

Global epidemiology: the importance of international comparisons and collaborations

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Abstract

Introduction

The methods and ways of thinking about the health of populations that will be required for epidemiology in the 21st century are in some instances quite different from the standard epidemiological techniques that are taught in most textbooks and courses today. As health problems become more global, it is important to take a global approach to health research. In particular, it is important that we consider the importance of international comparisons and collaborations. There are at least five reasons why they are important: (i) most of our good ideas (i.e., hypothesis generation) have come from population comparisons; (ii) lack of variation of exposure within high income countries; (iii) lack of generalisability between high income and low income countries; (iv) lack of exposure in high income countries and (v) the importance of addressing the most important public health problems on a global basis. International comparisons, despite all their methodological difficulties, will therefore remain a key part of the process of epidemiological research in the 21st century. The aim of this review was to discuss the importance of international comparisons and collaborations in global epidemiology.

Conclusion

International collaborative studies will continue to have a major role in epidemiological research.

Introduction

The last decade has brought striking advances in biomedical technology which are yielding major benefits for epidemiology at the molecular level, including new techniques for studies of genetic and epigenetic factors¹. At the same time, health problems are becoming more global². Thus, as we develop epidemiological methods for addressing the scientific and public health problems of the 21st century, it is important that we consider the importance of international comparisons and collaborations, while incorporating the latest technological advances at the molecular level. Thus, the methods that will be required for epidemiology in the 21st century are likely to be quite different from the standard epidemiological techniques that are taught in most textbooks and courses today^{3,4}. In particular, a global multi-level approach is required, rather than focusing on molecular-based studies in western countries⁵.

In this paper, I discuss five reasons why international comparisons and collaborations are important in this regard, primarily using examples from asthma epidemiology, and I consider some of the methodological issues involved.

Most of our good ideas come from population comparisons

The key area in which epidemiologists have been able to 'add value' in the past has been through their unique population focus³. For example, many of the discoveries on the causes of cancer (including dietary factors and colon cancer, hepatitis B and liver cancer, aflatoxins and liver cancer, human papilloma virus and cervical cancer) have their origins, directly or indirectly, in the systematic international

comparisons of cancer incidence conducted in the 1950s and 1960s. These suggested hypotheses concerning the possible causes of the international patterns, which were investigated in more depth in further studies. In some instances, these hypotheses were consistent with biological knowledge at the time, but in other instances, they were new and striking, and might not have been proposed, or investigated further, if the population level analyses had not been done. More recently, a huge amount of funding has been spent on studying the 'known' causes of asthma in affluent countries (e.g., air pollution, allergen exposure), and it is only now that standardised studies are revealing major international differences in asthma prevalence that are not explained by these 'established' risk factors^{6,7}. Similarly, of the 30–40 known occupational causes of cancer, almost all of them were apparently first 'discovered' in clinical case reports and epidemiological studies^{8,9}; in some instances (e.g., arsenic, benzene), it took many years of laboratory research to replicate the epidemiological findings and to establish the etiologic mechanisms involved. Thus, population epidemiology (including population, individual and micro-level hypotheses) has been most successful in discovering 'new' risk factors, whereas micro-level and laboratory-based studies have been most successful in subsequently establishing the etiologic mechanisms⁴.

It should be acknowledged that many suspected determinants of disease (e.g., dietary factors) have been hypothesised on the basis of international comparisons, but have not subsequently been confirmed in studies with better internal validity. International comparisons serve as

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part of the process of hypothesis generation and give us many ideas, some valid, some invalid. Such comparisons are not foolproof, but they are an essential part of the scientific process of hypothesis generation and testing.

Lack of variation within high-income countries

The most important population-level determinants of disease may vary little within a particular population or time period, and therefore may not be easily identifiable with our 'standard' epidemiological methods. This will not always be the case, and some factors (e.g., hygiene) may vary within low-and-middle-income countries, even if they do not vary much within high income countries. Thus, this is an argument to not restrict our research to Western countries, and to conduct both international comparisons as well as more focused studies in countries where there is sufficient exposure variation.

For example, the recent striking increases in asthma prevalence globally cannot be primarily due to genetic factors, since they are occurring too rapidly, and therefore they must be occurring due to changes in environmental exposures¹⁰. It seems that as a result of this 'package' of changes in the intrauterine and infant environment, we are seeing an increased susceptibility to the development of asthma and/or allergy. There are a number of elements of this 'package' including changes in maternal diet, increased foetal growth, smaller family size, reduced infant infections and increased use of antibiotics and immunisation, all of which have been (inconsistently) associated with an increased risk of childhood asthma, but none of which can alone explain the increases in prevalence¹¹. Thus, it is important that we consider the 'forest' of changes that occur with Westernisation, as well as doing studies of specific 'trees'. It is likely that the 'package' is more than the sum of its parts, and that these social and

environmental changes are all pushing infants' immune systems in the same direction. Thus, the increases in asthma prevalence in western countries may reflect changes in immune function as a result of the 'cleaner' environment that occurs with Westernisation. This evidence from epidemiological studies is now supported by clinical and immunological studies, and is producing a major shift in etiologic thinking and new research initiatives at the population, individual and micro levels. These developments may have occurred anyway, but have been greatly enhanced by the epidemiological evidence from international comparisons¹².

Thus, international comparisons have, and will continue to have, a major role in terms of testing and questioning the established paradigms, and developing new ones.¹⁰ In fact, it will be very difficult to identify the key asthma risk factors solely from studies within specific western countries, as almost all children in these countries are exposed to more-or-less the same environments. There are some specific exceptions such as children living anthroposophic lifestyles¹⁰, but these important subgroups are small and will not necessarily be identifiable from general population-based risk factor studies.

Rose¹³ lists other similar examples of ubiquitous risk factors, including softness of the public water supply in Scotland and cardiovascular disease rates, dietary fat and coronary heart disease, and diet and blood pressure and overweight; further examples are added by Khaw and Marmot in the recently published new edition of Rose's book¹⁴. Rose, Khaw and Marmot¹⁴ thus note that entire populations may be exposed to a particular risk factor and there is usually a continuum of disease risk (rather than a clear distinction between the 'sick' and the 'healthy') across the population. Small improvements in the health of a 'sick population' may be more effective than attempts to treat

or prevent illness in 'sick individuals'^{13,14}. However, before such public health measures are adopted, the important near-ubiquitous risk factors must first be identified.

Lack of generalisability between high-income and low-income countries

The strength, and even the direction, of associations between risk factors and disease may vary between populations and over time. For example, coronary heart disease was at one time a disease of the affluent, but has become a disease of the poor as smoking and eating habits have changed over time¹⁵. Thus, appropriate preventive measures at the population level will differ widely between populations. Furthermore, although many specific risk factors will play an important role in any population, their contributions to disease risk will be modified by the baseline disease risk and the presence of various co-factors, making it impossible to assume a universal dose-response relationship¹⁶. A related issue is the importance of considering inter-relationships between causes rather than considering each cause in isolation¹⁷.

In some instances, these differences in exposure-response between populations are not solely of public health interest, but may also be of major scientific importance. For example, 10 years ago, it was widely believed that asthma was an atopic disease caused by allergen exposure. The fundamental etiological mechanism was that allergen exposure, particularly in infancy, produced atopic sensitisation and continued exposure resulted in asthma through the development of eosinophilic airways inflammation, bronchial hyper-responsiveness and reversible airflow obstruction. In recent years, it has become increasingly evident that this picture is, at best, too simplistic^{18,19}. A systematic review of population-based studies²⁰ has shown that the proportion of asthma cases that are attributable to atopy (defined as skin prick test positivity) is usually less than

one-half. Standardised comparisons across populations or time periods also show only weak and inconsistent associations between the prevalence of asthma and the prevalence of atopy. For instance, a comparison of asthma and atopy in 9- to 11-year olds in Albania and the UK²¹ showed large differences in the prevalence of current wheeze (4.4 and 9.7%, respectively) and exercise-induced bronchial reactivity (0.8 and 5.4%) but not in skin prick test positivity (15.0 and 17.8%) suggesting that large variations in asthma prevalence can occur without differences in frequency of atopy. This was confirmed by the International Study on Allergies and Asthma in Children (ISAAC; see below) which showed that the association between atopy and asthma symptoms differed markedly between populations, and increased with economic development¹⁹. In this study, the fraction of current wheeze attributable to atopy ranged from 0% in Ankara (Turkey) to 93.8% in Guangzhou (China); the overall proportion of asthma cases that were attributable to atopy was only 40.7% in affluent countries and 20.3% in non-affluent countries. Moreover, the European Community Respiratory Health Survey (see below) showed that asthma attributable to atopy in adults ranged from 4 to 61% between individual study centres with an overall estimate of only 30% for all centres combined²². These differences are important, because they support other evidence that the role of atopy in asthma may have been over-emphasised, and in many instances may not be causal²⁰.

Lack of exposure in high income countries

In many instances, exposures may not occur at all, or may be at negligible levels, in high-income countries. For example, lack of exercise has become such a pervasive aspect of daily life that it requires a historical perspective to realise how much daily life has changed²³, and that what appears

'normal' now would have been far from normal 50 years ago²⁴.

These issues may particularly apply to occupational and environmental exposures. For example, total bans on the use of asbestos are in place in 52 countries including those of the European Union, Australia, Japan and South Africa²; and its use is tightly restricted in the USA, New Zealand and Canada – the last, ironically, among the world's largest exporters of the material²⁵. However, the global production, sale and use of asbestos continue to flourish and even increase. In 1994, I edited a book²⁶ on occupational cancer in developing countries for the International Agency for Research on Cancer and reported that global asbestos production and use had not declined; rather, the problem was simply being moved from Western countries to emergent economies. Unhappily, the situation has not improved in the intervening 17 years. In India, for example, the use of asbestos has doubled in the last decade to about 300,000 tonnes a year by an industry that now employs an estimated 100,000 workers²⁵. Other major users include China, Brazil, Russia, Ukraine, Kazakhstan and Indonesia. In these parts of the world, where occupational exposures may be difficult to control and enforce, the great majority of asbestos is mixed with cement in the manufacture of sheets for roofing or pipes for sanitation and irrigation in contrast to the uses once common in Europe and North America. The same issues apply more generally to many occupational and environmental exposures – the epicentre of exposure is often in low and middle income countries, whereas exposures are considerably lower, or non-existent, in high-income countries²⁷.

The importance of addressing the most important public health problems on a global basis

Finally, the global population level is fundamental to 'public health

epidemiology' in which the aim is to eventually use epidemiological findings for 'the control of health problems'⁴. The population level is fundamental in the sense that it is important to use research methods that are appropriate to the level at which intervention will eventually take place²⁸. In addition, there are more fundamental scientific issues regarding the process by which knowledge about population determinants is obtained. The 'top-down' approach emphasises that, although all of the levels of analysis are valuable, if our ultimate aim is to find out which factors are most important at the population level, then it is essential that we should start at, and continually refer back to, the population level for a 'reality check'³. It is this 'top down' process, rather than an exclusive focus on the population level, that characterises the population approach to epidemiology. This does not mean that the population level is fundamental in any causal sense (although one could mount an argument that it is). It is merely recognising that if our goal is to ascertain the main determinants of disease in populations, then the population level is fundamental in terms of this particular goal. Such a macro level approach is not unusual in science. Although some molecular biologists may regard their own discipline as the 'gold standard' of science (even though most molecular biology studies are observational), there are numerous established sciences (e.g., cosmology, astronomy, geology, evolutionary biology, climatology), and some less established sciences (e.g., econometrics and the macro-level social sciences) that are observational and that are focused on macro-level systems. The analysis of such complex systems is becoming increasingly important in many areas of research and it is increasingly recognised that some phenomena can be best understood at the macro-level²⁹.

Furthermore, it is increasingly recognised that 'Western' epidemiologists now have global

responsibilities²⁷. For example, the limited success of legislative measures in industrialised countries has led the tobacco industry to shift its promotional activities to developing countries so that more people are exposed to tobacco smoke than ever before⁴. As noted above, similar shifts have occurred for some occupational carcinogens⁵ and for other occupational hazards⁶. The global 'achievement' of the public health movement has often been to move public health problems from rich countries to poor countries. Just as 'the West' represents a minority of the world's population, but uses the majority of the resources, only about 10% of the world's health research funding is allocated to the 90% of the world's health problems which occur in non-Western populations⁷. However, it should be stressed that what is required is not that Western epidemiologists engage in 'volunteerism' to enable the 'benefits' of Western approaches to epidemiology to be shared by the non-Western world. In contrast, Ebrahim and Davey Smith⁸ argue that the individual-focussed methods of health promotion for coronary heart disease and stroke have had limited success in the West and that we are now 'exporting our tired and failed models of health promotion to developing countries'. This does not mean that there is nothing that non-Western epidemiologists can learn from the West; clearly there is a great deal, but what is needed is a dialogue rather than a monologue¹. With increasing globalisation, we are all in it together.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies,

gave informed consent to participate in these studies.

So can the role of near-ubiquitous risk factors be studied and their importance for disease causation quantified? Yes they can, but it is not easy, and they cannot always be studied with our 'standard' methods such as randomised controlled trials, cohort studies or case-control studies. In particular, ecological comparisons between populations (i.e., comparisons in which we only have both exposures and outcome data on countries or regions, not on individuals), and comparisons over time, have played a major role in generating hypotheses and identifying important population risk factors for disease. They play a particularly important role when important risk factors are ubiquitous, or nearly ubiquitous, in particular countries, or in particular time periods. Of course, such studies are fraught with difficulties because of problems of 'the ecologic fallacy'³⁰. Thus, ecologic studies provide virtually no evidence as to causation. On the other hand, they may be the best way (or the only way) to identify the major population-level determinants of disease, which can then be studied in depth using other study designs, for example, national or multi-national cohort or case-control studies. Thus, while ecologic studies are not sufficient in themselves for identifying risk factors or establishing causation, they are an essential part of a wider scientific process⁵. In this context, it is important to emphasise that the appropriateness of any research methodology depends on the phenomenon under study: its magnitude, the setting, the current state of theory and knowledge, the availability of valid measurement tools, and the proposed uses of the information to be gathered. The appropriateness of a research method in epidemiology is determined by the nature of the problem under consideration, the community resources and skills available and the prevailing norms and values at the national, regional or local

level³¹. If we want to discover (or at least generate hypotheses about) the major population-level determinants of disease, then ecologic studies will play an essential role in those processes, despite their methodological limitations.

Once a particular hypothesis has been proposed, studies can be conducted within particular countries, even if there is little variation in exposure to a particular risk factor, provided that at least some people are exposed and some are not. For example, suppose we have two countries, in one of which 50% of the population are smokers, and in the other 95% are smokers. The percentage of population variation explained will be different in the two countries, and will in fact be greater in the country in which only 50% smoke. However, the incidence rate ratio comparing smokers and non-smokers, and the dose-response curve, will be about the same in the two countries (i.e., about a 10-fold risk for smoking a pack a day for many years). Thus, it is still possible in principle to identify the major risk factors for disease, provided that there is at least some population variation. However, the problem is that too often the major population risk factors will not be hypothesised (and therefore will not be studied) when they are ubiquitous.

Thus, we do not just need better methods. We also need better hypotheses. Historically, these have usually come from population comparisons, rather than from laboratory-based research. Despite the major advances in methodology for molecular-based epidemiology in the last decade, our best ideas are likely to continue to arise from population comparisons, as the complex exposure patterns of 'free range' humans will continue to create disease risks which are unlikely to be routinely identified in the laboratory. Furthermore, a global approach is likely to yield the best dividends in public health as well as scientific terms. For these reasons, the globalisation of epidemiology is going

to occur as inevitably as economic globalisation is occurring, and in both instances the issue is what form that globalisation will take²⁷. Will we simply 'export failure' through our 'volunteerism', and our exporting of epidemiologic methods developed specifically for studies of individual lifestyle risk factors in Western countries?³² Or will a truly global epidemiology develop to address the major global public health problems using appropriate methodology? If we are to take the latter approach, then international comparisons and collaborations will continue to play a key role.

Conclusion

International collaborative studies will continue to have a major role in epidemiological research.

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