We appreciate the comments of Macleod and Davey Smith on our article reporting an association between systemic inflammation markers and socioeconomic status. In their letter, Macleod and Davey Smith state that our findings, particularly the association of fibrinogen with socioeconomic status, and its interpretation is not correct, and runs contrary to the principle of “Mendelian randomisation”. As the evidence, they refer to the finding that plasma fibrinogen concentrations are related to a polymorphism in the fibrinogen gene, with the presence of the “T” allele being associated with higher levels. According to the authors, this finding is in keeping with the evidence from controlled trials that suggests that drugs lowering fibrinogen do not decrease the risk of coronary heart disease (CHD) and therefore, the association between plasma fibrinogen and CHD risk is most probably not causal. We believe, however, that the authors have misinterpreted our findings and conclusions to some extent. Firstly, we did not study the relation of fibrinogen to the risk of cardiovascular disease, but our aim was merely to study the association of systemic inflammation markers and socioeconomic status in a cross sectional design. The relation of plasma fibrinogen level to CHD risk has been found in a number of prospective observational studies. Data on clinical trials are scarce, and do not in our understanding justify any conclusions about the causality on the observed association at the moment.

Moreover, we did not state that the fibrinogen-social position link is not a reflection of the social patterning of prevalent disease, or other health related behavioural or biological factors (smoking, obesity, etc.). In our article we said that systemic inflammation is a biologically plausible mediator between socioeconomic status and the risk of cardiovascular disease but our intention was not to state that socioeconomic position as such causes chronic systemic inflammation. Therefore, we concluded also that other factors, which were not included in the analyses, such as prevalent or sub-clinical diseases, and behavioural and environmental factors, such as diet, exercise, and exposure to toxic substances at work or elsewhere, and low birth weight may be involved.

We suspect also that the concept of “Mendelian randomisation”, if used the way the authors are using it, is not going to be very helpful for untangling the causal roles of factors that lead to the disease outcomes. They take one single nucleotide polymorphism (SNP) of a single gene, in this case the fibrinogen β gene, and draw inferences from that to the plasma fibrinogen concentration and to the causal effects of fibrinogen on the CHD risk. This is a simplistic view, which does not take properly into account the complex genetic background of a multifactorial disease. Usually, the repeatability of these single gene-single SNP studies has been poor. As to fibrinogen, there are three genes encoding the fibrinogen molecule, fibrinogen α, fibrinogen β, and fibrinogen γ. At least 157 SNPs are known in these three genes. Further, other genes, such as the IL6 gene, are likely to have an effect on the fibrinogen concentration. There is enormous potential for interactions between these different genetic variants as well as between the genetic variants and “environmental” factors. In addition, pleiotropy and epistasis are common. Therefore, we think that the concept of “Mendelian randomisation” is, in most cases, a cross oversimplification of the underlying biology of a complex, multifactorial disease. We suspect that its applicability is likely to be rare and limited to few special occasions.

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