

PostScript

LETTER

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Fibrinogen, social position, and "Mendelian randomisation"

We appreciate the comments of Macleod and Davey Smith on our article reporting an association between systemic inflammation markers and socioeconomic status.^{1,2} 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 β -fibrinogen gene, with 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 and 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.³

Furthermore, 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.^{4,5}

Furthermore, 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, pleiotropism 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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BOOK REVIEW

The politics of the healthy life: an international perspective

Edited by E Rodríguez-Ocaña. Sheffield: European Association for the History of Medicine and Health Publications, 2002, £37.92, pp 288. ISBN 0-9536522-5-4

The first part of the 20th century is a fascinating period in the history of public health. In the north Atlantic countries mortality decline accelerated and social gradients in survival chances steepened. The pace of health improvement was set not by technical advance but by social reorganisation.

The essays gathered together in this book mostly centre on this period with the six essays of the second part, on "the international theatre and the locus of expertise", being of special interest. Paul Weindling deals with the transition from "moral exhortation to the new [sic] public health, 1918-45", instancing especially the Rockefeller medicine men who "advanced holistic initiatives in community health, and generated a wave of radical experimentation on how to measure health and produce the healthy life in the modern mass society" (page 127). Moser and Fleischacker show how the intellectual response among German hygienists to the demographic shock of the first world war prepared the ground for the German medical profession's embrace of "racial hygiene" in the 1930s. Murard and Zylberman present a dense and colourful account of the French "public health map" in the 1930s—including the "road not taken" to socialist medicine. The public health leader Hazemann, although a member of the Communist Party, heaped "praise on planning by, not Soviet, but American hygienists": "Some day, mathematical formula will replace social relations". Gillespie offers a fascinating account of the creation of the WHO after the conflagration of the second world war, concentrating on the central roles of the US and the UK. Hostility to international agencies was rising in the US and they were especially determined that medical insurance should not be a topic of international deliberation. The US Congress had still not relaxed its opposition to full US participation in the WHO on the eve of the first World Health Assembly in 1948. The WHO played it safe and "spent its first two decades absorbed in disease eradication campaigns and technical work on standards and nomenclature" (page 234). A consolidated bibliography and an introductory essay by the editor add further value to this work.

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