P06.027.C Monogenic and polygenic predisposition to thrombophilia is associated with higher risk of peripheral artery disease

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Background: Recent GWAS studies have reported significant associations between loci including genes involved in thrombosis and peripheral artery disease (PAD). However, the respective contribution of monogenic vs polygenic thrombophilia to PAD remains unclear.

Study design: To address this question, we analyzed clinical and genetic data from 469,814 individuals (45-69 years old) from the UK Biobank. Exome sequencing and imputed genotyping array data were used to identify individuals with monogenic (F5 [rs6025] and F2 variants [rs1799963]) or polygenic thrombophilia (venous thromboembolism polygenic risk score [PRS-VTE] using 248 variants excluding SNPs defining F5 and F2 mutation).

Results: Monogenic F5 and F2 genetic variants were found with a higher cumulative frequency in 699 PAD cases (7.4%, $N_{cases} = 9{,}504$) compared to 38,348 in the control group (6.6%, $N_{controls} = 460{,}310$) ($P_{chi\text{-}square} = 0.003$). Carriers of these variants were significantly more likely to experience a PAD event (OR: 1.13 [95% CI: 1.04-1.22]) compared to non-carriers. In contrast, these variants were not associated with coronary artery disease (CAD) ($P = 0.72$) nor cerebrovascular disease (CVD) ($P = 0.58$). The PRS-VTE was also associated with PAD (OR: 1.05 [95% CI: 1.03-1.04], per 1SD increase in PRS).

Conclusions: Both monogenic and polygenic thrombophilia are associated with an increased risk of PAD. This study points to a particular benefit of anti-coagulants in preventing or treating PAD in a subset of patients genetically predisposed to thrombophilia.

Conflict of Interest: Katerina Trajanoska: None declared, Vincent Mooser Has received honoraria from DalGene, Has received shares from MedeLoop

P06.028.D Genetically raised dietary antioxidants and cardio-respiratory health

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Background: Observational studies of raised dietary antioxidants suggest a beneficial effect on health but the results from interventional studies generally show no effect. There are no robust studies targetting people exposed to high levels of environmental oxidants where any effects of raised antioxidants might plausibly be stronger.

Objectives: We used Mendelian randomization to explore whether raised serum antioxidants are associated with markers of cardio-respiratory health. Using continuous markers of cardio-respiratory health provided sufficient statistical precision to test for effect modification by exposure to cigarette smoke, air pollution and poor diet.

Methods: Outcome data on forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the pulse wave arterial stiffness index was derived from UK Biobank participants. We identified single-nucleotide polymorphisms (SNPs) associated with serum ascorbate (vitamin C), retinol (vitamin A), and β-carotene from external data sources. We performed two sample Mendelian randomization analysis using exposure beta coefficients from the literature and outcome coefficients from the UK Biobank.

Results: 317,754 participants were included. We found no consistent relationship between genetically raised serum antioxidant levels and cardio-respiratory health measures (serum ascorbate $p = 0.57$, retinol $p = 0.41$, and β-carotene $p = 0.44$). There was no evidence of effect modification by levels of environmental oxidants.

Conclusions: Our findings support interventional studies showing no causal relationship between dietary antioxidants and cardio-respiratory disease outcomes. Further, our results do not support interventions to increase serum levels of ascorbate, retinol, or β-carotene in people exposed to high levels of environmental oxidants (Wellcome Grant ID: 209207/Z/17/Z).

Conflict of Interest: Azam Saied NHS, Laura Horsfall Full, Wellcome Trust Grants: 209207/Z/17/Z and 225195/Z/22/Z

P06.030.B Genetic uptake in Loeys-dietz syndrome genes is highest in spontaneous coronary artery dissection patients with extra-coronary arterial involvement

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Spontaneous coronary artery dissection (SCAD) is the prime cause of acute myocardial infarction in women below the age of 50 as well as in pregnant or postpartum mothers. To date, its genetic etiology is relatively poorly studied. We recently reported that rare variants in the known Loeys-Dietz syndrome (LDS) genes are significantly enriched in SCAD patients as compared to the general population (4.5% versus 1.5%). We aimed to validate our prior findings in an independent cohort of SCAD patients ($N = 99$) using haloplex-based gene panel sequencing of the coding regions and exon/intron boundaries of TGFB2/3, SMAD2/3 and TGFBR1/2. Only one novel heterozygous missense variant in SMAD2 (variant of unknown significance, 0.5% of alleles) was identified in the replication cohort, revealing a significantly lower uptake than what was observed in the discovery cohort (Chi2 $p = 0.02$). Both patient groups were compared with respect to the proportion of patients exhibiting connective tissue disease manifestations, fibromuscular dysplasia, extra-coronary arterial involvement, a positive family history and hypertension by means of Chi2 statistics, but no meaningful differences could be observed. Upon phenotypic comparison of the pooled variant-positive to variant-negative patients, extra-coronary artery manifestations were found to be more common in SCAD patients with extra-coronary arterial manifestations (Chi2 $p = 0.04$). Additional SCAD patients are being recruited and genetically tested to confirm this finding. Taken together, our findings suggest that the genetic uptake in LDS genes may differ between discrete SCAD endophenotypes.

Conflict of Interest: None declared

P06.031.C Exome sequencing to identify causative variants of blood clot dysfunction

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