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Published by Oxford University Press on behalf of the International Epidemiological Association

International Journal of Epidemiology 2009;**38**:787–790
doi:10.1093/ije/dyp187

Commentary: Understanding the pathophysiology of poverty

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Accepted 12 March 2009

Simanek *et al*.'s article in this issue of the Journal[1] brings together two fields of research, both of which have a long history and have recently enjoyed a resurgence of interest. The first is the infectious hypothesis of atherosclerosis and the second is the social determinants model for cardiovascular disease (CVD).

The hypothesis that infections might be involved as aetiologic factors in CVD dates back to the late 1800s, though it all but disappeared for most of the 20th century. Interest in his hypothesis, however, surged again during the last two decades of the century, when both experimental and epidemiologic evidence documented its plausibility.[2–4] Similarly, even though discussion of the social determinants of health dates back to the very origins of public health,[5] newcomers to this field might be surprised to learn that there was a time, not long ago, when 'social epidemiology' did not exist as a distinct subspecialty. The recently published 5th edition of Last's 'A Dictionary of Epidemiology' (now edited by M. Porta) is the first one to include the term.[6] Furthermore, a PubMed search using 'social epidemiology' as a single keyword returns only two citations in the entire 1960s decade, six in the 1970s, several more in the 1980s and 1990s, and then a sharp epidemic-like surge starting at the turn of the century (Figure 1).

It is also worth noting that this surge in social epidemiology research coincides with the rapid emergence of 'health disparities' as a priority among public health goals for the USA (Figure 1). Whereas health disparities were not even mentioned among the 1990 US Health Objectives, *reducing* health disparities was one of three overarching goals for

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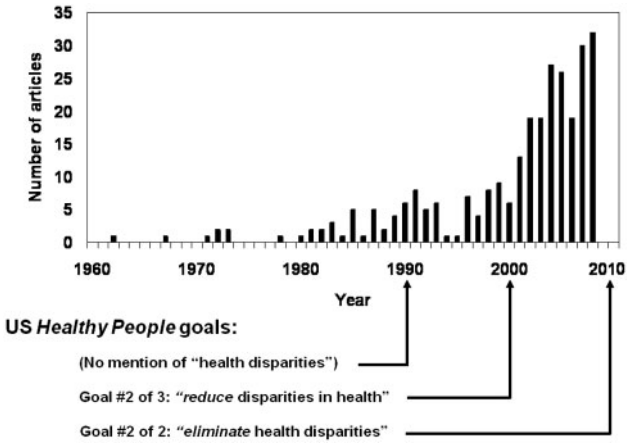

Figure 1 The epidemic of social epidemiology research. The top of the figure graphs the number of articles per year in a PubMed search with 'social epidemiology' as the keyword (1960–2008). The bottom half of the figure shows the chronology of use of the term 'health disparities' in the US 1990 Health Objectives, Healthy People 2000 and Healthy People 2010[7]

Healthy People 2000, and *eliminating* health disparities is one of the two goals for Healthy People 2010.[7] It is not clear whether academic attention to the subject is promoting the increased prominence of social epidemiology in the national public health agenda or the reverse, but this question might provide for a spirited epidemiological debate. Nevertheless, there is no question that this plethora of research over the last few decades has produced overwhelming evidence demonstrating that socio-economic position over the life course is a key upstream determinant of health and disease outcomes.[5,8–10] Furthermore, responding to earlier criticisms,[11–13] the discipline has recently been moving more and more beyond the 'black-box'[14] and purely descriptive approaches (e.g. 'being poor is bad for your health'), and trying to find ways to explain *why* social position is so strongly and consistently associated with practically every conceivable health outcome. The hope is that if we understand the mechanisms, more effective ways to alleviate the ill effects of health disparities could be identified.

Most previous attempts for understanding the pathophysiology of poverty have focused mainly on conventional CVD risk factors (smoking, diabetes, hypertension, dyslipidaemias and psycho-behavioural characteristics). Surprisingly, even though a majority of subjects with clinical CVD has at least one of the well-established risk factors,[15] in relative terms, only a small fraction of CVD incidence (15–40%) appears to be explained by the conventional risk factors.[16,17]

Simanek *et al*.'s article explores the possible mediating role of a relatively novel putative risk factor for CVD, namely chronic herpes virus infections. The rationale for this analysis is straightforward: herpes virus infections are more prevalent among individuals in lower socioeconomic position[18,19] and evidence from basic laboratory, pathology and epidemiology research has shown that these infections (especially cytomegalovirus, or CMV) are associated with clinical and subclinical CVD.[20–22]

Simanek *et al*. used cross-sectional data from the US National Health and Nutrition Examination Survey (NHANES) and a series of logistic regression models to explore the mutual associations between socioeconomic position (measured by educational level), CMV seroprevalence, and self-reported history of CVD. Confirming results from previous research, they found that socioeconomic position is associated with CVD independently of other covariates. Consistent with the author's hypothesis, the odds ratio for the association between lower education and CVD was reduced by ~8% (from 1.83 to 1.69) when CMV infection was added to the model. This attenuation in the odds ratio (OR) was statistically significant and interpreted as evidence that CMV infection partially mediates the relation between socioeconomic position and CVD. The alternative hypothesis (namely, that socioeconomic position is a confounder of the association between CMV infection and CVD) was ruled out by the fact that the CMV–CVD association was still significant after controlling for educational level [OR = 1.75, 95% confidence interval (CI) 1.21–2.54].

As Simanek *et al*. recognize, this interpretation is potentially limited by the problem of uncontrolled confounding. Like other infections, CMV seroprevalence is correlated with many other markers of poor health, including, but not limited to, the CVD risk factors considered in this study. Noticeably absent in these analyses is hypercholesterolaemia, even though CMV prevalence has been associated with high cholesterol levels in other studies.[18] Furthermore, potential confounders such as BMI, diabetes and smoking were dropped from some of the models because they were not associated with CVD and/or with infections in these cross-sectional analyses. The latter, however, might be an artefact of study design. For example, youth body mass index might truly be related to CMV infection during the life-course and to the risk of CVD in later life—and thus be a true confounder; yet, when analysed cross-sectionally (after CVD has occurred) this association might not be apparent due to survival bias or reverse causation. On the other hand, cross-sectional biases might be operating in opposite ways as well; e.g. if infections are associated with decreased survival among people with CVD as suggested by previous studies,[23,24] then the risk ratios estimated from cross-sectional data tend to underestimate the true relative risk.

With these caveats in mind, the most striking finding of Simanek *et al*.'s study is that the relatively modest OR of CVD associated with CMV infection translates into an estimate of the population attributable risk or attributable fraction of CVD of ~40%. As

the authors point out, this is a result of the high prevalence of this infection in this study (~88%), which is in line with previously published results in other populations.[18,19] For risk factors with prevalence close to 90%, even modest relative risks (e.g. 1.5–2.0) will result in attributable fraction estimates comparable with that of a risk factor affecting 10% of the population and associated with a relative risk of ~7.0–8.0, or to a risk factor affecting 5% of the population with a relative risk ~15.0. What is striking about this 40% attributable fraction estimate is the implication that eliminating CMV infection would prevent as many CVD cases as the complete removal of smoking and almost twice as many as the elimination of either hypercholesterolaemia or hypertension from the population.[25]

Is this a realistic conclusion? Simanek *et al*. properly acknowledge the strong assumptions involved in the interpretation of attributable fraction estimates, namely the need to assume that the relation between CMV infection and CVD is causal in nature. Given the complex pathophysiology of atherosclerosis, it is also unrealistic to assume that CMV or any other putative CVD risk factor would act independently of other risk factors. In Nilsson *et al*.'s analysis of data from the Malmö preventive project, the constellation of conventional risk factors accounted for >100% of the population CVD risk,[25] an obviously absurd result, which highlights the pitfalls associated with this type of estimate when applied to complex multifactorial diseases such as atherosclerosis.[26,27]

The implication of this particular finding, however, is especially significant because, according to Simanek *et al*., 'it is realistic to conceive that we could attain 'unexposed' status among those currently exposed through primary prevention measures such as vaccination without necessarily altering other conventional CVD risk factors, such as smoking and diabetes.'[1] If CMV infection is eventually proven to be causally related to CVD, then the development and mass administration of a CMV vaccine could have a profound impact on reducing the population CVD burden. However, aiming at preventing one single infection as a means of reducing CVD might be a futile endeavour if, as suggested by Simanek *et al*., multiple infections might have atherogenesis potential. CMV is only one of the many microbes that have been implicated in previous laboratory and epidemiological studies. In Simanek *et al*.'s study, the association with herpes simplex virus type-1 was only slightly weaker than that for CMV but, somewhat simplistically,[28] dismissed as 'non-significant' because the lower bound of the 95% confidence interval barely included the null value (adjusted OR 1.51, 95% confidence interval 0.99–2.31). Moreover, in addition to herpes viruses, historically, many other common pathogens have been found capable of infecting and inducing inflammatory changes in arterial tissue.[2,4,24,29] The laboratory and epidemiologic evidence in support of *Chlamydia pneumonia* as an atherogenic agent is at least as strong or stronger than that for CMV.[30–32] Epstein *et al*.'s 'pathogen burden' model represents an attempt to quantitatively demonstrate this generic infectious hypothesis,[24] but has not always produced consistent results.

Despite the disappointing negative results from recent randomized controlled trials testing whether antibiotics are effective for the secondary prevention of CVD,[33–36] evidence supporting the role of infections in early stages of atherogenesis remains strong.[37–39] However, even if the role of infections in atherogenesis is eventually proven, the practical implications for primary prevention are uncertain, as mass use of antibiotics might not be feasible due to costs, risks of antibiotic resistance and lack of efficacy for the treatment of certain infections (e.g. viral).

It is clear that there are many unresolved issues in these areas of research. Consequently, the hypotheses and questions posed by Simanek *et al*. are highly relevant; they represent a step forward toward the goal of better understanding of the complex relation between socioeconomic position and CVD. The fact that their results seem to raise more questions than answers leads us nowhere but back to the well-worn researchers' mantra: 'further research is needed.'

Funding

University of Wisconsin Institute for Clinical and Translational Research and the Wisconsin Partnership Program (to F.J.N., partial).

Acknowledgements

The author is grateful to Marion Ceraso and Patrick Remington for their useful criticism of earlier versions of this manuscript and to Patty Grubb for her editorial assistance.

Conflict of interest: None declared.

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