

# Sick genes, sick individuals or sick populations with chronic disease? The emergence of diabetes and high blood pressure in African-origin populations

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<b>Aim and Methods</b>	To discuss evidence for and against genetic 'causes' of type 2 diabetes, illustrated by standardized study of glucose intolerance and high blood pressure in four representative African origin populations. Comparison of two genetically closer sites: rural (site 1) and urban Cameroon (2); then Jamaica (3) and Caribbean migrants to Britain (80% from Jamaica—4).
<b>Background</b>	Alternatives to the reductionist search for genetic 'causes' of chronic disease include Rose's concept that populations give rise to 'sick' individuals. Twin studies offer little support to genetic hypotheses because monozygotic twins share more than genes <i>in utero</i> and suffer from ascertainment bias. Non-genetic intergenerational mechanisms include amniotic fluid growth factors and maternal exposures. Type 2 diabetes and hypertension incidence accelerate in low-risk European populations from body mass $\geq 23$ kg/m <sup>2</sup> , well within 'desirable' limits. Transition from subsistence agriculture in West Africa occurred this century and from western hemisphere slavery only six generations ago, with slow escape from intergenerational poverty since.
<b>Results</b>	'Caseness' increased clearly within and between genetically similar populations: age-adjusted diabetes rates were 0.8, 2.4, 8.5 and 16.4% for sites 1–4, respectively; for 'hypertension', rates were 7, 16, 21 and 34%, with small shifts in risk factors. Body mass index rose similarly.
<b>Conclusion</b>	Energy imbalance and intergenerational socioeconomic influences are much more likely causes of diabetes (and most chronic disease) than ethnic/genetic variation, which does occur, poorly related to phenotype. The newer method of 'proteomics' holds promise for identifying environmental triggers influencing gene products. Even in lower prevalence 'westernized' societies, genetic screening <i>per se</i> for diabetes/chronic disease is likely to be imprecise and inefficient hence unreliable and expensive.
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'Of all the vulgar modes ..., the most vulgar is that of attributing the diversities of conduct and character to inherent natural differences'. JS Mill, as quoted by Oakley.<sup>1</sup>

'There is only one science—physics; all the rest is social work'. JS Watson 1994, as quoted to Steven Rose.<sup>2</sup>

Many researchers in biomedical science justify their work as unravelling causes of disease. The vital distinction, that 'causes' or aetiological factors initiate a disease process (mechanism or pathogenesis), on which most researchers work, is often blurred. Increasingly, genes are sought as causes, not mechanistic

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components, of chronic disease, often to account for higher prevalence in particular populations. Examples include type 2 diabetes or high blood pressure. Here in an international context using migration examples, we argue that gene defects or variation are unlikely to, indeed in most conditions do not, account for major variation in disease frequency.

## Sick populations

Rose popularized an alternative concept of disease causation whereby populations with complex patterns of social history, current stimuli and resulting behaviour give rise to 'ill' individuals.<sup>3,4</sup> That such individuals or groups 'track' through generations without germline inheritance is part of the hypothesis outlined here. 'Sick' individuals represent relatively extreme deviations from the population average of 'chronic' risk factors. That average determines the proportion of subjects with 'high' blood pressure or 'high' blood cholesterol, or with overt (type 2) diabetes on the spectrum of the blood glucose distribution. Similar definitions apply to osteoporosis or clinical depression. Prevalence or 'caseness' is arbitrarily defined at some point on the risk factor spectrum. For those doubting how arbitrary 'case' definitions can become, recent discussions over changing the diagnostic threshold for diabetes from fasting blood glucose levels are illustrative. American criteria proposed in 1997<sup>5</sup> alter total prevalence variably by some per cent in different populations from that previously defined on WHO 1985 criteria. Yet up to 40% of the individuals affected change—do these new 40% share the same predisposing genotype(s) as those previously but no longer so defined?<sup>6,7</sup> Similar issues arise when considering differences between criteria for 'hypertension' (previously  $\geq 160$  and 95 or 90 mmHg), now moving towards a more integrated approach by using absolute cardiovascular risk, while American criteria traditionally use  $\geq 140$  mmHg.<sup>8</sup> Perhaps an older operational definition of hypertension may help thinking in all these practical or aetiological areas—the level of blood pressure at which treatment does more good than harm'.<sup>9,10</sup>

Many, perhaps most, clinicians and clinical scientists, reasoning at the level of individual patients or with small numbers in laboratory experiments, find this approach alien and difficult to handle. However, large randomized clinical trials, now accepted as the main method for making evidence-based treatment decisions, are the logical outcome of thinking in distributions.<sup>11,12</sup> Yet trials only produce average results—'numbers needed to treat' of, say, 23 patients for 5 years to prevent one cardiovascular event.<sup>13</sup> Grimley Evans highlighted the clinical paradox of daily individual decision-making: which one of my 23 patients will benefit?<sup>14</sup> The paradox similarly applies to causation.

The preventive or social medicine imperative is to remove or reduce the stimuli ('exposures') promoting a high (or low) average risk factor level. Primary prevention or illness delay should require only a small shift in a risk factor's mean, such as reducing population mean blood pressure 2–3 mmHg to reduce stroke incidence by 20–30%. Unfortunately, once 'high' risk factor levels are attained, lifestyle methods have so far achieved only small reductions in absolute risk in individuals.<sup>4,15</sup> Serum cholesterol reduction by diet averages some 6%<sup>16</sup> while statin drug treatment reduces levels by over 30% with dramatic but accurately predictable declines in cardiovascular events.<sup>17</sup> However, promoting such treatment at the expense of *primary*

prevention<sup>18</sup> ignores the lifetime exposure to accumulate risk and the vital issue that most cases of 'disease' arise below 'cut-offs' where drug treatment can never be cost- and person-effective.

## Impact of distributions, not just 'cases', on aetiology (cause)

Type 2 diabetes and hypertension's rapid emergence in less affluent populations leads to confusion for genetic hypotheses. Genotypes are unchanged in two generations so do all such populations carry 'thrifty genes rendered detrimental by progress'<sup>19</sup> or do the few with lower prevalence (e.g. Europeans) carry 'mutant' genes allowing some escape?<sup>20</sup> Are gene defects relevant at all?

## What is the evidence that type 2 diabetes is a genetic condition?

Textbooks describe type 2 diabetes as 'strongly genetically determined',<sup>21</sup> primarily based on high concordance in monozygotic twins, strong family history and ethnic differences *per se*.<sup>22</sup> Twin data from specialist clinics claiming some 90% monozygotic concordance rates illustrate the serious consequences of ascertainment bias.<sup>23–25</sup> National population twin registers, ascertained solely because of twin status and unrelated to health, produced different results. Of 4000 Finnish twins, 505 had known type 2 diabetes; monozygotic concordance dropped below 25%;<sup>26</sup> however without testing for diabetes, rates could be artificially low. In Denmark, 305 nationally registered twin pairs were both tested; monozygotic concordance was 50% compared with 37% in dizygotic pairs,<sup>27</sup> despite limitations due to relatively small numbers and response. Monozygotic twins share uterine blood supply and placental function limiting conclusions favouring genetic over environmental inheritance, as discussed elsewhere.<sup>25,28</sup> The Danish glucose intolerant twins' birthweights averaged 200 g lighter than non-diabetic co-twins,<sup>29</sup> entirely consistent with the Barker/Hales 'thrifty phenotype' hypothesis.<sup>30,31</sup> A publicized finding that a gene may modify birthweight came from rare MODY pedigrees forming <1% of the hyperglycaemic population;<sup>32,33</sup> its relevance to general hyperglycaemia or to whole populations with low birthweights remains uncertain, despite promoting a testable hypothesis.<sup>32</sup> Evidence for non-genetic but intergenerational aetiology of type 2 diabetes, in Britain and in Dutch famine survivors' offspring,<sup>34</sup> is also found in high-risk populations in India<sup>35</sup> and the Caribbean.<sup>36</sup> Similarly, the role of previously widespread post-natal malnutrition with subsequent excess weight gain is being explored.<sup>37</sup> Attributable risk of such effects remains to be established.

Other intergenerational but not genetic mechanisms may have important population impacts. In women with gestational diabetes, amniotic fluid insulin (and probably other growth factors) was double that of controls, directly affecting the new-born whose cord blood C-peptide concentrations doubled.<sup>38</sup> While gestational diabetes is uncommon, lesser undetected but more prevalent maternal glucose intolerance likely exposes many more fetuses to hyperinsulinaemia and other factors. The variability of maternal nutrient consumption, blood levels and supply to the placenta, followed by the many external factors affecting placental transfer will all affect final nutrient delivery to the fetus at critical growth stages. More detailed mechanisms are discussed elsewhere.<sup>39</sup>

## The neglected role of obesity in the upper range of 'desirable' body mass index (BMI)

Two 12-year follow-up studies in low-risk cohorts suggest that weight and weight gain over BMI of 23 kg/m<sup>2</sup> are closely associated with excess incident diabetes.<sup>40,41</sup> (The upper limit of 'desirable' is generally some 25 kg/m<sup>2</sup>.) In representative samples of white British men, relative risk of known diabetes was fourfold at body mass indices of 25 and 10-fold over 30 compared with risk below 23 kg/m<sup>2</sup>.<sup>40</sup> In 112 000 US nurses, almost all white Europeans of high socioeconomic status, weight gain from 23 kg/m<sup>2</sup> had similar excess diabetes risk.<sup>41</sup> Both underestimate incidence as neither study used glucose challenge. Body mass index is the integral or balance between long-term energy intake and energy expenditure; the average BMI has risen sharply in all high-risk communities so that the population impact of such slight increases within the 'usual' range may be large.

## International comparative study

To examine potential nutritional influences on emerging high blood pressure and glucose intolerance, using standardized methods we compared four West African origin populations.<sup>42-44</sup> While all share some common genetic background, the study design compared two genetically closer samples: rural and urban Cameroon, and Jamaica and Caribbean migrants to Britain. Some 80% of the latter were first generation migrants born in Jamaica. Inspecting the blood pressure and venous plasma glucose distributions in relation to arbitrarily defined diabetes and hypertension is informative (Figures 1 and 2). Small distribution shifts within the West African sites and between

Jamaica and Caribbeans in Manchester are reflected in relatively large changes in prevalence rates for both chronic diseases. Each is associated with obesity, despite briefer exposure due to young mean age in urban Cameroon. Mean BMI in men rose from 21.3 in rural to 25.2 kg/m<sup>2</sup> in urban Cameroon, and from 22.5 in Jamaica (reflected in lower diabetes prevalence) to 26.8 kg/m<sup>2</sup> in Manchester, UK. Respective means for women rose more consistently, from 21.9 to 26.8 in Cameroon and 26.9 to 28.2 kg/m<sup>2</sup> in African-Caribbeans, as did prevalence of both diabetes and hypertension.

Artificial restriction of each distribution's upper tail by increasing treatment rates across sites is also shown, separated from those newly detected (Inserts on Figures). Median blood pressure and glucose values rose clearly across site.<sup>42</sup>

## Implications for aetiology

Our conclusion is that environmental factors play an overwhelming role in these genetically similar populations, even if that similarity is not yet formally measured. Clearly this study has not assessed all possible environmental factors. However, 'genes' or genetic variations—either ethnic-specific or general—*per se* would contribute little or nothing to change in 'disease' prevalence within the two separate comparisons or across all sites. Issues of genetic admixture in Caribbean populations, which might introduce new haplotypes with as yet undiscovered modulatory effects, do not apply within our Cameroon site. Population attributable risk from obesity, using a high cut-off of 25 kg/m<sup>2</sup>, was as high as 40% in our previous analysis of just known diabetes.<sup>45</sup> The impact from lesser degrees of fatness may be even greater,<sup>40,41</sup> as may be differences in body composition for the same body mass at critical periods of earlier life.

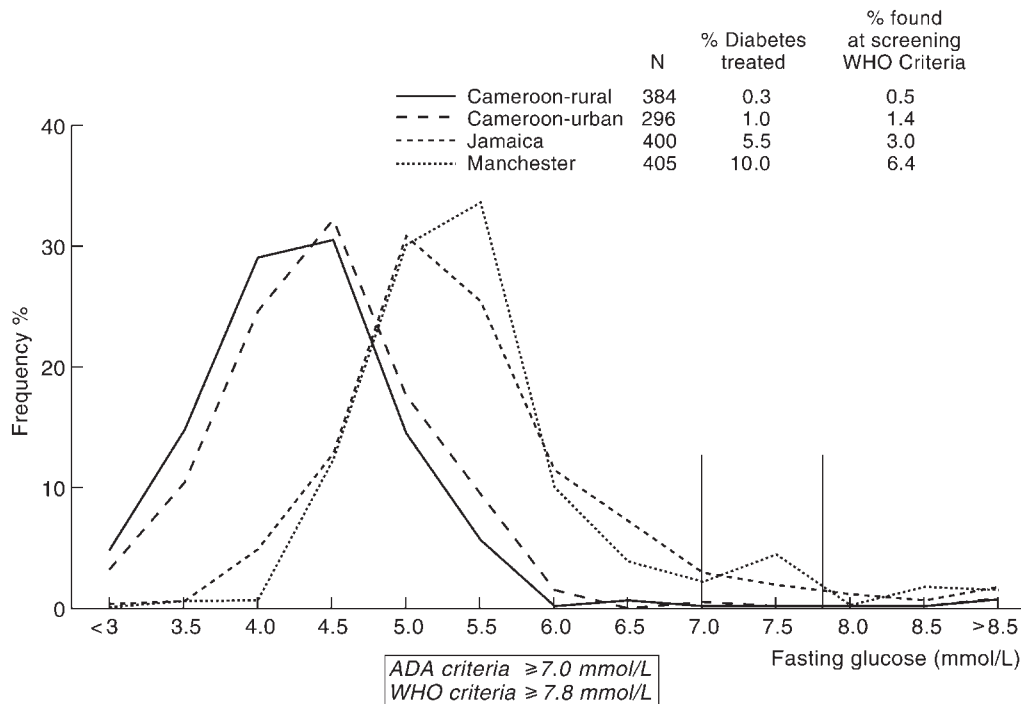


Figure 1 Distribution of fasting glucose by site

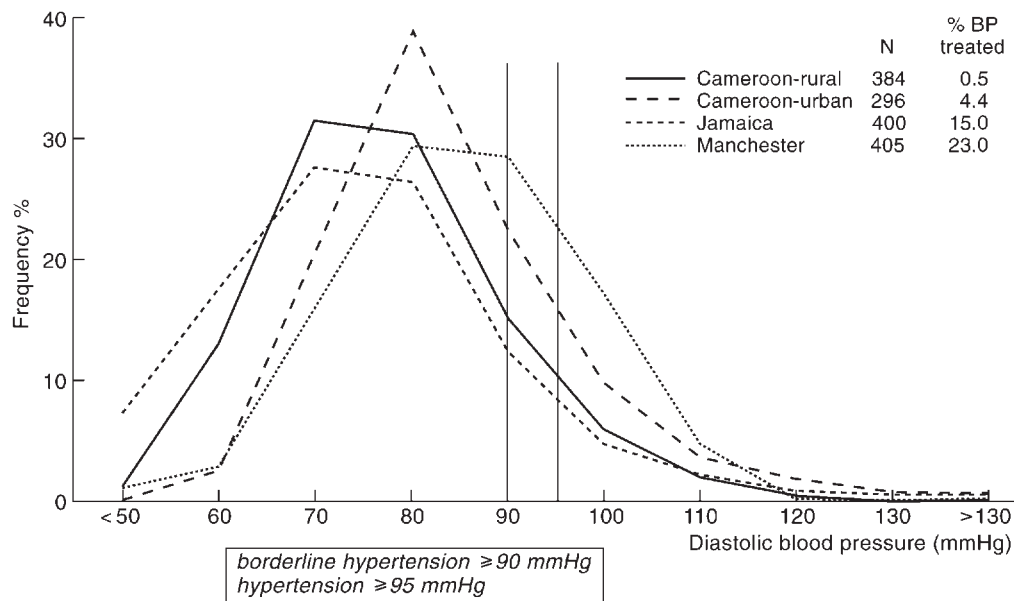


Figure 2 Distribution of diastolic blood pressure (BP) by site

Other complex nutritional influences occur over the life-span, including before and during pregnancy and post-natally.<sup>31,39</sup> While nutritional quantity exceeding energy expenditure (physical activity) to produce chronic positive energy balance and obesity is one component, nutritional quality is another. We have found an important example of this issue among Manchester Caribbeans, whose dietary intake was 7% lower in per cent energy from total fat, and 3% lower in saturated fat, with more fruit and vegetables, than the British national average.<sup>43</sup> That diet is associated with the group's continuing lower coronary heart disease rates, despite higher blood pressure and diabetes rates, as illustrated here. However, younger people's diets are similar to those nationally so that again cumulative absolute risk is likely a key feature in putting this community at higher risk of both coronary disease and diabetes in the coming generation. Clearly there are opportunities for environment-gene interactions in this type of setting but again, putative polymorphic variants would not be the causes *per se* of any beneficial or deleterious outcome, rather the variable nutrients interacting with them.

### Socioeconomic issues

Finally, the social and historical context in which these emerging epidemics are occurring is surely relevant to their causation. The inverse social gradient of chronic disease in the 'West', higher in poorer people, is currently reversed in urban West Africa. Yet West African origin people in the western hemisphere are generally descendants of slavery survivors of only some six generations ago.<sup>46</sup> Poverty and subsistence living conditions after emancipation transmitted to subsequent generations poor health indices which persist, as they do in western society between social grades even if individuals are employed, but on an inverse gradient.<sup>47,48</sup> Income disparities and the 'health gap' between African and European Americans only recently began

to narrow<sup>49</sup> as more African-Americans become wealthier. A genetic basis for long-standing differences in mean birthweight of 200–300 g is undermined by findings of similar birthweights to those of whites for infants born in the US to better-off 'black' women of direct West African birth.<sup>50</sup> Birthweights in recently better-off Barbados were some 30–40 g higher than among similar women in Jamaica.<sup>51,52</sup> Other examples of phenotype change within one or two generations include height increase in Japanese and Japanese migrants to Hawaii and west coast America or in children of Indian subcontinent origin people in Britain.

These are currently mere arguments by association, wholly inadequate to attribute cause, yet they remain the imprecise broad-brush strokes of history, which subtly determine human health.<sup>53,54</sup> The examples cited are relevant to many other societies with emergent chronic disease, whether in Saudi Arabia or among Pacific islanders, for whom other social pressures operate.

We thus favour a hypothesis for the emergence of type 2 diabetes of acute-on-chronic energy imbalance, which has the profound implication of being reversible without 'labelling' currently afflicted societies as 'genetically susceptible', a potentially dangerous form of investigator bias. Thus energy-dense nutrient intakes, notably fat-based foods (for example 'beignets', deep-fried cassava balls popular as snacks on Yaoundé's streets), provide intakes which exceed energy expenditure from physical activity over many years from childhood or adolescence. Resulting weight gain and/or obesity promotes gradual insulin resistance secondary, not primary,<sup>55</sup> to these insults, with resulting pancreatic B-cell exhaustion and insulin deficiency along the lines of the thrifty phenotype hypothesis, leading to overt 'diabetes'. The mechanisms underlying these causes may be related to chronic excess free fatty acid flux in portal blood<sup>56,57</sup> so that hepatic insulin handling is disturbed while poor muscle insulin sensitivity is maintained by inadequate

physical activity. Finally, it is hardly surprising that such trends run in families so that what is familial, as for tuberculosis a hundred years ago, is not necessarily genetic.

While playing down a primary genetic role in chronic disease causation, clearly important ethnic genetic differences exist, as recently for a lipoprotein lipase gene-promoter polymorphism<sup>58</sup> or earlier around the renin gene.<sup>59</sup> In hypertension, the sodium channel's B subunit variation was found in just 8% of cases and 2% of controls of African-Caribbean origin<sup>60</sup> and current interest in the angiotensin converting enzyme gene's role is diluted by its potential impact being small, sex-specific and poorly reproducible.<sup>61,62</sup> Similarly in diabetes, reports of a major susceptibility locus<sup>63</sup> are rapidly contradicted by another. The view outlined here suggests that this is not just the ebb and flow of experimental science but a conceptual gap which has to date excluded more multi-level causation in its framework.<sup>64</sup> Genetic links are found with other markers of environmental influences in population samples but as yet in humans these are by association only,<sup>60,65</sup> a criticism that should be equally levelled at much risk factor epidemiology.<sup>64</sup> Even though their impact remains uncertain, the attraction of gene-outcome studies is at least they are re-testable, a quality which cannot make up for conceptual limitations. Clearly rapid body composition, dietary and activity changes can conceivably accentuate differences in gene-environment interaction by (ethnic) gene variation.

To date, if at all, candidate genes have been weakly and imprecisely related to chronic disease phenotype when they occur. This is despite many millions of dollars spent in research funding and years of searching, which might also suggest publication bias. Thus the genetic task becomes one of statistical aggregation with multiple weak genetic markers (rather than 'cause[s]') each contributing very little to population variance of phenotype. Contributions from genotype alteration are insignificant compared with rapid changes in phenotype within one or two generations, as in the example of height mentioned above. Even where rapid genotypic change has been postulated, such as following the huge mortality from the 'middle passage' transport to slavery, evidence for phenotypic change is unclear. For instance such a mechanism was postulated to account for the high prevalence of hypertension and its sequellae among African-origin peoples in the western hemisphere.<sup>66</sup> Yet currently, as our data begin to show here, rates of hypertension within urban West Africa never subject to slavery are as high or higher than in Jamaica, but critically not yet as high as in Jamaican migrants to Britain. However, the coming method of 'proteomics', the study of gene products (peptides/proteins) helped by identifying the gene producing them, should help throw light on the environmental triggers influencing their transcription.<sup>67</sup> Conceptually such identification is quite separate to suggesting that the genomic alterations *per se* (i.e. putative 'causal genes'), which do occur polymorphically but with variable impact on amino acid alterations and if so, generally at low frequency, are responsible themselves for disease phenotype.

## Dubious validity of genetic screening for chronic disease and conclusion

If this discussion has any validity and practical implication, genetic screening for chronic disease will have little or no application, in high-risk or other populations. Screening for chronic disease

with as yet undiscovered genuine genetic markers will not only detect very few individuals but, of great concern to both the individuals 'detected' and for those paying for any such programme, will do so imprecisely and unreliably. On this basis, research funding agencies and insurance companies need to appreciate that benefits from genetic screening for chronic disease seem extremely unlikely for individuals or populations. Light may be being shed on chronic disease mechanism, which optimistically may allow later detection of external cause(s) and certainly will contribute to more targeted therapy. However, the view outlined here shifts research emphasis in aetiology (as opposed to mechanism) away from genes back to whole organism physiology and upwards and outwards through clinical epidemiology to the social conditions prevailing through history<sup>53,54</sup> and to those current in society. While the laboratory challenge will be to find genes interacting with nutritional and other environmental stimuli, responsibility for chronic disease control again falls onto politicians, public health and perhaps most likely, those in the media who can manipulate public attitudes and behaviour within and across societies and generations.<sup>68</sup>

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