.

Perinatal exposure to maternal smoking also showed an interaction with genetically determined smoking on MI, but no interactions were found on total CVD and stroke.

These results indicate that perinatal exposure to maternal smoking is associated with increased risks of CVD events, and such relations are modified by adulthood smoking behaviors. Simultaneous avoidance of both perinatal and adulthood exposure to smoking may further prevent CVD.