increasing in those parts of the world that have so far been spared.

Acknowledgements
Written with warm recollections of my co-author, colleague and friend, Ken Jones.

Conflict of interest: None declared.

References

Commentary: Shaper and Jones, ‘Serum-cholesterol, diet and coronary heart-disease in Africans and Asians in Uganda’: 50-year-old findings only need interpretational fine tuning to come up to speed!

Neil R. Poulter* and Nishi Chaturvedi

International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, UK

*Corresponding author. International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, 59-61 North Wharf Road, London W2 1LA, UK. E-mail: n.poulter@imperial.ac.uk

Accepted 24 July 2012

Comparison of risk factors and of disease between populations, investigation of particularly high- or low-risk populations, and the study of migrant populations, have provided significant valuable insights into the aetiology of disease. The classical Seven Country Study of Ancel Keys noted the marked inter-country differences in total cholesterol, which mapped to inter-country differences in coronary heart disease (CHD). 3 Comparison of Japanese migrants to Honolulu and USA with Japanese men in Japan demonstrates the marked effect of dietary changes on total cholesterol, and the pivotal role of lipids in determining the different reported CHD event rates at the population level of Japanese men in these three settings. 2

In 1959, Shaper and Jones 3 exploited the natural experiment of two ethnic groups—Africans and Indian Asians—living in Uganda, with apparently marked differences in CHD events. They compared ethnic differences in serum cholesterol and reported two striking and distinct findings. Firstly, Africans had significantly lower serum cholesterol than Indian Asians, and secondly, an age-related increase in cholesterol was only apparent in Indian Asians.

Favourable cholesterol levels, and indeed lipoprotein profiles, have been and continue to be observed in people of Black African descent worldwide. 4–8 Similarly, adverse lipid profiles have been consistently reported among Indian Asian populations wherever they have been studied around the world. 9–11 Shaper and Jones anticipated interest in lifecourse epidemiology by several decades, demonstrating that ethnic differences in serum cholesterol, which they observe in childhood, are maintained in middle age, and propose, therefore, that explanations for ethnic differences must operate from an early age. In recent years, any discussion of explanations for either the low cholesterol, and the associated generally
favourable atherogenic lipoprotein profile in people of Black African descent or the unfavourable profile in South Asian populations would have had to include genetic factors, without which publication would be impossible. Several genetic loci that associate with circulating lipid and lipoprotein levels, and which may control key steps in cholesterol bioactivity, have been identified. Genetic markers can be used to estimate the degree of African or European ancestry for a given individual, demonstrating a dose–response relationship between degree of African ancestry and lipoprotein levels and suggesting that genetic factors are responsible in determining lipid levels and in accounting for ethnic differences in the atherogenic lipoprotein profile. Yet, for people of Black African descent and Indian Asians, the search for the candidate locus or loci has proved somewhat disappointing, with genetic factors explaining only a small part of the variance of lipid levels within populations and of differences between populations. Shaper and Jones do not even mention a genetic explanation for their findings. With hindsight, this omission seems appropriate! Instead, they identify differences in diets as a key factor. Interestingly, exercise is considered an unlikely explanation for lipid differences, although details of exercise output are not provided. The Africans in this sample were from an agricultural background, working on the land or in unskilled occupations. Diets were reportedly relatively high in fruit, vegetable and cereal intake, and low in dietary fat and protein—particularly expensive animal protein. In contrast, the Indian Asians, although living in roughly the same geographical setting, were wealthier and could afford a diet that was high in dietary fat and protein, and for the non-vegetarians in particular, who had the highest serum cholesterol levels, included a significant amount of animal protein. There is at least a one standard deviation difference in serum cholesterol between ethnicities; hence, any single explanation for this ethnic difference would have to be powerful. Shaper and Jones reported that although dietary fat contributed 10–15% of the total calorie intake in Africans, this figure was around 30–45% in Indian Asians. Indeed, Shaper and Jones suggest that the low serum cholesterol in Africans is indicative of relative malnutrition, and imply that total cholesterol levels of below 170 mg are less than ideal—for that reason. How do these findings relate to the hypothesis, and the evidence albeit limited, that ethnic differences are genetically determined? Racial admixture and acculturation are highly correlated. Thus, the dose–response association between racial admixture and lipid profiles observed in African–Americans may be confounded by the effects of acculturation, and acculturation, which includes dietary preferences, is known to impact on risk of chronic disease.

Shaper and Jones advanced a similar, but subtly distinct explanation for the finding that serum cholesterol increases with age in Indian Asians, but not in Africans. They suggest that physiological mechanisms, present or set in youth, are able to buffer the adverse effects of high dietary cholesterol intake. This ability attenuates with ageing, and persistence of the insult thereafter results in higher cholesterol levels, rather in the way that the pancreas fails to produce sufficient insulin to overcome insulin resistance, eventually leading to type 2 diabetes. Again, they anticipated recent developments in evolutionary biology, which suggest that responses to a given environmental stressor are governed by the interplay between robustness and plasticity at the level of the organism. Thus, early influences, including diet, could determine the degree of robustness, or resilience, to environmental stressors. A change in or persistence of a given environmental stressor to or at adverse levels could overcome this resilience, and, dependent on the degree of plasticity, result in greater or lesser emergence of a given risk factor or disease. Shaper and Jones reviewed findings on the association between age and cholesterol, and conclude that changes in total cholesterol from youth to middle age are environment specific, i.e. these changes depend firstly on ‘background’ dietary consumption and age at which individual dietary intake changes. Their findings in Indian Asians suggest that a marked rise in serum cholesterol occurs after the age of 20 years, somewhat later than the age when vulnerable fatty streaks in the cardiovascular system start to be converted to raised plaques. The authors do not perform discuss whether ethnic differences in serum cholesterol are sufficient to account for the observed excess cardiovascular mortality in Indian Asians. Other lipid subfractions, such as high-density lipoprotein-C and other major risk factors, strikingly smoking and diabetes, are not considered here. However, in the context of Indian Asians, the commonly found excess prevalence of diabetes and dyslipidaemia is not characterized by raised total cholesterol—but rather by low high-density lipoprotein-C and high triglyceride. Interestingly, some data from the UK suggest that ethnic differences in lipid and lipoprotein profiles do not account for ethnic differences in cardiovascular disease.

Thus, Shaper and Jones identified dietary intake, a key, modifiable, established and well-recognized risk factor for myocardial infarction, as the explanation for the greater serum cholesterol and the age-dependent increase in cholesterol in Indian Asians compared with Africans, without needing to invoke novel, as yet undiscovered risk factors. This contrasts with the rather desperate search for ever newer cardiovascular risk factors that typified the end of the last century and reflects the more rational understanding of CHD disease risk. Interestingly, in the global contemporary setting of INTERHEART, the ratio of ApoA/ApoB was a better predictor of acute myocardial infarction, than total cholesterol or low-density lipoprotein cholesterol.
The considerations explored by Shaper and Jones are not simply of historical interest. Urbanization in low- to middle-income countries currently occurring at a speed unprecedented in higher-income countries, on a background of recent severe disadvantage, threatens a global epidemic of obesity, dyslipidaemia and diabetes and thereby cardiovascular disease.21

Funding
N.R. Poulter is a recipient of the National Institute for Health Research Senior Investigator awards and is supported by the Biomedical Research Centre award to Imperial College Healthcare NHS Trust.

Conflict of interest: None declared.

References
18 Forouhi NG, Sattar N, Tillin T, McKeigue PM, Chaturvedi N. Do known risk factors explain the higher coronary heart disease mortality in South Asian compared with European men? Prospective follow-up of the Southall and Brent studies, UK. Diabetologia 2006;49:2580–88.