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A genetic risk score to identify young individuals (aged 32-47) at increased risk of non-zero CAC

Introduction: Using data from the Multiethnic Study of Atherosclerosis (MESA), we have previously demonstrated that a genetic risk score (GRS) derived from single nucleotide polymorphisms (SNPs) associated with coronary heart disease (CHD) can identify individuals at increased probability of non-zero CAC. This GRS can be used to calculate the age (44-84) at which an individual's probability for CAC presence reaches a predetermined threshold. However, some high-risk individuals have a probability of CAC >25% by age 44 and may benefit from CAC screening at a younger age. Here, we incorporate data from the Coronary Artery Risk Development in Young Adults (CARDIA) study to expand the analysis to include subjects 32-84 years of age.

Methods: The GRS was derived from 142 CHD risk loci that were imputed with high quality in both the MESA and CARDIA cohorts. A GRS was calculated for each individual using a linear combination of the number of risk alleles at each CHD SNP (0, 1, 2) weighted by the SNP's odds ratio for CHD. We evaluated the GRS in the CARDIA dataset to determine if it was predictive of non-zero CAC in this younger population as well as in the CARDIA and MESA datasets combined to assess the age at which the probability of CAC crosses a predetermined threshold across a wide range of ages and genetic risk profiles.

Results: Among individuals aged 32-47 in the CARDIA dataset, CAC presence increased with increasing genetic risk category, and the highest GRS quintile had a 14.5% rate of CAC compared to the lowest GRS quintile at 8.8%. In separate analysis of males only, the highest GRS quintile had nearly double the rate of CAC presence (24.1%) compared to the lowest GRS quintile (12.1%). However, the total non-zero CAC rate in CARDIA females was <7%, and the GRS was not predictive in this group. In analysis of both the CARDIA and MESA cohorts combined (ages 32-84), the age at which CAC probability crossed a 25% threshold was more than 10 years different in individuals with a GRS 2 standard deviations above the population mean compared to those 2 standard deviations below (51 vs 40 years for males and 62 vs 51 years for females).

Conclusion: A GRS can identify young people who are at high risk for CAC presence and may be used to determine the optimal age for a first CAC screening in individuals aged 32-84.