Mendelian randomization identifies sex differences in pain manifestation of coronary artery disease

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Background and aim: Clinical manifestation of atherogenic cardiovascular disease differs between men and women. Men often present with classical symptoms i.e., chest pain radiating to left arm and jaw. Women may show a wide range of symptoms considered atypical, including but not limited to back pain and nausea. Anatomical pathways feeding cardiac pain have not been properly characterized with respect to sex-related differences in human at population level.

Methods: We performed sex-stratified GWAS analysis on CAD as well as chest, neck and shoulder, back and facial pain using the UK Biobank cohort (men N = 203,823; women N = 239,631). To unravel given differences in pain manifestation of atherogenic cardiovascular disease in men and women, we performed Mendelian Randomization to approximate the causal associations between coronary artery disease (CAD) and a variety of pain locations.

Results: We identified 32 and 19 independent instrumental variables (R² < 0.001, p-value 5x10⁻⁶) associated with CAD for men and women, respectively. MR analysis revealed potential causality between CAD and self-reported chest pain for men (OR: 1.33, CI: 1.25 – 1.41) and women (OR: 1.44, CI: 1.20 – 1.73) as well as a link between CAD and clinical chest pain for both sexes (men OR: 1.22, CI: 1.17 – 1.26; women OR: 1.31, CI: 1.18 – 1.46). MR displayed a relationship between CAD and back pain in women (OR: 1.35, CI: 1.03 – 1.66) but not in men (OR: 0.99, CI: 0.90 – 1.11, p-value difference: 0.036). Manifestation of neck and shoulder pain revealed a suggestive difference in causality between men and women (p-value difference: 0.051).

Discussion: Our study provided evidence supporting a causal association between CAD with manifestation of chest pain in both men and women. Additionally, no stronger effect in men was found contrary to clinical observations suggesting pain perception of the chest at population level could be similar between the sexes. Manifestation of back pain with CAD, however, showed a more causal effect in women compared to men. Here we show that pain perception of the heart is not limited to the chest in women at population level. Future research is required to identify what drives these differences at multiple levels.