Response: Talking about mediation

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To The Editor

Werneck[1] reflects on the definition of "mediation" in relation to our recently published findings on TV viewing, inflammatory markers and mortality.[2] In epidemiological research, the interpretation of mediation should be based both on conceptual and empirical grounds. Our study was built on a strong conceptual framework as there is good evidence from both observational[3] and experimental[4] work to suggest sedentary behaviours may cause inflammatory responses; in addition, inflammatory processes have been mechanistically implicated in atherosclerosis and the ageing cardiovascular system.[5] In our paper we demonstrated that inflammatory markers were indeed independently associated with mortality in fully adjusted models. We also confirm the other precondition to mediation was met with TV viewing being associated with CRP and fibrinogen after adjustment for variables reported in Model 2 (age, sex, physical activity, smoking, alcohol intake, depressive symptoms, long standing illness, disability).[3] Thus, the consistently replicated association between TV viewing and mortality[6] may be plausibly explained (mediated), in part, through inflammatory markers.

Over and above the analyses presented in our paper, Werneck suggests it is highly recommended to test the indirect effect, which could be made through Sobel test or resampling methods. These methods, however, were primarily designed to be conducted on continuous data and not time to event analyses. To our knowledge, robust approaches to mediation analysis with continuous mediators and survival outcomes are still under methodological development and lack available coding in common statistical packages. Under these circumstances, making inferences about the degree of mediation from the attenuation of Hazard Ratios when adding the possible mediator into the survival model

remains a common approach in epidemiology, including in large international collaborations.[7]

The issue of possible interaction between mediators is raised. We decided to separately model groups of mediators (ie, inflammatory, metabolic) that shared common mechanistic pathways so as to counteract possible interactions between them inside the models. However, there is less reason to suspect an interaction between variables within the same category. This was demonstrated in subsequent analyses where we modelled each mediator separately (Table 1); results or interpretation are not appreciably changed to those reported in the paper.

In summary, we agree it is important to undertake robust approaches to test mediation, although interpretation should not only be based on empirical grounds, but also in combination with a strong underlying conceptual framework and biological plausibility.

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Table 1. Biological mediation analyses of TV viewing and mortality (n=5,033)

	Basic model[a]	Basic + CRP	Basic + Fibrinogen	Basic + HbA1C	Basic + HDL-C	Basic + triglycerides
All cause mortality (149 events)						
HR per SD unit[b]	1.24 (1.07, 1.44)	1.20 (1.04, 1.39)	1.21 (1.04, 1.40)	1.24 (1.07, 1.44)	1.24 (1.07, 1.44)	1.24 (1.07, 1.44)
In HR	0.217	0.183	0.190	0.216	0.216	0.216
CVD mortality (29 events)						
HR per SD unit[b]	1.50 (1.11, 2.03)	1.44 (1.06, 1.95)	1.45 (1.07, 1.97)	1.51 (1.11, 2.05)	1.49 (1.10, 2.02)	1.49 (1.10, 2.03)
In HR	0.404	0.361	0.374	0.411	0.398	0.400

[a]adjusted for age, sex, physical activity, smoking, alcohol intake, depressive symptoms, long standing illness, disability (ADLs/IADLs), body mass index, systolic blood pressure.

[b]Hazard ratio (HR) for TV viewing modelled continuously per SD increase (4.2 hrs/d)

Conflict of interest

None of the authors report any conflicts of interest.

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