Synopses of Research Articles

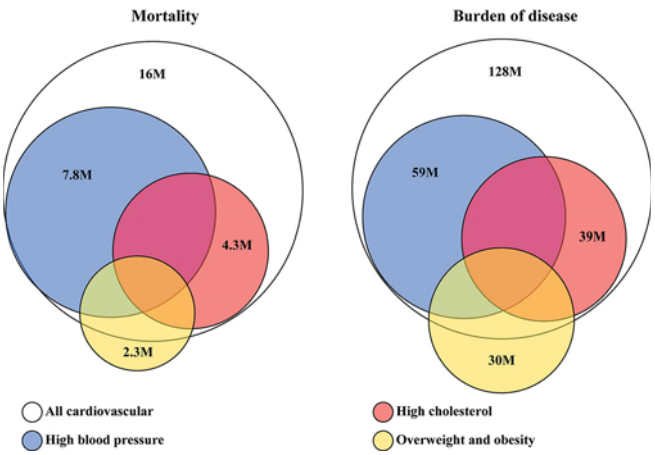
Affluence and the Worldwide Distribution of Cardiovascular Disease Risks

DOI: 10.1371/journal.pmed.0020148

Cardiovascular diseases (CVDs) are responsible for more than 16 million deaths worldwide, about 30% of total global deaths. Many of these deaths could be prevented by tackling major risk factors such as overweight and obesity as a result of unhealthy diet and physical inactivity, and smoking. Traditionally, CVDs have been considered a "Western" disease or a "disease of affluence" and not a pressing public health concern for low-income populations. However, within upper-middle-income and high-income countries, CVDs and their associated risk factors are increasingly concentrated among the lowest socioeconomic groups, and globally, 80% of all CVD deaths are in low-income and middle-income countries.

In this month's *PLoS Medicine*, Majid Ezzati and colleagues conclude that a large proportion of the world's population living in low-income and middle-income countries should indeed be the focus of attention for CVD risk factors. This attention is needed because the aging populations of the currently low-income and middle-income countries are expected to be those among whom major cardiovascular risk factors will increasingly be concentrated.

The patterns of risks in relation to one another and to economic variables such as income are not fully established at the population level but need to be understood if better long-term policies and interventions are to be deployed. Ezzati and colleagues examined when interventions should be started by looking at the relationship between nutritional cardiovascular risk factors—overweight and obesity, and elevated blood pressure and cholesterol—and three economic indicators, using data for more than 100 countries. Their analysis uncovered economic–epidemiological patterns more complex than the "Western" or "affluence" labels would suggest. They found that body mass index (BMI) and cholesterol increased rapidly in relation to national income, then flattened, and eventually declined. BMI increased most rapidly until an income of about I$5,000 (international dollars) and peaked at about I$12,500 for women and I$17,000 for men. Cholesterol showed a similar pattern, but with some delay. The authors also found an inverse relationship between BMI/cholesterol and the share of household expenditure put towards food, and a positive relationship with proportion of population in urban centers, which may be due to changes in patterns of diet and physical activity with city life. For blood pressure and cholesterol, possible contributors to the decline at higher levels of income include dietary changes and use of pharmacological interventions.



DOI: 10.1371/journal.pmed.0020148.g001

Global burden from cardiovascular disease

As more interventions for blood pressure and cholesterol are adopted in high-income societies, the three risk factors will become a feature of low-income and middle-income nations, the authors say. Demographic and technological changes are increasingly modifying the income patterns of cardiovascular risk factors and shifting their burden to the developing world; as a result, low-income and middle-income countries will simultaneously face the burden of infectious disease and cardiovascular risk factors. Unless better interventions are pursued, we will face a world in which all major diseases are the diseases of the poor, the authors warn. (See also the Perspective by Thomas Novotny [DOI: 10.1371/journal.pmed.002010].)

Ezzati M, Vander Hoorn S, Lawes CMM, Leach R, James WPT, et al. (2005) Rethinking the "diseases of affluence" paradigm: Global patterns of nutritional risks in relation to economic development. DOI: 10.1371/journal.pmed.0020133

Patterns of Statin Prescribing

DOI: 10.1371/journal.pmed.0020149

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in developed countries, and identifying and treating patients with high cholesterol has an essential role in the prevention of CHD. Therapeutic lifestyle changes are important for general reduction of risk overall, but patients who are more likely to develop CHD, or who have high cholesterol, should be treated with statins. Statins inhibit HMG-CoA reductase—a key enzyme in the cholesterol synthesis pathway.

Although we know that not all patients who may benefit from statins receive treatment, there is limited information on how patients are treated according to their estimated risk of developing CHD. Patients may be classified as at low, medium, or high risk of developing CHD according to the presence of CHD, some other medical conditions (for example, diabetes), and major risk factors including cholesterol level, smoking, lifestyle, and family history. Jun Ma and colleagues analyzed data from the National Ambulatory Medical Care Survey and the outpatient department component of the National Hospital Ambulatory Medical Care Survey to identify changes in treatment from 1993 to 2002, and to identify current clinical practice. These surveys have been validated against other data sources, and used in past research on cholesterol management.

The researchers found that between 1993 and 2002 the use of statins increased nearly 5-fold, from 9% to 49%, in ambulatory visits by patients with high cholesterol, but then declined to 36% in 2002. Overall, the use of statins was three times more likely in 2001 and 2002 than in 1995 and 1996. Patients at high risk of CHD were more likely to use statins than other patients. However, among patients whose visit had a reported high cholesterol, only 50% of patient visits at high risk of CHD and 44% of those at moderate risk were prescribed statins in 2002, well below the recommendations of current guidelines. Less than half the patient visits that arguably represent optimal opportunities for counseling services received counseling about how they might change their lifestyle. The study also showed inequities in use of statins for patients with different social and clinical characteristics, with lower usage in younger patients, females, African-Americans, and patients cared for by doctors who are not cardiologists.

As the authors declare, the study was funded by a maker of one of the statins, but the information acquired is of general interest. Persistent gaps in statin therapy suggest a need for improved identification of patients who may develop CHD, and treatment with statins when indicated, the authors say. A particular focus should be patients who are at risk of developing CHD. Education should be aimed at improving the practice of physicians—above all, those who are not heart specialists—so that they adhere to evidence-based medicine and published guidelines for cardiovascular risk reduction. In an accompanying Perspective (DOI: 10.1371/journal.pmed.0020131), Fiona Turnbull from the George Institute for International Health says that physicians need to move away from making treatment decisions based on single risk factors and instead use an approach based on absolute risk. "An understanding of the concept of 'absolute risk'—the probability of a patient developing a cardiovascular event over a specified time period—is crucial," she says.

Ma J, Sehgal NL, Ayanian JZ, Stafford RS (2005) National trends in statin use by coronary heart disease risk category. DOI: 10.1371/journal.pmed.0020123

Sickle Cell and Malaria

DOI: 10.1371/journal.pmed.0020150

There are at least 300 million acute cases of malaria each year globally, resulting in more than a million deaths. Ninety percent of deaths due to malaria occur in Africa south of the Sahara, and most occur in young children. Of the four types of human malaria—*Plasmodium vivax, P. malariae, P. ovale*, and *P. falciparum*—*P. falciparum* malaria is most common in Africa, and it accounts for most of the extremely high mortality south of the Sahara.

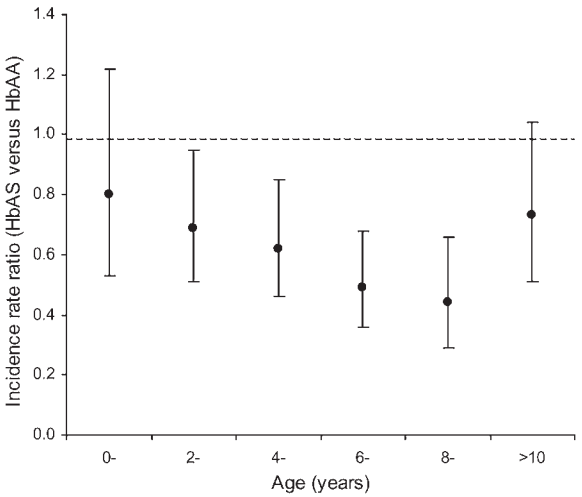
Malaria parasites are developing unacceptable levels of drug resistance, and many insecticides are no longer useful against mosquitoes transmitting the disease. Vaccine research has produced few hopeful candidates, and although millions of dollars are poured into research, an effective vaccine is years away.

One recurring theme in malaria vaccine research has been the high frequency of the gene for sickle cell hemoglobin (HbS) in malaria endemic regions, which is believed to be due to a heterozygote (HbAS) advantage against fatal malaria. The mechanism behind the high degree of resistance conferred by HbAS in severe and complicated malaria is still unknown, but recent observations have suggested the mechanism might involve an immune component.

In this month's *PLoS Medicine*, Thomas Williams and colleagues reason that the best way to test whether malaria protection by HbAS has a significant immune component is to see whether protection varies with age. They studied the age-specific malaria pattern in 1,054 children and adults living in Kilifi District on the coast of Kenya. They argued that if the malaria protection provided by HbAS were innate, it should be independent of malaria exposure and remain constant with age. However, if immune mechanisms were involved, protection should increase with age until children become functionally immune, when additional immunological advantage should be lost.

They found that overall HbAS was nearly 40% protective against mild clinical malaria. Protection varied with age, increasing from 20% to 60% during the first ten years of life, and thereafter returning to 30% in children more than ten years old.

The authors admit that this observation could be due to any factor that affects malaria risk and varies with age but state that accelerated immune acquisition seems the most likely explanation. They suggest several mechanisms for how HbAS could accelerate immune acquisition; for example, immunity could be mediated by accelerated acquisition of antibodies to altered host antigens expressed on the parasite-infected red cell surface.



DOI: 10.1371/journal.pmed.0020150.g001

Incidence rate ratio for malaria in HbAS versus HbAA children by age and genotypic group

In discussing their findings the authors point out that their study focused on mild malaria. For accelerated malaria-specific immunity to be relevant to HbAS selection it would have to operate within a period of maximum risk for severe and fatal malaria. They note that in a recent study, conducted by another group in western Kenya, protection against severe malaria by HbAS was only seen in children 2–16 months old, but that in that study, no analysis was presented that addressed the effect of age within that range.

The authors conclude that the relevance of their current observations on mild clinical malaria to protection against severe and fatal malaria are unknown, and that further work must be done to better understand the role of HbAS in protection against malaria.

Williams TN, Mwangi TW, Roberts DJ, Alexander ND, Weatherall DJ, et al. (2005) An immune basis for malaria protection by the sickle cell trait. DOI: 10.1371/journal.pmed.0020128

Comparison of Homocysteine-Lowering Drugs

DOI: 10.1371/journal.pmed.0020145

A link between high levels of homocysteine, a sulfur-containing amino acid, and heart disease was first suggested in the 1960s, when it became clear that patients with inborn errors of homocysteine metabolism were prone to develop severe cardiovascular disease in their teens and twenties. Treatment with homocysteine-lowering substances such as folate, vitamin B12, and betaine reduces the incidence of heart attacks and strokes in these patients.

This led to the hypothesis that mildly elevated levels of homocysteine might contribute to vascular disease. Subsequently, several studies have found higher mean homocysteine levels in patients with coronary, peripheral, and cerebral vascular disease, particularly in those with vascular disease not readily explained by conventional risk factors such as high low-density lipoprotein (LDL) cholesterol, diabetes, or smoking. Several studies then sought to determine whether elevated homocysteine levels were a cause or effect of cardiovascular disease, and evidence for a causal relationship is accumulating. However, whether reduction in homocysteine levels translates into a reduction in heart disease is still an open question.

"We are keenly awaiting the results from several ongoing trials. In the meantime, our group is trying to determine the risks and benefits associated with different homocysteine-lowering nutrients," said Margreet Olthof. She and her colleagues at the Wageningen Centre for Food Science analyzed four independent, placebo-controlled, randomized intervention studies that examined the effects of betaine, folic acid, and phosphatidylcholine on plasma homocysteine concentrations in healthy volunteers. They combined blood lipid data from the individual studies and compared changes in blood lipid concentrations between individuals taking homocysteine-lowering nutrients and those taking placebo.

They found that that betaine supplementation, while effective at lowering homocysteine, also increased LDL cholesterol and triacylglycerol.
This raises the possibility that any potential benefits for cardiovascular health would be undermined by the adverse effects on blood lipids, and make betaine less suitable as a homocysteine-lowering agent in healthy individuals.
The data on phosphatidylcholine were inconclusive, but supplementation of folic acid—the most common way to lower homocysteine levels—does not seem to affect blood lipids.
The researchers conclude that folic acid "therefore remains the preferred treatment for lowering of blood homocysteine concentrations" in healthy individuals.

Olthof MR, van Vliet T, Verhoef P, Zock PL, Katan MB (2005) Effect of homocysteine-lowering nutrients on blood lipids: Results from four randomised, placebo-controlled studies in healthy humans. DOI: 10.1371/journal.pmed.0020135

How Prevalent Is Schizophrenia?

DOI: 10.1371/journal.pmed.0020146

Schizophrenia is a devastating mental illness and a major contributor to the global burden of disease. In their quest to understand schizophrenia epidemiology, John McGrath and colleagues have previously undertaken a systematic review of schizophrenia incidence—that is, the number of new cases diagnosed each year in a specified population (see *BMC Medicine* 2: e13). They now report results from a second systematic review that examines published studies on the prevalence of the disease—i.e., on the number of people who are suffering from the disease at a given time or within a specified time interval. (Incidence studies can suggest risk factors that may underlie variations in the disease. Prevalence studies are central to health systems planning.)

Analyzing a total of 1,721 estimates from 188 studies and covering 46 countries, they calculated the following median prevalence estimates: 4.6 per 1,000 for point prevalence (defined as prevalence during any interval of less than a month), 3.3 for period prevalence (defined as prevalence during a period from 1 to 12 months), 4.0 for lifetime prevalence (the proportion of individuals in the population who have ever manifested the disease and who are alive on a given day), and 7.2 for lifetime morbid risk (which attempts to include the entire lifetime of a birth cohort, both past and future, and includes those deceased at the time of the survey).

These numbers are consistent with key policy documents about point prevalence, but suggest that the 0.5%–1% estimate for lifetime prevalence given in many textbooks is an overestimate. This estimate, the authors suggest, "is another example where the research community needs to review their belief systems in the face of data." Another often quoted statistic, namely that "schizophrenia affects about one in a hundred"

DOI: 10.1371/journal.pmed.0020146.g001

This painting is frequently used to teach undergraduates what a person with schizophrenia experiences (Painting: Craig Finn)

most sensibly refers to lifetime morbid risk data. Here as well, the systematic analysis suggests that the reality is somewhat lower, and the authors suggest that "if we wish to provide the general public with a measure of the likelihood that individuals will develop schizophrenia during their lifetime, then a more accurate statement would be that about seven to eight individuals per 1,000 will be affected."

The authors were surprised to find no difference in prevalence between males and females, because their incidence review had found a male/female risk ratio of 1.4. On the other hand, the incidence study had revealed a higher incidence among migrant groups than among native-born individuals, and this was true for prevalence estimates as well. Compared to economically developed nations, the prevalence of schizophrenia is lower in developing nations, which is consistent with the literature showing that the course (i.e., prognosis) of schizophrenia is better in developing nations.

Systematic reviews are secondary research, where the object of scrutiny is not the prevalence of schizophrenia per se but the literature on the topic, and the estimates in this review have to be treated accordingly. Regardless of exact numbers, however, the authors conclude that "many people with schizophrenia have persisting symptoms, despite the best mix of interventions we can offer." It has been estimated that current interventions can at most reduce 25% of disease burden, thus the authors conclude that "this is a powerful argument for investing in applied and basic research."

Saha S, Chant D, Welham J, McGrath J (2005) A systematic review of the prevalence of schizophrenia. DOI: 10.1371/journal.pmed.0020141