Circulating levels of metabolic biomarkers of site-specific and sex-specific arterial calcification in the multi-cohort BBMRI setting

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Background/Introduction: Increasing evidence shows that greater arterial calcification leads to an elevated risk of atherosclerotic cardiovascular disease. Risk factors and prognosis of arterial calcification seems to vary per site and between women and men. However, the underlying biological mechanisms of site-specific calcification and the associated sex differences are largely unknown. Within the BBMRI framework, we performed a multi-cohort study on the associations of the circulating levels of metabolic biomarkers with arterial calcification at various sites among women and men.

Purpose: To examine the associations of the circulating levels of metabolic biomarkers with coronary artery (CAC), aortic arch (AAC) and the aortic valve (AVC) calcifications among women and men.

Methods: We included a total of 1,114 participants from the population-based Rotterdam Study and 390 from the Leiden Longevity Study. Study populations were comparable concerning study characteristics. Blood samples were used to determine a wide range of plasma metabolic biomarkers by proton nuclear magnetic resonance (NMR). Participants underwent non-contrast computed tomography to quantify the volume of CAC, AAC, and AVC. Linear regression modelling adjusted for relevant covariates was used to assess the associations of 166 metabolic biomarkers with CAC, AAC, and AVC. Correction for multiple testing was based on 33 independent metabolic biomarkers (p-value 0.05/33 = 1.5 x 10–3).

Results: Mean (standard deviation - SD) age was 69.5 (6.8) and 780 (52.0%) of the study population were women. One SD increase in concentration of a1-acid glycoprotein, was associated with a 0.10 SD (standard error (SE) = 0.03) increase in AAC (p-value = 9.5x10–4) in the overall population (Figure 1). When we stratified our analyses based on sex, this association was mainly driven by men [beta (SE) per SD: 0.12 (0.05), p-value = 0.007]. Moreover, an SD increase in acetate was associated with a 0.14 SD (SE = 0.04) decrease in CAC (p-value $1.7x10^{-4}$) in women but not in men [beta (SE) per SD: –0.04 (0.03), p-value = 0.22] (Figure 1).

Conclusion(s): Higher levels of circulating glycoproteins were associated with increased AAC in men. Moreover, lower levels of circulating acetate were associated with increased CAC in women. These results provide evidence for location-specific differences and sex-specific effects in the underlying biological mechanisms of atherosclerosis. Our findings carry the potential to contribute to the early detection of individuals at increased risk for developing atherosclerotic cardiovascular disease and to a better understanding of disease etiology.

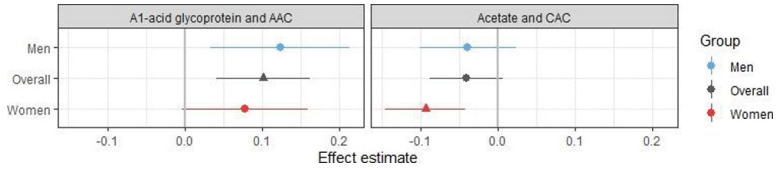

Figure 1