Summary points

Observational epidemiological studies have often identified spurious apparent causes of disease

Confounding has probably contributed to many of these misidentifications

Genetic variants that proxy for environmentally modifiable risk factors are not subject to confounding

Mendelian randomisation (use of genetic variations as proxies for modifiable risk factors in observational studies) is a powerful new strategy in epidemiology

in tissue structure and function that counterbalance its effects—so called canalisation.⁷

Conclusion

Study of genetic variants can lead to inferences on how population-wide changes in environmental exposures could reduce risk of disease.^{17–20} Importantly, the inferences are concerned with attribution of causality that is relevant to whole populations and are not concerned with targeting interventions on those with specific genetic variants. By applying the increasing knowledge of human genetics, it is possible to improve knowledge of how diverse environmental exposures, many of which are socially patterned, shape population health and where future public health prevention should be targeted.

We thank Nancy Krieger, John Lynch, and Neil Pearce for their comments.

Contributors and sources: GDS and SE are experienced epidemiologists who have set up and maintain large observational cohort studies. Both authors planned the content and drafted the manuscript. The authors reviewed every hit produced by “Mendelian randomisation” and “Mendelian randomization” on

Google and Google Scholar and all Web of Science citations to key references.

Competing interests: None declared.

- 1 Le Fanu J. *The rise and fall of modern medicine*. New York: Little Brown, 1999.
- 2 Lawlor DA, Davey Smith G, Ebrahim S. The hormone replacement–coronary heart disease conundrum: is this the death of observational epidemiology? *Int J Epidemiol* 2004;33:464–7.
- 3 Lawlor DA, Davey Smith G, Kundu D, Bruckdorfer KR, Ebrahim S. Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet* 2004;363:1724–7.
- 4 Little J, Khoury MJ. Mendelian randomization: a new spin or real progress? *Lancet* 2003;362:930–1.
- 5 Clayton D, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 2001;358:1356–60.
- 6 Keavney B. Genetic epidemiological studies of coronary heart disease. *Int J Epidemiol* 2002;31:730–6.
- 7 Davey Smith G, Ebrahim S. “Mendelian randomization”: can genetic epidemiology contribute to understanding environmental causes of disease? *Int J Epidemiol* 2003;32:1–22.
- 8 Takagi S, Iwai N, Yamauchi R, Kojima S, Yasuno S, Baba T, et al. Aldehyde dehydrogenase 2 gene is a risk factor for myocardial infarction in Japanese men. *Hypertens Res* 2002;25:677–81.
- 9 Davey Smith G, Harbord R, Ebrahim S. Fibrinogen, C-reactive protein and CHD: does Mendelian randomization suggest the associations are non-causal? *Q J Med* 2004;97:163–6.
- 10 Cherry N, Mackness M, Durrington P, Povey A, Dipnall M, Smith T, Mackness B. Paraoxonase (PON1) polymorphisms in farmers attributing ill health to sheep dip. *Lancet* 2002;359:763–4.
- 11 Botto LD, Yang Q. 5, 10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. *Am J Epidemiol* 2000;151:862–77.
- 12 Davey Smith G, Ebrahim S. Mendelian randomization: prospects, potentials and limitations. *Int J Epidemiol* 2004;33:30–42.
- 13 Colhoun H, McKeigue PM, Davey Smith G. Problems of reporting genetic associations with complex outcomes. *Lancet* 2003;361:865–72.
- 14 Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence of causality from a meta-analysis. *BMJ* 2002;325:1202–6.
- 15 Wald NJ, Law MR. A strategy to reduce cardiovascular risk by more than 80%. *BMJ* 2003;326:1419–23.
- 16 Frederiksen J, Juul K, Grande P, Jensen GB, Schroeder TV, Tybjaerg-Hansen A et al. Methylenetetrahydrofolate reductase polymorphism (C677T), hyperhomocysteinemia, and risk of ischemic cardiovascular disease and venous thromboembolism: prospective and case-control studies from the Copenhagen city heart study. *Blood* 2004;104:3046–51.
- 17 Katan MB. Mendelian randomization, 18 years on. *Int J Epidemiol* 2004;33:10–11.
- 18 Tobin MD, Minelli C, Burton PR, Thompson JR. Development of mendelian randomization: from hypothesis test to “mendelian deconfounding”. *Int J Epidemiol* 2004;33:26–9.
- 19 Brennan P. Mendelian randomization and gene-environment interaction. *Int J Epidemiol* 2004;33:17–21.
- 20 Keavney B. Katan’s remarkable foresight: genes and causality 18 years on. *Int J Epidemiol* 2004;33:11–4.

(Accepted 4 February 2005)

Trouble comes in twos

We recently admitted two cases of tuberculous meningitis to our hospital within a week. Although this is an urban area, the condition is by no means common here. Both patients presented with confusion and a right sixth nerve palsy. One patient recovered fully, but the other remains affected. We applied the lessons we learnt from the first case to the second. The literature on the condition has been read, re-read, and consolidated.

In the past year we have admitted two cases of wound botulism to our hospital. Both occurred after “skin-popping” (injecting heroin subcutaneously when intravenous access is no longer easy). This rare condition has an annual incidence of 20 cases.¹ In the first case we did make the diagnosis for some time, thus missing an opportunity for prompt treatment with the antitoxin. The second case presented at 7 am and was diagnosed and treated by 2 pm. The doctors who made the diagnosis in the second case remembered the first and made an instant diagnosis. This enabled early administration of the antitoxin, which is known to reduce mortality and morbidity particularly if given at the onset of symptoms.²

Some years ago, I worked as a senior house officer in accident and emergency. I remember thinking that patients’ diseases were like buses; you don’t see something for months, then three cases come at once—a day of suturing right thumbs or a day of cardioverting ventricular tachycardias. As the years have passed such groupings seem to have changed. These days I treat two pneumothoraces in a day or two patients with tuberculosis. Sometimes I feel that someone somewhere is hoping to educate us. See one, learn from it, and treat one perhaps?

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- 1 Health Protection Agency. *Wound botulism cases in injecting drug users*. www.hpa.org.uk/infections/topics_az/botulism/Wound_Bot_Info.pdf (accessed 17 Mar 2005).
- 2 Chang G, Ganguly G. Early antitoxin treatment in wound botulism results in better outcome. *Eur Neurol* 2003;49:151–3.