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Biomarkers of Vascular Injury and Cardiometabolic Diseases Risk in the General Population

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Vascular injury and platelet activation have been implicated in several chronic medical conditions, including coronary heart diseases, cerebrovascular diseases and metabolic diseases, such as insulin resistance and type 2 diabetes. Given the lack of population-based prospective studies on biomarkers of vascular injury and risk of major cardiometabolic diseases, it was the aim of this thesis to assess the associations between P-Selectin, E-Selectin, intercellular adhesion molecule 3, thrombomodulin, thrombopoietin, glycoprotein IIb/IIIa as well as fibrinogen and (a) lifestyle factors and established cardiovascular risk factors, (b) myocardial infarction , (c) stroke and (d) type 2 diabetes risk in population-based individuals.

Data from a case-cohort subset, including a random subcohort of n=2,418, of the European Prospective Investigation into Cancer and Nutrition-Heidelberg was analysed, and concentrations of vascular injury biomarkers were measured in baseline blood samples of this population. Multivariable-adjusted Cox regression models were used to explore associations between baseline concentrations of vascular injury biomarkers and the risk of developing myocardial infarction (n=369 cases), stroke (n=335 cases) and type 2 diabetes (n=163 cases). Additionally, a systematic review and meta-analysis on these seven vascular injury markers and type 2 diabetes risk was conducted in order to contextualize results derived from the local cohort.

Analyses on cross-sectional data revealed numerous associations between vascular injury markers and cardiovascular risk factors and lifestyle parameters indicating that the analysed biomarkers are reflective of an increased cardio-metabolic risk profile. In line with this observation, only fibrinogen, but none of the more novel biomarkers were significantly associated with the risk of myocardial infarction upon adjustment for established risk factors. By contrast, individuals who presented increased levels of intercellular adhesion molecule 3 at baseline were at higher risk of developing a stroke, with a hazard ratio 1.64 (95% confidence interval 1.15, 2.32). This association was more apparent for ischaemic than for haemorrhagic stroke. On the contrary, in stratified analyses, P-Selectin was associated with increased risk of haemorrhagic stroke. At the same time, intercellular adhesion molecule 3 levels were inversely associated with type 2 diabetes risk. The present analyses further showed that higher E-Selectin and lower thrombomodulin concentrations may be associated with the risk of type 2 diabetes. The latter findings were corroborated by the meta-analysis.

Overall, the present thesis indicates that intercellular adhesion molecule 3 could be a novel risk factor for ischaemic stroke and that P-Selectin could be a risk factor for haemorrhagic stroke, while neither intercellular adhesion molecule 3 nor one of the other biomarkers of vascular injury beyond fibrinogen were associated with the risk of myocardial infarction upon multivariable adjustment for established risk factors. With regard to type 2 diabetes, E-Selectin and thrombomodulin may be interesting novel risk markers. However, the observed associations, particularly on intercellular adhesion molecule 3, require external validation and functional follow-up by mechanistic studies, before stronger conclusions on the etiological role of the analysed biomarkers and their instrumental usefulness for risk prediction can be drawn.