The relationship between epigenetic age and myocardial infarction/acute coronary syndrome and in a population based nested case-control study

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Background: The measure of "epigenetic age" (EA) derived from DNA methylation (DNAm) is considered as biomarker of ageing.

Objective: We investigated the relationship between EA and Myocardial Infarction (MI) /Acute coronary syndrome (ACS) in a nested case-control study of the elderly population.

Methods: A random population sample was examined at baseline (2003/05, n=9360, age 45–69, the Russian arm of the HAPIEE Project), re-examined in 2006/08, 2015/17, and followed up for an average 15 years for fatal and non-fatal events. Using a nested case-control study design, we selected participants with incident MI/ACS (cases) and age-and sex-stratified controls among those free from baseline CVD. We performed DNAm profiling of the whole blood samples (using Illumina EPIC arrays) collected at baseline. After quality control, 135 cases and 185 controls were included in the analysis. Baseline EA was calculated using Horvath, Hannum, PhenoAge and Skin and Blood DNAm clocks; the differences between EA and chronological age (CA) were denoted as DAHr, DAHn, DAPh, DASB, respectively.

Results: DNAm ages calculated with Horvath's, Hannum's and Skin and Blood clocks were close to the CA; the corresponding median absolute differences (MAD) were 3.38, 3.64 and 2.79 years, and mean (SD) –0.85 (5.37), 1.96 (5.18) and 2.10 (3.94) for DAHr, DAHn and DASB respectively. As expected, PhenoAge's predictions were less precise with MAD=9.41 and DAPh mean (SD) 8.94 (6.38). The mean DAHr and DAHn were significantly higher in MI/ACS compared to controls (0.99 (5.38) vs. –1.55 (5.27), p=0.007, and 2.89 (6.37) vs. 1.28 (4.95), p=0.006 correspondingly), DASB was borderline higher in MI/ACS vs controls and DAPh was similar in cases and controls. After controlling for sex, the risk of MI/ACS was higher in DAHr terciles 2 and 3 vs. tercile 1 (OR=1.08 [95% CI 0.61–1.89], p=0.799 and OR=2.09 [1.19–3.66], p=0.010); the association was independent of smoking but it was largely explained (or mediated) by metabolic factors (blood pressure, body mass index, total and LDL-cholesterol). Similarly, the risk of MI/ACS was increased in terciles 2 and 3 of DAHn; compared with lowest tercile, the OR were 1.52 [0.86–2.71], p=0.152 and 2.41 [1.34–4.34], p=0.003), respectively; again, the association was largely explained by metabolic factors. There was no association found between baseline DAPh or DASB and the risk of MI/ACS.

Conclusion: In this case-control study nested in a prospective population-based cohort, we found an association between acceleration of epigenetic age and increased risk of MI/ACS independent of sex and smoking. The risk of MI/ACS was about 2-fold higher in the top tercile of difference between epigenetic and chronological age. The excess risk is appeared to be modulated by metabolic factors.