

Commentary: Incubation of coronary heart disease—recent developments

Peter McCarron^{1*} and George Davey Smith²

Over 20 years ago Geoffrey Rose, using data from the Seven Countries' study,¹ reported that ecological correlations between cholesterol levels (and to a lesser extent blood pressure) and coronary heart disease (CHD) mortality were stronger for cholesterol measured many years before mortality was assessed, than if contemporaneous cholesterol measures and CHD mortality were correlated. Commenting for a tobacco company soon after publication, Peter Lee, criticized the analyses, and dismissed the evidence Rose used to propose that CHD has at least a 10 year incubation time as being 'so weak as not to be worth publishing'.² Rose, however, was aware of many of the weaknesses, and, anticipating Lee's final comment, advised that individual-level comparison of long-term and short-term predictive power should be undertaken.

Three main hypotheses flow from Rose's conclusions. First, CHD is set in train long before it manifests clinically; second, measuring risk factors earlier in life provides a better measure of risk than relying on later measures; and third, at any level of CHD risk factors in late adulthood, those who have not been exposed in early years will have lower risk of CHD. Although he highlighted several statistical weaknesses, Lee himself was not wholly dismissive of the paper, accepting that 'some or all of the conclusions may be true'.² Here we attempt to examine the truth of Rose's conclusions.

Evidence for the early origin of CHD

Rose's findings were published at a time when CHD epidemiology was overwhelmingly focused on the role of mid-life behavioural, physiological, and social factors. However, it was becoming clear that this approach could not fully account for CHD distribution by social class, geographical region, or ethnic group. There was also disappointing news for advocates of prevention of CHD by risk factor modification in later life: published just five months after the Rose paper, the Multiple Risk Factor Intervention Trial found that intensive multi-factorial intervention produced no reduction in CHD event rate.³ These findings alerted some investigators to strands of research conducted over the previous 50 years that had suggested that CHD risk originated early in the life course.⁴

Autopsies of soldiers who were killed in the Korean and Vietnam wars demonstrated that atherosclerosis was already present in young men,^{5,6} and in Norway, Anders Forsdahl, showed that areas with high infant mortality rates in the early part of the 20th century had high CHD rates 70 years later. These results lead Forsdahl to propose that deprivation in early life increased risk of later CHD.^{7,8}

Two large US research programmes confirmed the earlier autopsy findings. In the Pathological Determinants of Atherosclerosis in Youth (PDAY) study, fatty streaks and fibrous plaques were observed at post-mortem in population-representative 15–34 year olds who succumbed to external causes, the prevalence and size of the lesions increasing with age.⁹ Elaborating on these findings, researchers in Bogalusa, Louisiana discovered that among children and adolescents who died in young adulthood from accidents, homicides, or suicides, CHD risk factors measured years earlier were associated with atherosclerotic lesions.^{10,11} On the other side of the Atlantic, Barker and colleagues in Southampton, England, capitalized on the availability of records of babies born in the early 20th century to refine the insights of Forsdahl.^{12,13} They established that intrauterine and childhood development contribute to later cardiovascular risk, and proceeded to hypothesize that *in utero* biological programming—due to maternal and fetal under-nutrition—had deleterious long-term health consequences. Other epidemiologists, while recognizing that early life exposures were important, discovered that investigation of the accumulation and interaction of exposures from before birth and then across the life course gave added insight into the mechanisms of cardiovascular risk.^{14,15}

Lag period and CHD risk

Indirect assessment, of the finding that the correlation between cholesterol level and disease risk strengthened over time, had to wait until 10 years after Rose's initial report. In attempting to account for the paradox of lower CHD rates in France compared with those in UK, despite both countries having broadly similar saturated fat intake and cholesterol levels, Nestle¹⁶ and, then in greater detail, Law and Wald¹⁷ proposed that the French were at lower risk of coronary death because of their previously much lower exposure to dietary lipids. Consistent with this, was the finding that mortality from CHD in France correlated strongly with levels of animal fat consumption and serum cholesterol in the past, but only weakly with recent levels.¹⁷ This finding lends weight to Rose's notion of the temporal strengthening of risk and the existence of an incubation period, and while not stated by the authors, also supports the hypothesis that early life exposure—in the French population, exposure to low levels of cholesterol—affects future health. The phenomenon is also witnessed in randomized controlled trials of cholesterol lowering, which show that the relative reduction in CHD risk amongst those allocated to statins increases with duration of treatment.¹⁸

Direct evidence from individual-level studies took a little longer to accrue but it is now clear that the strengthening in exposure–disease correlation over time was not simply the

¹ Department of Epidemiology and Public Health, Queen's University Belfast, Mulhouse Building, Grosvenor Road, Belfast, Ireland BT12 6BJ, UK.

² Department of Social Medicine, University of Bristol, Bristol, UK.

* Corresponding author. E-mail: Peter.McCarron@qub.ac.uk

result of random fluctuations or the ecological fallacy. Follow-up of the Bogalusa cohorts demonstrated that several traditional risk factors, in particular childhood low-density lipoprotein cholesterol (LDL-C) level and body mass index (BMI), predicted increased carotid intima-media thickness (IMT) in adulthood, and that this was as good as, and independent of, prediction derived from current adult measures of these risk factors.¹⁹ Similarly, findings from Finland indicated that risk factors in childhood and the early teenage years are associated with permanent damage to the arterial wall after accounting for current risk factors.²⁰ Substantiating Rose's original notion, serial measurements of risk factors over many years in these studies did not predict carotid IMT appreciably better than measurements obtained in childhood.

Early life salutogenic profile and later disease risk

If deleterious exposures in early life confer increased coronary risk, does their absence at that period result in coronary benefit? Again, indirect affirmative evidence is available, a corollary of the lag-time hypothesis being that reduced exposure to cardiovascular risk in early life is associated with lower coronary mortality in later years.^{16,17} Direct evidence has also accumulated. In reports over the last few years from large prospective cohorts with long-term follow-up into older age, multiple favourable consequences of baseline low-risk status have been delineated, first in young men,²¹ and subsequently in young women.²² Broadly similar results were noted in each group: individuals who in earlier life had low levels of cholesterol, blood pressure, and smoking experienced less subclinical coronary atherosclerosis,²³ and lower risk of CHD.²⁴

Attenuation by errors

Single measures of cholesterol, whether in earlier or later life, will be poor proxies for long-term average cholesterol that appears to underlie the development of atherosclerosis and CHD risk.^{25–27} Klag and colleagues demonstrated this effect empirically. In a follow-up of the Johns Hopkins Precursor Study, the relative risk of coronary death using the average (the mean of measurements 1–11) cholesterol level was 2.01 per 0.93 mmol/l (36 mg/dl) increase in serum cholesterol, which was attenuated to 1.77 when the single baseline measure was substituted.²⁸ Better estimation of usual level also appears to increase predictive ability for blood pressure.²⁹ Recent analyses of the combined contribution of usual measures of cholesterol, blood pressure, and cigarette smoking, simultaneously accounting for regression bias, demonstrated that at least 80% of major CHD events in middle-aged men could be attributed to these three risk factors.³⁰ This figure is in keeping with the remarks of Magnus and Beaglehole that novel cardiovascular risk factors have little to contribute to disease prevention.^{31,32} The novel factor that does need to be taken into account is, rather, the life course levels of the classical risk factors, as Rose's work and these recent analyses suggest. However, this begs the question as to the distal determinants of these conventional risk factors, and here processes such as programming during fetal life or infancy could play important roles.

Application of Mendelian randomization

Genetic analyses now saturate epidemiological studies and will continue to do so. Determining which studies are best for which questions is an important task for the immediate future. One fruitful avenue of research may be to utilize Mendelian randomization. Since analysis of genetic variants associated with a difference in intermediate phenotypes such as cholesterol levels or blood pressure will index lifetime differences in such exposures they will therefore yield estimates that are not susceptible to attenuation by errors.³³ Such risk estimates will have more robust predictive power than coefficients based on single measures of risk.³⁴ Some limited empirical data are available for cholesterol; for example, lifetime differences in cholesterol levels generated by genetic variants such as that underlying familial defective apolipoprotein B are consistent with considerably greater effects of lifetime cholesterol levels than are seen with single measures.^{33,34}

Preventing future incubation of CHD

It should be apparent that epidemiological research over the last 20 years has supported Rose's insights into the nature of coronary disease origin and progression. Undoubtedly, better studies, such as the large cohort studies underway in Europe^{35,36} and the US,³⁷ along with more sophisticated modelling, including the incorporation of genetic analysis, will lead to more precise unravelling of the nature and timing of CHD risk onset. But, Rose's 'short and very superficial paper',² has proven remarkably prescient and it also points the way towards potentially more successful prevention, starting in childhood. Moreover, the time for this is now, since along with warnings about the imminent epidemic of CHD in developing countries,³⁸ the large secular increases in obesity levels in Europe and the US also give cause for concern that the hard-won decline in the coronary disease burden in the developed world may not continue indefinitely. The measures needed to achieve these goals are unfortunately neither easy to implement, nor glamorous, but as Rose stated, 'what they lack in excitement they gain in their potential impact on health, precisely because they deal with the major causes of common disease and disabilities'.³⁹ His remark that the barriers to achieving these goals 'are substantially economic, industrial, and political' still holds true today. Indeed, the surging levels of childhood overweight give an indication of the need for action. Yet the initially half-hearted measures undertaken prompt concern that preventive programmes have, like CHD, a long incubation period.

Acknowledgements

P.M. is supported by a career scientist award funded by the Research & Development Office for Health and Personal Social Services in Northern Ireland.

References

- ¹ Coronary heart disease in seven countries. *Circulation* 1970;**41**–**42** (Suppl.):1–211.
- ² Lee PN. Paper 111: Incubation period of coronary heart disease. Available at: http://tobaccodocuments.org/mayo_clinic/23_156.html.

- ³ Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. *JAMA* 1982;**248**:1465–77.
- ⁴ Kuh D, Davey Smith G. The life course and adult chronic disease: an historical perspective with particular reference to coronary heart disease. In: Kuh D, Ben-Shlomo Y (eds). *A Life Course Approach to Chronic Disease Epidemiology*, 2nd edn. Oxford: Oxford University Press, 2004, pp. 15–41.
- ⁵ Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea. *JAMA* 1953;**152**:1090–93. (Reprinted *JAMA* 1986;**256**:2859–62.)
- ⁶ McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. *JAMA* 1971;**216**:1185–87.
- ⁷ Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prev Soc Med* 1977;**31**:91–95.
- ⁸ Forsdahl A. Living conditions in childhood and subsequent development of risk factors for arteriosclerotic heart disease. The cardiovascular survey in Finnmark 1974–75. *J Epidemiol Community Health* 1978;**32**:34–37.
- ⁹ Strong JP, Malcom GT, McMahan CA *et al.* Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA* 1999;**281**:727–35.
- ¹⁰ Berenson GS, Wattigney WA, Tracy RE *et al.* Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart Study). *Am J Cardiol* 1992;**70**:851–58.
- ¹¹ Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med* 1998;**338**:1650–56.
- ¹² Barker DJP. *Fetal and Infant Origins of Adult Disease*. London: BMJ Publishing, 1992.
- ¹³ Barker DJP. *Mothers, Babies and Health in Later Life*. London: Churchill Livingstone, 1998.
- ¹⁴ Davey Smith G, Kuh D. When is mortality risk determined? Historical insights into a current debate. *Soc His Med* 1993;**6**:101–23.
- ¹⁵ Kuh D, Ben Shlomo Y (eds). *A Life Course Approach to Chronic Disease Epidemiology*. Oxford: Oxford University Press, 2004.
- ¹⁶ Nestle M. Wine and coronary heart disease. *Lancet* 1992;**40**:314–15.
- ¹⁷ Law M, Wald N. Why heart disease mortality is low in France: the time lag explanation. *BMJ* 1999;**318**:1471–76.
- ¹⁸ Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
- ¹⁹ Li S, Chen W, Srinivasan SR *et al.* Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA* 2003;**290**:2271–76.
- ²⁰ Raitakari OT, Juonala M, Kähönen M *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA* 2003;**290**:2277–83.
- ²¹ Stamler J, Stamler R, Neaton JD *et al.* Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA* 1999;**282**:2012–18.
- ²² Daviglius ML, Stamler J, Pirzada A *et al.* Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *JAMA* 2004;**292**:1588–92.
- ²³ Daviglius ML, Pirzada A, Liu K *et al.* Comparison of low risk and higher risk profiles in middle age to frequency and quantity of coronary artery calcium years later. *Am J Cardiol* 2004;**94**:367–69.
- ²⁴ Rosengren A, Dotevall A, Eriksson H, Wilhelmsen L. Optimal risk factors in the population: prognosis, prevalence, and secular trends; data from Goteborg population studies. *Eur Heart J* 2001;**22**:136–44.
- ²⁵ Davis CE, Rifkind BM, Brenner H, Gordon DJ. A single cholesterol measurement underestimates the risk of coronary heart disease. An empirical example from the Lipid Research Clinics Mortality Follow-up Study. *JAMA* 1990;**264**:3044–46.
- ²⁶ Tornberg SA, Jakobsson KF, Eklund GA. Stability and validity of a single serum cholesterol measurement in a prospective cohort study. *Int J Epidemiol* 1988;**17**:797–803.
- ²⁷ Clarke R, Shipley M, Lewington S *et al.* Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;**150**:341–53.
- ²⁸ Klag MJ, Ford DE, Mead LA *et al.* Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med* 1993;**328**:313–18.
- ²⁹ Hart CL, Hole DJ, Davey Smith G. Are two really better than one? Empirical examination of repeat blood pressure measurements and stroke risk. *Stroke* 2001;**32**:2697–99.
- ³⁰ Emberson JR, Whincup PH, Morris RW, Walker M. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. *Eur Heart J* 2003;**24**:1719–26.
- ³¹ Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the ‘only-50%’ myth. *Arch Intern Med* 2001;**161**:2657–60.
- ³² Beaglehole R, Magnus P. The search for new risk factors for coronary heart disease: occupational therapy for epidemiologists? *Int J Epidemiol* 2002;**31**:1117–22.
- ³³ Davey Smith G, Ebrahim S. ‘Mendelian randomization’: can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003;**32**:1–22.
- ³⁴ Davey Smith G, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* 2004;**33**:30–42.
- ³⁵ ALSPAC. Children of the nineties. Available at: <http://www.alspac.bristol.ac.uk/>.
- ³⁶ Olsen J, Melbye M, Olsen SF *et al.* The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health* 2000;**29**:300–7.
- ³⁷ The National Children’s Study. Available at: <http://www.nationalchildrensstudy.gov/>.
- ³⁸ Murray CJL, Lopez AD (eds). *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020*. Cambridge, USA: Harvard University Press on behalf of WHO and the World Bank, 1996.
- ³⁹ Rose Geoffrey. *The Strategy of Preventive Medicine*. Oxford: Oxford University Press, 1992.