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# Proteomics insights on how physical inactivity can influence cardiovascular health

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The World Health Organization (WHO) has set a global target to reduce physical inactivity by 10% by 2025,<sup>1</sup> but according to a pooled analysis of 1.9 million participants during 2001 to 2016, the progress of the WHO target is “*not on track*”.<sup>2</sup> This analysis indicated a prevalence of 28% of adults, or approximately 1.4 billion people worldwide, to be physically inactive.<sup>2</sup> Sedentary behaviour and poor physical fitness are described as major modifiable risk factors and also implicated in cardiovascular disease morbidity and mortality.<sup>3</sup> The enormous adversity of physical inactivity on the human body ranges from increased oxidative stress, proinflammation, subcutaneous and visceral adiposity, high blood pressure and subsequently type 2 diabetes mellitus, to coronary artery disease, heart failure, stroke as well as various cancers and mental disorders.<sup>4</sup>

The current study is based on two large Swedish cohorts namely the Epidemiology for Health (EpiHealth)<sup>5</sup> and the Swedish Mammography Clinical Cohort (SMCC),<sup>6</sup> initially aiming to investigate gene–lifestyle interactions in the pathogenesis of common diseases and lifestyle and genetic factors with morbidity and mortality in middle-aged and elderly women, respectively. The study by Stattin and colleagues<sup>7</sup> performed a cross-sectional analysis to investigate associations between leisure-time physical activity and plasma protein biomarkers determined by cardiovascular multiplex panels, which included a combined 184 proteomics biomarkers. They additionally tested whether these associations were independent of body fat percentage and can be replicated in the participants of the SMCC. The study included 2239 men and women from EpiHealth and 4320 women from SMCC. Physical activity was determined by validated (against accelerometry) questionnaires to determine occupational physical activity, weekly leisure exercise and daily time spent walking or cycling. The authors considered various confounders in their analysis including sex, age, occupational physical activity, daily servings of fruit and vegetables and meat, self-reported smoking status, self-reported alcohol consumption,

level of education, current cohabitation status, kidney (glomerular filtration rate based on creatinine and cystatin C) and liver (alanine aminotransferase) function. Body fat percentage was measured using bioimpedance for EpiHealth and dual-energy x-ray absorptiometry for SMCC, and considered a mediating factor in the cross-sectional analysis, or an additional confounder.

The average age of the two study cohorts were 64.4 years with men having a body fat percentage of 24.9% and women of 36.8% (average of both EpiHealth and SMCC women). In both cohorts, higher physical activity was supported by more fruit and vegetable consumption, lower body fat percentage, lower number of smokers and less sedentary occupations. Systolic blood pressure was highest in the men who reported the lowest leisure-time physical activity (those sitting mostly) versus men participating in straining activity for 60 minutes per day (142 mmHg vs. 138 mmHg). In women, no marked difference was observed in blood pressures across levels of physical activity, except for those hardly ever walking having the highest systolic blood pressure compared to women walking more than 90 minutes per day (136 mmHg vs. 132 mmHg). The authors did not provide the statistical significance of these differences, nor commented on blood pressure lowering drugs use in these cohorts. A total of 28 proteomics biomarkers were replicated between the two cohorts. These 28 biomarkers indicated similar trends for leisure-time physical activity (EpiHealth, men and women combined), exercise and walking or cycling in women (SMCC). Interestingly, at the lowest levels of physical activity (indicated by standard deviation

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change per level of leisure-time physical activity), the biomarkers indicative of various atherosclerotic processes including the regulation of low-density lipoprotein oxidation, protein degradation, and immune cell adhesion and migration, all showed to be adversely linked to physical inactivity. In addition, when body fat percentage was added to the adjusted model, only seven of these biomarkers were replicated in both cohorts, whereas only four of these biomarkers (including fatty acid binding protein 4 (FABP4), cystatin B (CSTB), paraoxonase 3 (PON3) and interleukin-1 receptor antagonist (IL1ra)) associated in the exercise and walking or cycling models (in women) independently of body fat percentage.

The link between poor physical activity and especially PON3, indicates the potential compromise of the anti-inflammatory, anti-oxidation and cell proliferation inhibitory properties of PON3,<sup>8</sup> as well as the link with IL1ra, with its biological role to attenuate the potent biological consequences of interleukin-1 both in normal physiology and in pathophysiological conditions.<sup>9</sup> The associations of physical inactivity seen with FABP4 (also known as adipocyte FABP (A-FABP) or aP2), suggests overexpression of FABP4 in adipocytes and macrophages which contributes to the development of insulin resistance and atherosclerosis.<sup>10</sup> These insights of human proteomics biomarkers, especially in relation to modifiable risk factors for cardiovascular disease, remain of importance to identify novel biomarkers associated with tissue injury and muscle remodeling in response to physical activity.

The findings of this study are supported by a recent paper that showed higher self-reported physical activity to associate with proteins involved in mitochondria, tricarboxylic acid cycle enzymes, structural and contractile muscle and genome maintenance.<sup>11</sup> The same paper indicated proteins related to the spliceosome, transcription regulation, immune function, and apoptosis, DNA damage, and senescence were lower in participants with higher self-reported activity.<sup>11</sup>

Even though the work presented in this study is important and contributes to the potential mechanisms involved in lifestyle related cardiovascular risk, the authors have dismissed some essential shortcomings in their analyses. Some of the limitations include the use of questionnaires to quantify physical activity instead of accelerometry (despite the validation clause presented), as well as the non-validation between the Likert scale and the questionnaire developed and validated for the SMCC. Whether these different survey methods correlate to one another is not known. Although blood pressure data were presented in the supplementary tables, the authors failed to report on the prevalence of hypertension, type 2 diabetes mellitus and the use of antihypertensive medication, and the

potential impact of those drugs on particular proteomics biomarkers. The associations observed in the study were also performed without considering blood pressure as a confounding or contributing factor – albeit these associations identified cardiovascular related pathways and the authors concluded that these pathways may yield new insights into how physical activity affects cardiovascular health.

The authors are congratulated on this proteomics approach in identifying the pathways involved in cardiovascular compromise due to physical inactivity. The data presented led to the understanding of various proteins and enzymes involved in potential atherosclerotic processes involved in sedentary individuals and that higher physical activity is linked to potential protective or preventative pathways including anti-inflammation, anti-oxidation and cell proliferation inhibition. However, future prospects can aim to delineate proteomics pathways along with the impact of physical inactivity (measured by accelerometry) on hypertension, type 2 diabetes mellitus, and investigate similar trends among younger adults and children or adolescents.

#### Declaration of conflicting interests

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