of 1.21(1.08-1.35) for all-cause dementia, 1.31(1.11-1.54) for non-Alzheimer's dementia, 1.13(0.98-1.31) for Alzheimer's disease, 1.19(1.02-1.39) for all-cause AMD, 1.10(0.90-1.36) for dry AMD, 1.20(1.00-1.45) for wet AMD, and 1.06 (0.98-1.14) for IHD.
**Conclusions:** Genetically high HDL cholesterol due to variation in ABCA1 was associated with higher risk of all-cause dementia, non-Alzheimer's dementia, and age-related macular degeneration, but not with Alzheimer's disease or ischemic heart disease.

## S030 / #698, SAAG 05 - TALES OF THE MYSTERIOUS HDL 05-30-2021 7:00 AM - 7:00 PM.
## HDL COMPARTMENTALISATION REGULATES PCSK9 ACTIVITY

S.A. Burnap [1], K. Sattler [2], R. Pechlaner [3], K. Theofilatos [1], K. Takov [1], G. Heusch [2], S. Tsimikas [4], C. Fernández-Hernando [5], S.E. Berry [6], W. Hall [6], M. Notdurfter [7], G. Rungger [3], J. Willeit [3], S. Kiechl [3], B. Levkau [8], M. Mayr [1]. [1] *King's College London, Cardiovascular Division, London, United Kingdom;* [2] *University Hospital Essen, Institute For Pathophysiology, Essen, Germany;* [3] *Medical University of Innsbruck, Department Of Neurology, Innsbruck, Austria;* [4] *University of California San Diego, Cardiovascular Institute, La Jolla, United States of America;* [5] *Yale University School of Medicine, Vascular Biology And Therapeutics Program, New Haven, United States of America;* [6] *King's College London, Department Of Nutritional Sciences, London, United Kingdom;* [7] *Medical University of Innsbruck, Department Of Internal Medicine, Innsbruck, Austria;* [8] *Heinrich-Heine-University, Institute For Molecular Medicine Iii, Düsseldorf, Germany*

**Background and Aims:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) circulates in a free and lipoprotein-bound form in plasma. This study sought to interrogate the novel relationship between PCSK9 and high-density lipoprotein (HDL).

**Methods:** Nuclear magnetic resonance (NMR) lipoprotein profiling, proteomics and lipidomics were combined to study the associations of HDL and PCSK9 in the setting of cardiovascular disease and postprandial lipaemia.
**Results:** Quantitative proteomics in isolated HDL of patients with coronary artery disease (n=172) returned PCSK9 as a core member of the HDL proteome. Combined interrogation of the HDL proteome and lipidome revealed a distinct cluster of PCSK9, phospholipid transfer protein, clusterin and apolipoprotein-E within the HDL proteome, positively correlating with sphingomyelin. Combining lipoprotein profiles by NMR, targeted proteomic measurements of apolipoproteins and PCSK9 levels in the community-based Bruneck study (n=656) revealed a positive association of plasma PCSK9 with small HDL, alongside a highly significant positive correlation between plasma levels of PCSK9 and apolipoprotein-C3, an inhibitor of lipoprotein lipase. Thus, PCSK9-HDL compartmentalisation was determined during the postprandial response in two dietary studies (n=20 participants each, 8 times points). Peak triglyceride levels coincided with an attenuation of the PCSK9-HDL association, a loss of apolipoprotein-C3 from HDL and lower levels of small HDL as measured by NMR. Mechanistically, HDL facilitated PCSK9-mediated low-density lipoprotein receptor degradation by modulation of PCSK9 internalisation and multimerisation.
**Conclusions:** The combination of multiple -omic technologies across four human cohorts revealed postprandial lipaemia as a key driver of PCSK9 and apolipoprotein-C3 release from HDL.

## S031 / #164, SAAG 05 - TALES OF THE MYSTERIOUS HDL 05-30-2021 7:00 AM - 7:00 PM.
## CER-001 AMELIORATES LIPID PROFILE AND KIDNEY DISEASE IN A MOUSE MODEL OF FAMILIAL LCAT DEFICIENCY

A. Ossoli [1], A. Strazzella [1], D. Rottoli [2], C. Zanchi [2], M. Locatelli [2], C. Zoja [2], S. Simonelli [1], F. Veglia [3], R. Barbaras [4], C. Tupin [4], J.-L. Dasseux [4], L. Calabresi [1]. [1] *University of Milano, Pharmacological And Biomolecular Sciences, Milano, Italy;* [2] *Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Centro Anna Maria Astori, Bergamo, Italy;* [3] *Centro Cardiologico Monzino, Centro Cardiologico Monzino, Milano, Italy;* [4] *Abionyx Pharma, Toulouse, France*

**Background and Aims:** CER-001 is an HDL mimetic that has been tested in different pathological conditions, but never with LCAT deficiency. This study was designed to investigate whether the absence of LCAT affects the catabolic fate of CER-001, and to evaluate the effects of CER-001 on kidney disease associated with LCAT deficiency.

**Methods:** Lcat$^{-/-}$and wild-type mice received CER-001 (2.5, 5, 10 mg/kg) intravenously for 2 weeks. The plasma lipid/ lipoprotein profile and HDL subclasses were analyzed. In a second set of experiments, Lcat$^{-/-}$ mice were injected with LpX to induce renal disease and treated with CER-001 and then the plasma lipid profile, lipid accumulation in the kidney, albuminuria and glomerular podocyte markers were evaluated.
**Results:** In Lcat$^{-/-}$ mice a decrease in total cholesterol and triglycerides, and an increase in HDL-c was observed after CER-001 treatment. While in wild-type mice CER-001 entered the classical HDL remodeling pathway, in the absence of LCAT it disappeared from the plasma shortly after injection and ended up in the kidney. In a mouse model of renal disease in LCAT deficiency, treatment with CER-001 at 10 mg/kg for one month had beneficial effects not only on the lipid profile, but also on renal disease, by limiting albuminuria and podocyte dysfunction.
**Conclusions:** Treatment with CER-001 ameliorates the dyslipidemia typically associated with LCAT deficiency and more importantly limits renal damage in a mouse model of renal disease in LCAT deficiency. The present results provide a rationale for using CER-001 in FLD patients.

## S032 / #669, SAAG 06 - REACHING TO THE STARS WITH LIPIDOMICS, METABOLOMICS AND TRANSCRIPTOMICS 05-30-2021 7:00 AM - 7:00 PM.
## PER PARTICLE TRIGLYCERIDE-RICH LIPOPROTEINS IMPLY HIGHER MYOCARDIAL INFARCTION RISK THAN LOW-DENSITY LIPOPROTEINS: COPENHAGEN GENERAL POPULATION STUDY

M.Ø. Johansen [1,2,3], S. Vedel-Krogh [1,2,3], S.F. Nielsen [1,2,3], S. Afzal [1,2,3], G. Davey Smith [4,5], B.G. Nordestgaard [1,2,3]. [1] *Herlev and Gentofte Hospital, Department Of Clinical Biochemistry, Herlev, Denmark;* [2] *Herlev and Gentofte Hospital, The Copenhagen General Population Study, Herlev, Denmark;* [3] *University of Copenhagen, Institute Of Clinical Medicine, Faculty Of Health And Medical Sciences, Copenhagen, Denmark;* [4] *University of Bristol, Bristol Population Health Science Institute Mrc Integrative Epidemiology Unit, Bristol, United Kingdom;* [5] *University of Bristol, Population Health Sciences, Bristol Medical School, Bristol, United Kingdom*

**Background and Aims:** Apolipoprotein B (apoB)-containing triglyceride-rich lipoproteins and low-density lipoproteins (LDL) are each causal for myocardial infarction and atherosclerotic cardiovascular disease; however, the relative importance is unknown. We tested the hypothesis that for the same number of apoB-containing particles from smaller LDL through to larger triglyceride-rich lipoproteins, the risk of myocardial infarction is similar.

**Methods:** We included 29,039 individuals with no history of myocardial infarction nested within 109,751 individuals from the Copenhagen General Population Study. Particle number of apoB-containing lipoprotein subfractions were measured using nuclear magnetic resonance spectroscopy.
**Results:** During a mean follow-up of 10 years, 2,309 individuals developed myocardial infarction. Multivariable adjusted hazard ratios for myocardial infarction per $1 \cdot 10^{15}$ more particles were higher with larger size and more triglyceride content of apoB-containing lipoproteins using ten different subfractions, ranging from 11 (95% confidence interval, 5.6-22) for extra extra large very low-density lipoproteins (VLDL), to 1.06(1.05-1.07) for extra small VLDL, to 1.02 (1.01-1.02) for intermediate-density lipoproteins (IDL), through to 1.01 (1.01-1.01) for small LDL. When combining the particle number of six VLDL subfractions and combining IDL and three LDL subfractions, hazard ratios for myocardial infarction per $1 \cdot 10^{17}$ more particles were 3.5 (2.7-4.5) for VLDL and 1.3 (1.2-1.4) for IDL and LDL combined.