Evaluating Inflammation as a Mediator between Adiposity and Coronary Artery Diseases Using Mediation Models within the Epicor Study

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INTRODUCTION

Obesity and overweight are globally recognized as major modifiable risk factors for coronary artery disease (CAD), yet the mechanisms underlying this association are complex and multifaceted ([1],[2]). Beyond mechanical and metabolic alterations, a growing body of evidence suggests that chronic low-grade inflammation plays a central role among indirect factors increasing cardiovascular risk in obese individuals. This systemic inflammation is typically quantified by circulating biomarkers, including C-reactive protein (CRP) and Plasminogen Activator Inhibitor-1 (PAI-1), both of which have known pro-atherogenic properties. However, few studies have formally quantified the indirect role of inflammation in mediating the effect of excess weight on coronary outcomes using robust causal frameworks.

AIMS

The main objective of this study was to quantify the extent to which chronic low-grade inflammation, measured prospectively via CRP and PAI-1, mediates the relationship between body mass index (BMI) and the risk of CAD. By applying a formal mediation model adapted for time-to-event data, we aimed to provide a nuanced understanding of this relationship disentangling the direct and indirect components and considering their possible evolution over time.

METHODS

Data were derived from the EPICOR study ([3]), the cardiovascular branch of the EPIC Italy study (European Prospective Investigation into Cancer and Nutrition). Here 1416 participants were involved in a case-cohort design with 622 incident CAD cases (major coronary events or myocardial infarction). Baseline measures included BMI, CRP, and PAI-1. We estimated the total causal effect (TCE) of BMI categories on CAD and decomposed it into the pure direct effect (PDE) and the natural indirect effect (NIE) via inflammation, using a counterfactual-based weighting approach developed for survival outcomes ([4],[5]). This methodology allows valid mediation estimation even in the presence of non-rare outcomes, under the key assumptions of no unmeasured confounding of the exposure-outcome, exposure-mediator, and mediator-outcome relationships; and no mediator-outcome confounders affected by the exposure ([6]).

Flexible parametric Royston-Parmar survival models ([7]) were used to estimate hazard ratios (HRs), adjusting for age, sex, relative index of inequality ([8]), total physical activity, smoking status, and geographic area. CRP and PAI-1 levels were treated as continuous mediators. Sensitivity analyses excluded early events to reduce reverse causality risk. Mediation effects were computed at 1, 5, and 10 years post-enrollment, and stratified analyses were conducted by sex. The positivity assumption was verified, and no violations of identifiability conditions were detected.

RESULTS

The causal effects estimated as a function of time in terms of HRs are shown in the figure below for the intermediate BMI category (upper panels) and for the highest BMI category (lower panels) with respect to the normal weight one. A direct effect (panels A and D) was detected over the whole follow-up time. There was also evidence for an indirect effect (panels B

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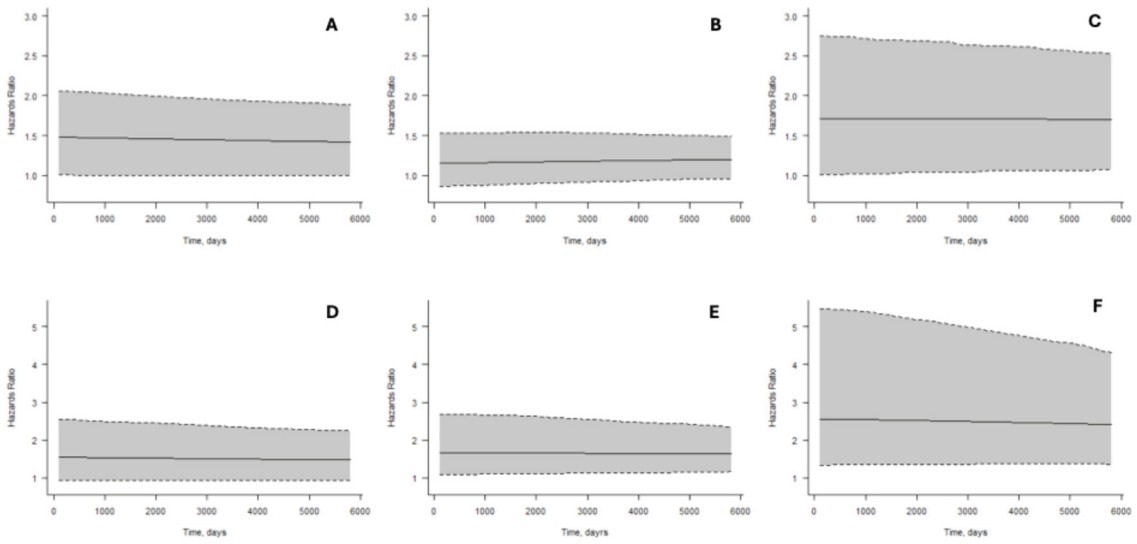
and E), more relevant for the third BMI category than for the second one with respect to the first one. Only in the first case these effects slightly increased with time. The TCEs (panels C and F) remained always significant with a slowly decreasing pattern for the highest BMI category. Point estimations of the effects at different time epochs confirmed this interpretation: at 10 years, the NIE for the intermediate BMI category was 1.19 [95% CI: 0.93–1.52], and for the highest one was 1.65 [95% CI: 1.14–2.48]. These indirect effects represent relevant portions of the total effect (TCE = 1.71 and 2.47, respectively), indicating that inflammation explains a meaningful share of the increased CAD risk in higher BMI categories. Notably, the NIE for obese individuals remained significant across all time points, with relatively stable HRs over time. The PDEs, while also statistically significant, showed smaller magnitudes, particularly at longer follow-up.

Stratified analyses confirmed the robustness of these findings. In both sexes, similar patterns of mediation were observed, although confidence intervals widened slightly. Similar analyses using waist-to-hip ratio WHR instead of BMI as a measure for obesity yielded consistent results, reinforcing the biological plausibility of the causal pathway.



Pure direct effects, natural indirect effects and total causal effects in the hazard ratio scale as a function of time for the intermediate category and for the highest BMI category (upper and lower panels respectively) versus the lowest one

CONCLUSIONS

Our findings provide strong epidemiological and methodological evidence that chronic low-grade inflammation, as measured by CRP and PAI-1, mediates a portion of the effect of excess adiposity on CAD. By adopting a formal mediation framework compatible with survival analysis, we disentangled the pathways linking BMI and cardiovascular outcomes, highlighting inflammation as a biologically plausible and statistically significant intermediate mechanism. These results underscore the importance of incorporating inflammatory biomarkers into cardiovascular risk prediction and may inform future prevention strategies. The study also illustrates how mediation analysis, when carefully implemented, can yield insights into the causal architecture of complex epidemiological relationships. This methodological approach may prove valuable in evaluating the effects of novel anti-inflammatory or weight-reducing therapies on cardiovascular outcomes through their impact and have potential implications for a better selection of patients for treatment.on systemic inflammation

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