

Synopsis of Research Articles

Which Treatment for Postherpetic Neuralgia?

DOI: 10.1371/journal.pmed.0020238

Postherpetic neuralgia (PHN) is a chronically painful condition that is a complication of shingles (acute herpes zoster), a recurrence of the varicella-zoster virus, which initially causes chickenpox. Although shingles usually resolves within a month, some people continue to feel the pain of PHN long after the rash and blisters heal, because of nerve damage (neuropathic pain) caused by the shingles. Not everyone who has had shingles develops PHN, although it is a common complication of shingles in older adults.

Despite advances in antiviral therapy during acute herpes zoster and the more recent introduction of vaccination against varicella zoster, PHN continues to be a significant clinical problem, with 10–20% of patients developing persistent neuropathic pain after acute herpes zoster reactivation. The nature of PHN pain is variable, which implies that a variety of mechanisms might be operating. This variability has led to the hypothesis that treatment plans could be optimised for individual patients on the basis of the individual pattern of their symptoms or the underlying mechanism of the pain.

However, the current evidence base for therapies in PHN is based on clinical trials of analgesics, which have examined PHN as a single disease entity. Furthermore, there is little evidence for the efficacy of drugs for specific sets of symptoms and no simple way to determine which pain mechanisms might be operating in an individual patient.

In this month's *PLoS Medicine*, Andrew Rice and colleagues reassessed the evidence base by doing a systematic review and meta-analysis of analgesic therapy for PHN, which has fundamentally changed in the wake of several major new trials. The authors searched the literature for trials of PHN and retrieved 62 articles, of which 35 were kept for final analysis.

Their analysis confirmed several previous research findings, although they cautioned that the meta-analytic study design of collecting data from a range of trials had several inherent pitfalls, and it is difficult to directly compare treatments across different trials.

However, they found evidence for analgesic efficacy in established PHN for

orally administered therapies, such as tricyclic antidepressants, some opioids, gabapentin, tramadol, and pregabalin. Some topically administered therapies, such as lidocaine and capsaicin, were associated with analgesic efficacy in selected patients. However, it appeared that therapies such as oral administration of certain NMDA receptor antagonists, codeine, ibuprofen, lorazepam, 5HT1 receptor agonists, and acyclovir were not efficacious in PHN.

Altogether, the authors conclude that the evidence base supports the first-line use of a tricyclic antidepressant for orally administered treatment of PHN, reserving the gabapentinoids for second-line use. Topical treatments, such as lidocaine or capsaicin, should be considered as first-line treatment if a patient falls into the “sensitised nociceptor” as opposed to “deafferentation” sub-group of PHN patients.

The role of intrathecal steroid is still not clear: one trial indicated that intrathecal steroids were associated with benefits in patients with PHN, but this therapy

might be hazardous, and the authors and other researchers have concluded that further high-quality trials of this therapy are needed. The authors found little evidence regarding possible synergistic effects of the various treatments to support or refute the concomitant use of combinations of drugs.

They stressed that any treatment plan must recognise the importance of the biopsychosocial model of chronic pain and that any pharmacologically based management of PHN should be combined with advice on and management of psychological and social aspects.

Finally, as there is no single pathophysiology that underlies PHN, they propose that future studies should use quantitative sensory evaluation to clearly categorise subsets of participants for better interpretation of treatment effects.

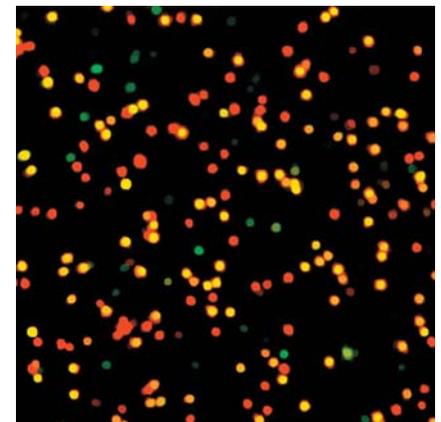
Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice ASC (2005) Analgesic therapy in postherpetic neuralgia: A quantitative systematic review. DOI: 10.1371/journal.pmed.0020164

Towards a Cheap and Easy Way to Monitor HIV/AIDS

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It doesn't take a trained physician to know that a disease needs to be diagnosed to be treated. And it doesn't take an economist to know that a disease cannot be diagnosed if the required tools are unaffordable or impractical. The absence of early diagnosis and treatment is particularly problematic for infectious disease, where the lack of early treatment or isolation can result in an epidemic.

Given the technological requirements, diagnosis and monitoring of HIV infection is problematic in resource-poor areas. The advent of rapid tests for diagnosing HIV infection represents one part of the solution. Less clear is how patients diagnosed with HIV infection will be monitored, given the importance of CD4 cell counts. A decrease in CD4⁺ T lymphocytes—a critical immune cell infected by HIV—is one of the hallmarks of HIV disease, and CD4⁺ cell number is a key factor in determining disease progression and monitoring treatment. The methods for determining CD4⁺ cell numbers are technically complex,



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Digital image of whole blood obtained using the prototype device: CD4⁺ T cells shown in yellow, monocytes in green, CD8⁺ T cells in red

expensive, and not easily transportable. These factors severely limit the ability to monitor HIV disease in locations where resources, training, and mobility are limited.

Lymphocytes are characterized by cell surface markers; thus, CD4⁺ lymphocytes express the CD4 marker on their surface. Antibody probes that specifically recognize this and other cell surface markers (such as CD8, which distinguishes that lymphocyte population from CD4⁺ lymphocytes, and CD3, which is a marker for all T lymphocytes) are used to count and differentiate various cell populations. By labeling cells with fluorescently tagged antibodies that recognize one or more cell surface molecules, the relative and absolute numbers of specific cells can be determined by a technique called flow cytometry. The labeled cells are passed through the flow cytometer, where the fluorescent probes are activated by lasers in a manner that can be read by specific detectors. The CD4⁺ cell number is directly correlated with the resultant fluorescent intensity and other light scatter properties. The problem is that flow cytometry requires costly reagents and substantial technical expertise—factors that limit its use in less developed areas.

Taking advantage of advances in microfluidics, digital imaging, and cell analysis, William Rodriguez and

colleagues now report on a way to count CD4⁺ cells in a relatively quick, easy, and affordable manner. Small volumes of blood (an amount that could be obtained by a finger prick as opposed to drawing blood from a vein) are labeled as in flow cytometry, but with far less of the expensive reagents. Microfiltration allows the labeled CD4⁺ cells to be captured and separated from red blood cells, another simplification relative to flow cytometry. Digital images of the labeled cells, obtained by digital fluorescence microscopy, are then analyzed by newly developed software that can distinguish the CD4, CD8, and CD3 labels, thus allowing determination of absolute CD4⁺ counts, CD4⁺ percentages, and CD4⁺:CD8⁺ lymphocyte ratios.

Rodriguez et al. found that this new method was less accurate than flow cytometry for determining absolute CD4⁺ lymphocyte counts above 500 cells/mm³ (levels that are typically not relevant for monitoring HIV-infected individuals). But the method was as accurate as flow cytometry at clinically relevant levels of CD4⁺ cells for HIV-infected adult individuals. Although only a small number of pediatric patients were examined (and thus statistical

significance could not be ascertained), the method appears to be also effective in determining CD4⁺ lymphocyte percentages in children.

The detection system used in the present report is a tabletop instrument that serves as a prototype for a fully portable handheld model, which is now under development. After some modest training, such a tool should allow a variety of health-care workers in remote areas to accurately analyze the CD4⁺ status of HIV-infected patients (the basis for treatment decisions) locally. In an accompanying Perspective discussing this new tool (DOI: 10.1371/journal.pmed.0020214), Zvi Bentwich argues that before it is ready for widespread use, several issues still need to be resolved, such as its final cost and its applicability to pediatric patients. “Despite these reservations,” he says, “the authors of this study should be commended for addressing an extremely important issue and developing this novel approach for counting CD4 in patients with HIV.”

Rodriguez WR, Christodoulides N, Floriano PN, Graham S, Mohanty S, et al. (2005) A microchip CD4 counting method for HIV monitoring in resource-poor settings. DOI: 10.1371/journal.pmed.0020182

Appropriate Modeling of Infectious Diseases

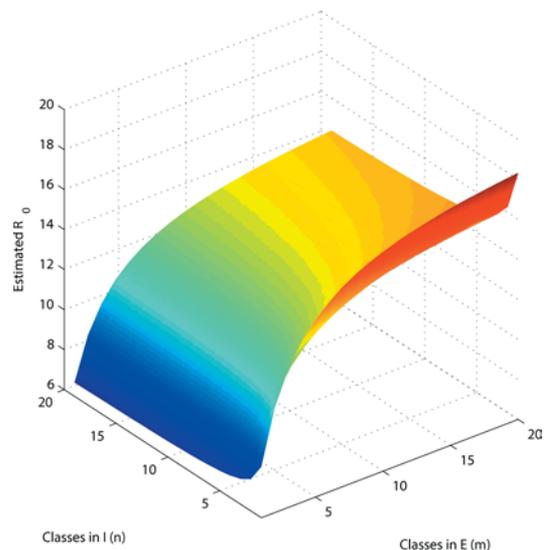
DOI: 10.1371/journal.pmed.0020239

When the SARS epidemic showed the first signs of waning, the World Health Organization proclaimed that the turnaround was a testament to the efficient response of health systems worldwide and justified its decisive action in issuing a global alert.

That swift response was partly due to infectious disease experts being able to use models of disease spread, even though SARS was a newly emerging disease, to help plan their next move. In fact, epidemiologists have used mathematical models to predict and understand the dynamics of infectious diseases for more than 200 years. The emergence of diseases such as Ebola, SARS, and West Nile virus, and multi-drug-resistant malaria—as well as the potential for diseases to be introduced by bioterrorism—has attached even greater importance to this management tool.

Models are used to provide information on such infections and predict the effect of alternative courses of action. In this month's *PLoS Medicine*, Helen Wearing and colleagues suggest, however, that many off-the-shelf models are inappropriate for making quantitative predictions because substantial biases have been introduced by two important, yet largely ignored, assumptions. The authors warn that if such biases are not corrected, health authorities risk making overly optimistic health policy decisions.

They begin with the “SEIR” class of models, in which the host population is classified according to infectious status, i.e., individuals are susceptible, exposed, infectious, or recovered. This



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Estimates of variation in the basic reproductive ratio

model assumes that the rate of leaving the exposed or infectious class is constant, irrespective of the time already spent in that class. Although mathematically convenient, this assumption gives rise to exponentially distributed latent (incubation) and infectious periods, which is epidemiologically unrealistic for most

infections, say the authors, who suggest instead that it would be more sensible to specify the probability of leaving a class as a function of the time spent within the class. Hence, initially, the chance of leaving the class is small but then increases as the mean infectious/incubation period is reached. This assumption would give a more realistic distribution of incubation and infectious periods.

The authors also note another issue that has received surprisingly little attention in infectious disease models, namely, the influence of incubation and infectious period distributions on the invasion dynamics of an infection into a largely susceptible population—despite its obvious application to emerging infections and possible “deliberate exposure.”

The impact of these differences on models could translate into potentially important public health concerns, say the authors. They tested their theory by using analytical methods to show that, first, ignoring the incubation period or, second, assuming exponentially distributed incubation and infectious periods (when including the incubation period) always resulted in underestimating the basic reproductive ratio of an infection from outbreak data. They then illustrated these points by fitting epidemic models to data from an influenza outbreak. Their results suggested that within a strict management setting, epidemiological details could make a crucial difference.

Although previous studies have shown the importance of using realistic distributions of incubation and infectious periods in endemic disease models, few studies have considered the effects associated with making predictions for an emerging disease. Discrepancies between estimates of reproductive ratio from exponentially distributed and gamma-distributed fits confirm the need to have precise distributions of incubation and infectious periods. Although such data are available from post hoc analyses of epidemics, they are lacking for novel emerging infections. The key point is that uncertainty about these distributions should be incorporated into models when making quantitative predictions.

The take home message is that when developing models for public health use, policy makers need to pay attention to the intrinsic assumptions within classical models. The authors note that while some practitioners are using their approach, most applied epidemiological studies still use models that incorporate exponentially distributed incubation and infectious periods; the authors hope their work will point to the next steps in delivering quantitatively accurate epidemiological models.

Wearing HJ, Rohani P, Keeling MJ (2005) Appropriate models for the management of infectious diseases. DOI: 10.1371/journal.pmed.0020174

Which Combination Therapy for Uncomplicated Malaria in Africa?

DOI: 10.1371/journal.pmed.0020236

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, mostly in young children. The number of deaths is increasing, and one key factor linked to this has been widespread drug resistance of *Plasmodium falciparum* to conventional antimalarials, such as sulfadoxine-pyrimethamine (SP); such resistance is widespread in southeast Asia, South America, and Africa. The inappropriate use of antimalarials during the past century has contributed to this increase in resistance. For example, there has been overreliance on quinolines (such as chloroquine) and antifolates (such as pyrimethamine) resulting in cross-resistance among these drug classes. However, in the past decade, a new group of antimalarials—the artemisinin compounds, such as artesunate, artemether, and dihydroartemisinin—have been deployed on an increasingly large scale.

These compounds produce a very rapid therapeutic response, are active against parasites resistant to multiple drugs, are well tolerated, and reduce



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A trial site in Uganda

gametocyte carriage. To date, no parasite resistance to these compounds has been detected.

If used alone, the artemisinins will cure falciparum malaria in seven days, but studies in southeast Asia have shown that combinations of artemisinin compounds with certain synthetic drugs produce high cure rates after just three days of treatment. There is also some evidence that combinations of therapies could greatly retard development of resistance to the partner drug. Although combinations including artemisinins have been widely advocated, they are

expensive and relatively untested in highly endemic areas.

In this month's *PLoS Medicine*, Adoke Yeka and colleagues compared artemisinin-based compounds and other combination therapies in four districts with varying transmission intensity in Uganda in 2,160 patients aged six months or greater with uncomplicated falciparum malaria. The team tested the combination of chloroquine and SP, currently the first-line therapy in Uganda, the combination of amodiaquine and SP, a cheap regimen proven to be efficacious in previous trials, and the combination of amodiaquine and artesunate.

During the 28-day study they collected data on the efficacy of the different regimens and examined the effect on recrudescence and new infections after therapy. Combined amodiaquine and artesunate was the most efficacious regimen for preventing recrudescence, but this benefit was outweighed by an increased risk of new infection. This result was probably due to artesunate being rapidly eliminated, leaving only amodiaquine to provide post-treatment prophylaxis. Considering all recurrent infections, the combination

of amodiaquine and SP was at least as efficacious as the other combinations at all sites and superior at the highest transmission sites.

In all, 72% of all recurrent infections were due to new infections, and with the two most efficacious regimens (amodiaquine and SP, and amodiaquine and artesunate) this proportion was 80%. The identification of new infections stressed the need for other malaria control measures, such as bed nets, said the authors.

They also suggested that antimalarials should be judged not just on their impact on recrudescence but also

on their impact on the risk of new infections after therapy. Previous studies have suggested that patients who suffer recrudescence have a higher risk of complicated malaria and death. Artemisinins are highly attractive antimalarials, but when used as monotherapy, they have a high risk of recrudescence and hence must be combined with other antimalarials to achieve maximum efficacy. But whether the partner drug should be long or short acting remains unclear, said the authors.

Altogether, artemisinin combinations offer great hope for Africa, the authors say, although the ideal combination

regimen remains uncertain and cost is a problem. To compare the efficacy of the different therapies, bigger and longer controlled trials are needed in conditions of varied transmission intensity. Nevertheless, based on the results of this study and others, Uganda has chosen a combination of artemether and lumefantrine as its first-line therapy against malaria.

Yeka A, Banek K, Bakyaita N, Staedke SG, Kanya MR, et al. (2005) Artemisinin versus nonartemisinin combination therapy for uncomplicated malaria: Randomized clinical trials from four sites in Uganda. DOI: 10.1371/journal.pmed.0020190

Targeting of a Host Protein to Suppress Hepatitis B Virus Replication

DOI: 10.1371/journal.pmed.0020237

Hepatitis B is a serious global public health problem but is preventable with safe and effective vaccines that have been available since 1982. Despite these vaccines, about 2 billion people have been infected with hepatitis B virus (HBV), and more than 350 million have lifelong infections. These chronically infected people are at high risk of death from cirrhosis of the liver and liver cancer, which both kill about 1 million people each year.

Suppression of viral replication in chronic carriers of HBV is an effective approach to controlling disease progression. Current antiviral therapies include lamivudine and alpha-interferon, but long-term resolution of the disease is disappointing because of low seroconversion rates and the development of drug-resistant viral mutants.

In this month's *PLoS Medicine*, Lisa F. P. Ng and colleagues describe the identification of a host factor that has a significant effect on viral replication efficiency. The team began by examining the serum viral load of a group of carriers of hepatitis B in relation to the HBV genome carried. They found a significant association between high serum viral load and a natural sequence variant within the HBV enhancer II regulatory region at position 1752. Upon testing all four possible 1752 variants, the 1752A variant had the highest transcriptional activity.

Further investigation of this enhanced transcriptional activity revealed evidence of possible interaction with host DNA binding proteins. The team found that a protein present in the human host—hnRNPK—could be isolated by direct binding to a viral fragment derived from the HBV variant of these infected patients.

hnRNPK has previously been shown to be involved in several cellular functions—for example, as a regulator of signal transduction and of gene expression. On further examination of the role of hnRNPK in HBV replication, they established that hnRNPK is capable of acting on the full

length of HBV, rather than just a partial fragment. They compared four full-length replicative HBV clones, identical except for a single base change at position 1752, that were transfected with two different hnRNPK expression constructs and showed that 1752A was more efficient at promoting replication than the other three variants.

To further show the role of hnRNPK in HBV replication, the team tested the effect of over-expression and down-regulation of the cellular protein. Using siRNA, designed to reduce endogenous hnRNPK, they showed suppression of both hnRNPK mRNA and HBV viral load, whereas a control siRNA had no effect on HBV viral load.

Despite these findings, the mechanism behind hnRNPK on HBV replication needs further exploration, the authors say, concluding that viral replication efficiency was determined by a combination of viral sequence and interaction with specific host proteins. However, they suggest that these results indicate that although drug development of antivirals is an established research avenue, targeting the host is an untapped opportunity.

They describe parallels with anti-EGFR antibody treatment of breast cancer cells, which produced a decrease in cell replication rate and corresponding reduction in hnRNPK expression levels; this result suggested that hnRNPK levels could be modulated by anti-EGFR treatment, thus highlighting new treatment options for altering the HBV viral load in chronic carriers.

The authors conclude that the future of long-term viral clearance will require combination therapy of targeting the virus directly, blocking host support proteins, and using immuno-modulating agents.

Ng LFP, Chan M, Chan SH, Cheng PCP, Leung EHC, et al. (2005) Host heterogeneous ribonucleoprotein K (hnRNP K) as a potential target to suppress hepatitis B virus replication. DOI: 10.1371/journal.pmed.0020163

Twins' Health and Adult Socioeconomic Status

DOI: 10.1371/journal.pmed.0020235

Twins' research is a favorite tool of the human geneticist, but it has a controversial history. Nazi doctor Josef Mengele, infamous for his work at Auschwitz, was fascinated by twins. He sought them out at the extermination camp and used them in violent experiments. Later, British psychologist Cyril Burt worked on the heredity of intelligence, producing findings that some suspected were "too good"—and which later were shown to be based on fraudulent data involving invented twins.

In this month's *PLoS Medicine*, Nancy Krieger and colleagues examine the health of female twins from a very different perspective. To understand the impact of lifetime socioeconomic position on health, they studied twins who were raised together but who had different socioeconomic position after adolescence. Many studies have compared the health of twins raised separately since birth or early childhood, but few have investigated the adult health of twins raised together but who had different post-adolescent socioeconomic position. Such a study could clarify the impact of adult experiences on adult health in a population matched on early life experiences, the authors say.

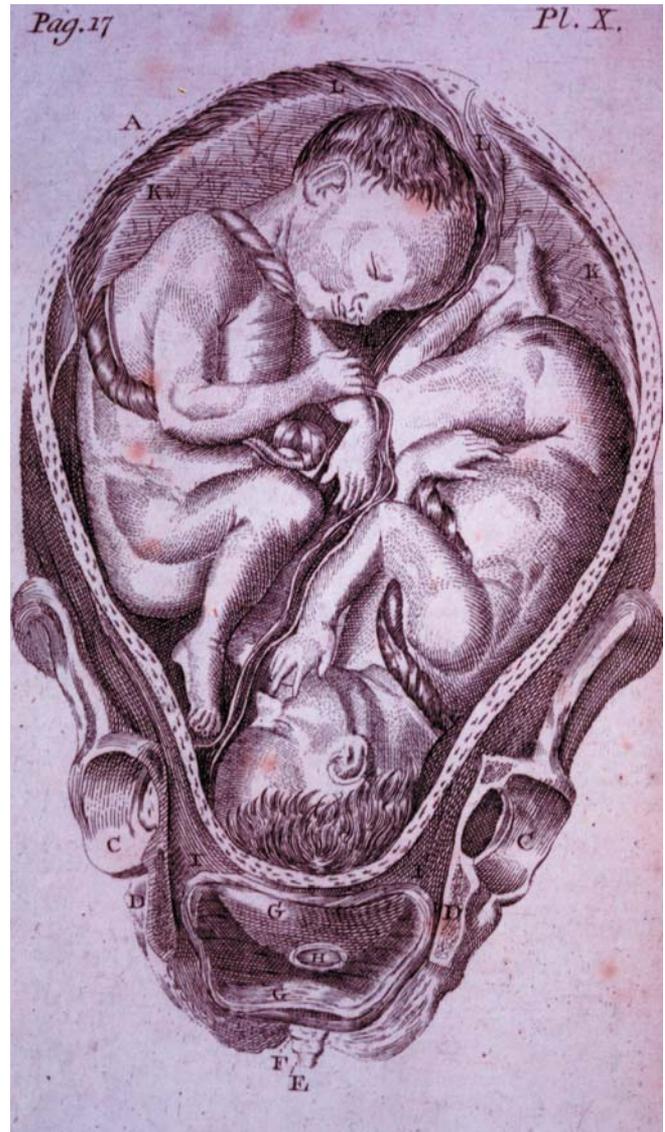
Krieger's team employed data from a cohort of 434 twins who lived in the San Francisco Bay area in 1978–1979; the average age at recruitment was 41 years old. The cohort was given a health and sociodemographic questionnaire. Data on anthropometric and biological characteristics were obtained by physical examination and laboratory analyses; the process was repeated at a second examination around 1989–1990. At the second phase of the study, 72 women (8.3%) did not return, of whom 36 had died, which left 352 twin pairs (58% monozygotic, 42% dizygotic), representing 81.1% of the original cohort.

The sociodemographic and health characteristics of the full cohort (352 pairs) and the cohort analyzed (those pairs where it was known both that they had lived together until at least age 14 and their joint socioeconomic was available—i.e., 308 pairs) were quite similar: 40% grew up in working-class households and 80% in households where the father had fewer than four years of college education.

At the second examination, 32% of the twin pairs in the analytic cohort had a difference in their adult household occupational class, and 20% had different levels of college education. The team found that health outcomes among monozygotic adult female twins who lived together through childhood varied by their subsequent socioeconomic position. Twins with differing occupational class differed in health status compared with twins with similar occupational class. The working-class twin had significantly higher systolic blood pressure, diastolic blood pressure, and LDL cholesterol than her professional, non-working-class twin. Twins discordant on educational level, however, had similar health status, likely reflecting the fact that current occupational class is a better measure for investigating the impact of lifetime socioeconomic position than is education (which is completed usually in early adulthood). Dizygotic twins with differing adult socioeconomic position, either occupational class or educational level, did not notably differ in their adult health status.

These novel findings lend support to the hypothesis that health is shaped not only by early life experiences but also by cumulative experiences across the lifecourse, the authors say.

As with many twin studies, the numbers of individuals studied is relatively limited. The lack of some biological and personal



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Twins in the womb (from the first US textbook on midwifery, *An Abridgement of the Practice of Midwifery*, by W. Smellie, 1786)

data such as detailed occupational class position over time, lack of data on income, poverty, wealth, debt, gestational age, birthweight, and birth order also limits the conclusions that can be drawn. These limitations are countered, however, by the tight matching of the twins on early life and childhood exposures, as well as by the matching for genetic endowment among the monozygotic twins. Together, the findings have important implications for health policy, since they suggest that adult socioeconomic position does have an impact on adult health above and beyond early life exposures, and they also add to our understanding of how societal conditions shape population patterns of health, disease, and well-being.

Krieger N, Chen JT, Coull BA, Selby JV (2005) Lifetime socioeconomic position and twins' health: An analysis of 308 pairs of United States women twins. DOI: 10.1371/journal.pmed.0020162