Commentary: It’s not all means and genes—socio-economic position, variation and genetic confounding

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The article by Johnson et al.1 makes two important contributions. First, it demonstrates the value of examining variation in health as a phenomenon of interest in and of itself. Secondly, it provides empirical evidence challenging the assertion that the association of socio-economic position and health is due primarily to shared genetic predispositions. Both contributions have important implications for future studies related to socio-economic exposures and population health.

Difference in variance

Johnson and colleagues find greater variation in physical health at lower levels of socio-economic position. In line with Johnson et al., studies examining multiple causes of mortality have also found both lower mean levels of health and more variation in health in more socio-economically deprived areas.2,3 Their study shows this effect in Denmark, which, compared with the USA or the UK, has a shallower socio-economic gradient and stronger safety nets to buffer potential health consequences of low socio-economic position.

In most research, variance across predictor variables is examined only to check for meeting the required assumptions of regression models. However, Levins brought to public health the concept of variance itself as a useful and critical metric of analysis in addition to the mean4 and its utility has been shown in relation to physiological markers.2 Johnson et al. extend this contribution by explicitly modeling genetic and environmental contributions to this difference. Their finding that most of the increased variance at lower levels of education is due to genetic factors points to genetics to explain why some individuals remain healthy at low levels of education while others do not. This runs counter to the idea that adversity may trump a favourable genetic profile. For example, under conditions of drought and food scarcity, the majority show stunted growth and genetics contributes less to height than when a population has adequate nutrition.5 Given this, one might expect a smaller genetic contribution to health for those with low education, rather than the larger impact found by Johnson et al.

While we applaud this research, we question the implications suggested by the authors of finding greater variation in health among those with less education. They interpret these to indicate that to increase population health, ‘helping individuals to manage their own health will likely be more effective’.1 However, the study includes no behavioural correlates of education and cannot determine how best to intervene. It does, however, provide more impetus for action. Improvements in the environment are more likely to engender health benefits where there is more sensitivity to conditions. Levins and Lopez6 suggest that interventions have greater potential for producing change where there is greater variance. The findings by Johnson et al. thus provide further justification for increased attention to the health of less advantaged populations, even though they do not establish what aspects of the environment or behaviour would be most effective in reducing variation. Identifying populations with higher variance on health, and greater capacity to change, may help target resources. In sum, examination of variance (along with non-linearities of mean associations7)
Genetic causation

Johnson et al. also find that prior common causes of education and health are not due to genotype at the lower end of the education distribution. They find confounding by genotype greater at high education (their figure 4), although with only a very small contribution to overall variance. This finding is critical because there is active (and unsupported) speculation regarding the extent to which unmeasured genetic factors may be prior common causes of both socio-economic position and health. This is one of the first studies to provide a rigorous quantitative test of this assertion. They find that at low levels of education genetic confounding of physical health is unlikely. This finding supports the utility of social and environmental interventions since it rules out a genetic prior common cause as reason for the observed associations.

Two caveats apply to this finding. First, the study does not assess confounding other than by age, and the association of education and health could be caused by a number of environmental and/or individual factors. Secondly, a general physical health outcome may mask genetic confounding of specific causes of death due to the aggregation (and therefore mismeasurement) of specific outcomes.

Considerations for future work on variation in health

Johnson et al. provide a useful model for thinking about variation and its sources. However, more work is needed before concluding that their findings represent a general phenomenon. Basic genetics work shows examples of strong non-linearities in environment effects dependent on genotype. An early experiment in which a selection of genetic clones of Potentilla glandulosa were planted at different elevations in the Sierra Nevada mountains showed that effects of the environment differed across genotype in a non-linear manner, with some genotypes growing better at low altitudes and some better at high altitudes.8

Prior studies in humans (including this one by Johnson and colleagues) may be underpowered to find these types of effects in human populations. The Danish twins study is one of the largest twin databases available. Yet even within this cohort there were extremely wide confidence intervals on some findings (e.g. the analysis of genetic confounding among men), lessening confidence in the results. Limitations in sample size can result in spurious findings between estimates of the effect of social environmental factors and particular gene variants and health outcomes.9 Large-scale studies will be needed, such as the Kaiser Permanente Research Program on Genes Environment and Health, which aims to collect socio-economic and genetic data on 500,000 individuals.10 Additional data linkages to social, contextual and economic time series data will also be necessary to provide more definitive answers to these questions.

Nevertheless, in this important work, Johnson et al. have demonstrated that non-gene specific descriptive work has the ability to offer important new insight into novel metrics for epidemiology, and to offer evidence against old speculative hypotheses of genetic confounding of socio-economic position and general health.

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References


