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FAMILIAL CO-AGGREGATION AND SHARED GENETICS OF CARDIOMETABOLIC DISORDERS AND TRAITS: DATA FROM THE MULTI-GENERATIONAL LIFELINES COHORT STUDY

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Background: It is unclear to what extent genetics can explain the familial clustering and the co-occurrence of distinct cardiometabolic disorders in the general population. We aim to quantify the familial (co-)aggregation of a range of cardiometabolic disorders, and to estimate the heritability of cardiometabolic traits and their genetic correlations.

Methods: We used baseline data of 162,416 participants from the three-generational Lifelines Cohort Study. Cardiometabolic disorders including type 2 diabetes (T2D), cardiovascular diseases, hypertension, obesity, hypercholesterolemia, and metabolic syndrome (MetS), were defined in adult participants. Fifteen cardiometabolic traits indexing obesity, blood pressure, inflammation, glucose regulation, and lipid levels were measured in participants >8 years old. Familial (co-)aggregation of cardiometabolic disorders were measured as recurrence risk ratios (λR) for first-degree relatives (FDR) and compared to those of spouses, using modified conditional Cox proportional hazards models. Heritability (h2), shared environment, and genetic correlation (rg) were estimated using variance decomposition methods, adjusted for age, age2, and sex.

Results: Having a first-degree relative with a cardiometabolic disorder increased risk of the same disorder, ranging from λFDR of 1.23 (95%CI: 1.20-1.25) for hypertension to λFDR of 2.48 (2.15-2.86) for T2D. Most of these estimates were higher than in spouses (λSpouses<λFDR), except for obesity (λSpouses: 1.92 (95%CI: 1.83-2.01) > λFDR: 1.85 (95%CI: 1.79-1.91)). The cardiometabolic traits presented moderate heritability (from h2CRP: 0.26 to h2HDL: 0.50). Cardiometabolic disorders showed positive familial co-aggregation, particularly between T2D, MetS, and obesity (from λFDR obesity-MetS: 1.28 (95%CI: 1.24-1.32) to λFDR MetS-T2D: 1.61 (95%CI: 1.52-1.70)), consistent with the genetic correlations between their continuous traits (ranging from rg HDL-Triglycerides: -0.53 to rg LDL-ApoB : 0.94).

Conclusions: There is positive familial (co-)aggregation of cardiometabolic disorders. Cardiometabolic traits are moderately heritable with moderate genetic correlations between each. These results highlight the importance of shared genetics and suggest a common genetic architecture underlying cardiometabolic disorders and traits.

Conflicts of interest to disclose: We declare no competing interests

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Shared genetic architecture and causality between Autism Spectrum Disorder and irritable bowel syndrome, pain, and fatigue

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Background: Autism spectrum disorder (ASD) often occurs with functional somatic syndromes (FSS), such as irritable bowel syndrome (IBS), pain, and fatigue. However, the underlying genetic mechanisms and potential causality have not been well studied.

Methods: Using large-scale genome-wide association study (GWAS) data, we investigated the shared genetic architecture and causality between ASD and FSS, including IBS, pain, and fatigue. Specifically, we first estimated genetic correlations and then conducted a multi-trait analysis of GWAS (MTAG) leveraging the correlations to detect potential novel genetic variants for single traits. Afterward, polygenic risk scores (PRS) of ASD were derived from GWAS and MTAG to examine the associations with phenotypes in a large Dutch cohort of Lifelines. Finally, we performed Mendelian randomization (MR) to evaluate the causality.

Results: We observed positive genetic correlations between ASD and FSS (IBS: rg = 0.27, adjusted p = 2.04×10-7; pain: rg = 0.13, adjusted p = 1.10×10-03; fatigue: rg = 0.33, adjusted p = 5.21×10-9). Leveraging these genetic correlations, we identified 4 novel genome-wide significant independent loci for ASD by conducting MTAG, some mapping to the previously unrevealed genes including NEDD4L, MFHAS1, and RP11-10A14.4. PRS of ASD derived from both GWAS and MTAG was associated with ASD and FSS symptoms in Lifelines. MTAG-derived PRS showed a bigger effect size and explained variance, and smaller p-values. We did not observe significant causality using MR.

Conclusion: Our study provided new evidence of shared genetic etiology between ASD and FSS, specifically with respect to IBS, pain, and fatigue. The findings advance our understanding of the co-occurrence mechanisms and may have important implications for the intervention and treatment that target these multiple conditions simultaneously.

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A Phenome-Wide Association Study of Cardiac Autonomic Function

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Introduction: Higher levels of heart rate variability (HRV), the beat-to-beat variation in heart rate, reflects better function of the cardiac autonomic nervous system (ANS). In this phenome-wide study, we aim to better understand cardiac ANS function in a wide range of disease related outcomes.

Methods: A phenome-wide Latent Causal Variable (LCV) analysis was used to estimate genetic correlations and potential causal relationships between four HRV traits (RMSSD, SDNN, raw and heart rate corrected) and over 1,400 traits available on the Complex Traits Genetics-Virtual Lab website (https://genoma.io/) using GWAS summary statistics. A Phenome-wide association study (PheWAS) was conducted to assess the association of four HRV genetic risk scores (GRSs) and 23 HRV single-nucleotide polymorphisms (SNPs) with 91 continuous and 115 binary (disease) traits using UK biobank data.

Results: The LCV analysis revealed that lower HRV causally increased diastolic blood pressure (DBP) and a wide range of hypertension-related traits. In addition, lower HRV was predicted to increase the risk of varicose veins of lower extremities and internal derangement of the knee. PheWAS results indicated that lower HRV GRSs were significantly associated with increased resting heart rate, increased DBP and mean arterial pressure, and decreased pulse pressure. Furthermore, associations were found with varicose veins in lower extremities, arterial stiffness and platelet indices. Results of the PheWAS with SNPs were consistent with GRSs, and additionally revealed that several HRV lowering alleles decreased risk of atrial fibrillation, heart arrhythmia, and supraventricular tachycardia. Moreover, the allele of SNP rs1906263 for lower HRV was strongly associated with increased insulin-like growth factor 1 (p-value=2.58×10-10).

Conclusion: ANS reflected by lower HRV was inferred to causally increase DBP, risk of hypertension and varicose veins. Furthermore, lower HRV GRSs and SNPs were associated with increased heart rate, arterial stiffness and platelet indices, and decreased risk of various heart rhythm problems.

Conflicts of interest to disclose: We declare no competing interests

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Epigenetic clock-derived age acceleration is associated with lung function in the population-based Lifelines cohort study

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Introduction: Lung function is an important marker of general health which naturally declines with aging. DNA methylation(DNAm) has been postulated as a marker of biological aging that can be estimated using epigenetic clocks. The difference between this estimated biological age and the chronological age is a measure of age acceleration(AA). Our study aimed to assess the association between AA and lung function and the mediation role of AA on the association between smoking and lung function.

Methods: We included 1618 study participants from the Lifelines cohort study. The lung function was measured with spirometry, and Forced Expiratory Volume in one second (FEV1) was used as the outcome. Skin Horvath, PhenoAge, DunedinPACE, and telomer length epigenetic clocks were used. Age acceleration was derived from the residuals of the regression of biological age on chronological age except for the DunedinPACE-clock. Linear regression and causal mediation analysis adjusted for confounders were used.

Results: Of 1618 participants, 927 (55%) were males with a mean age of 47 years. AA measured by PhenoAge and DunedinPACE epigenetic clocks was significantly associated with FEV1. FEV1 was 7.7ml lower (95% CI:-12.3,-3.19) for a one-year higher PhenoAge AA and 488.6 ml lower (95% CI:-728.83,248.39) for a one-year faster Dunedin pace of aging. Telomere length, Blup, and skin Horvath age acceleration were not associated with FEV1. PhenoAge AA and DunedinPACE mediated the well-known association between smoking and FEV1. PhenoAge AA explained 7% of the variance between smoking and FEV1, while DunedinPACE explained 29 %.

Conclusion: This study shows that age acceleration measured by the PhenoAge and DunedinPACE epigenetic clock is significantly associated with lower lung function. This suggests that faster biological aging accelerates natural lung function decline. Apart from the direct effect of smoking on the lungs, smoking leads to AA, and this AA leads to lower lung function.

Conflicts of interest to disclose: We declare no competing interests

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Mental illness and cardiovascular health: Observational and polygenic score analyses in a population-based cohort study

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Introduction: Individuals with serious mental illness have a markedly shorter life expectancy compared to the general population. A major contributor to premature death is cardiovascular disease, yet research on the relation between serious mental illness and cardiovascular disease is limited. We investigated associations of (genetic liability for) depressive disorder, bipolar disorder and schizophrenia with cardiovascular disease traits and examined to what degree these were driven by important confounders.

Methods: We included participants of the Dutch Lifelines cohort (N=147,337) with information on lifetime diagnosis of depressive disorder, bipolar disorder, and schizophrenia and cardiovascular disease traits. Employing linear mixed-effects models, we examined associations between mental illness diagnoses and cardiovascular disease, correcting for psychotropic medication, demographic and lifestyle factors. In a subsample, we repeated these analyses using polygenic scores (PGS) for the mental illnesses as independent variables.

Results: Of the participants, 14,735 were diagnosed with depressive disorder, 646 with bipolar disorder, and 130 with schizophrenia. Genome-wide genotype data were available for 46,423 participants. There was strong evidence that depressive disorder is associated with a higher risk of hypertension, arrhythmia, and atherosclerosis, and lower blood pressure, heart rate variability, and QRS duration, even after correcting for confounders. Positive associations were also found between a depression PGS and hypertension, arrhythmia, and atherosclerosis. Bipolar disorder was associated with a higher risk of nearly all cardiovascular disease traits, but most of these associations weakened after adjustment. While genetic liability to schizophrenia was associated with increased arrhythmia risk and lower heart rate variability, schizophrenia diagnosis was not.

Conclusion: Our study shows widespread associations of (genetic liability to) mental illness (primarily depressive disorder) with cardiovascular disease, even after confounder-adjustment. Future research should not only focus on modifiable risk factors, but also on clarifying potential causal pathways between mental illness and cardiovascular disease.

Conflicts of interest to disclose: We declare no competing interests

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Statin use is associated with a higher prevalence and volume of coronary artery calcification: A genetic instrumental variable analysis

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Introduction: Statins have demonstrated a well-established cardio-protective effect. However, recent pharmacological mechanism studies have shown statin's pleiotropic effects on increasing coronary artery calcification (CAC), a predictor of cardiovascular events. Prior studies on the effect of statins on CAC in human subjects are controversial or confounded. Therefore, we studied the effect of SLCOB1 function levels, a transporter of statins to the liver, as an instrumental variable in a general population.

Methods: This cross-sectional study included 2399 participants from the population-based Rotterdam Study cohort (mean age 69.0, SD=6.72, 52% women) who underwent non-contrast computed tomography (CT) for the assessment of CAC. Pharmacy-linked records from 1991 until the date of the CT scan were retrieved. Genetic variants related to the SLCOB1 function were obtained and phenotyped into three function levels. Multivariable logistic or linear regression models, adjusted for cardiovascular risk factors, including sex, age, and waist-to-hip ratio, were used for the association between statin use with presence or volume of CAC. Statin use was defined based on the use at the CT-date (current/past/never and long/short/never) and the cumulative duration of use preceding the CT date.

Results: Long-term and current statin use were associated with a higher prevalence (OR=1.69, 95%CI=1.22-2.28, OR=1.53, 95%CI=1.09-2.17 respectively) and larger volume of CAC (β=0.40, 95%CI= 0.30-0.50, β =0.39, 95%CI=0.28-0.49 respectively) but the cumulative duration of use was not associated with an increase in volume. The multivariate β for the stratified levels of SLCOB1 (normal function=reference) and volume of CAC among the long-term and current users were 0.11 (decreased function), and 0.28 (poor function) with a significant trend (P-trend= 0.04) but not among the never-users, implying possible causality.

Conclusions: In the general population, long-term and current statin use are associated with higher prevalence and volume of CAC. Future longitudinal studies are warranted to validate our findings and disentangle the underlying mechanisms.

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