American Journal of Epidemiology

DOI: 10.1093/aje/kwy221

## Commentary

# Epidemiologists of the Future: Data Collectors or Scientists?

**Lewis H. Kuller***

* Correspondence to Dr. Lewis H. Kuller, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 North Bellefield Avenue, Room 354, Pittsburgh, PA 15261 (e-mail: kullerl@edc.pitt.edu).

*Initially submitted July 19, 2018; accepted for publication September 21, 2018.*

Epidemiology is the study of epidemics. It is a biological science that includes expertise in many disciplines in social and behavioral sciences. Epidemiology is also a key component of preventive medicine and public health. Unfortunately, over recent years, academic epidemiology has lost its relationship with preventive medicine, as well as much of its focus on epidemics. The new "-omics" technologies to measure risk factors and phenotypes, and advances in genomics (e.g., host susceptibility) consistent with good epidemiology methods will likely enhance epidemiology research. There is a need based on these new technologies to modify training, especially for the first-level doctorate epidemiologist.

causality; cervical cancer; epidemics; genomics; preventive medicine; teaching

In 1992, Terris (1) published an important paper as part of the 25th anniversary of the Society of Epidemiological Research in which he defined epidemiology as the study of the health of human populations. He discussed 4 fundamental activities of epidemiology: 1) primary discovery of the causal agents of epidemics; 2) determining the magnitude and determinants of morbidity, mortality, and health in defined communities; 3) identifying high-risk populations; and 4) being independent evaluators of health programs. Terris focused epidemiology on population health and he and others noted that epidemiology was dependent on biological sciences.

The rapid development of genomics in the 1990s has had a dramatic effect on Terris' third objective, moving from identifying high-risk populations on the basis of demography (e.g., age, race, sex, socioeconomic status) to attempting to define individuals within populations on the basis of genomics (e.g., precision medicine) (2).

Terris, myself, and others were concerned about the growing loss of the important linkage between epidemiology at academic institutions and public health and preventive medicine (3). Sandro Galea has been a champion of urging epidemiology to be consequential (4).

## 1960S: DIFFERENCES BETWEEN CHRONIC AND INFECTIOUS DISEASE EPIDEMIOLOGY

A major controversy in the 1960s was the differences between infectious and chronic disease epidemiology (5). I explored these differences in 1987, defining epidemiology as the study of epidemics and stating that the goal of epidemiologic studies was to decrease morbidity and death and improve health by identifying the determinants of disease (6). There really was no difference between infectious and chronic disease epidemiology except for the longer incubation period. All diseases have a unique distribution in time, place, and person, because of variation in exposure(s) to causal agents and genetic host susceptibility. The absence of any variability of disease in relationship to these attributes suggests the disease of interest is pleiotropic (i.e., more than 1 disease with similar clinical phenotype) (7–9). Epidemics are caused by new exposures to agents due to changes in lifestyles and environment. Sometimes, however, changes in distribution of disease are a function of improved methods of ascertainment or disease classification (e.g., changing the criteria for hypertension) (10). The key to being a successful epidemiologist is to identify the epidemic as early as possible and the causal pathways, so potential public health, preventive medicine, and clinical medicine interventions to reduce morbidity and death can be applied. This is true for diseases requiring short or long incubation periods.

Good surveillance of defined populations and identification of unique events in subgroups at very high risk (11, 12) with unique characteristics often provide clues to evolving epidemics. Hopefully, new and better technologies for monitoring populations, especially large samples, will provide expanded approaches to earlier identification of epidemics (13).

## THE EPIDEMIOLOGIC APPROACH TO STUDYING DISEASE ETIOLOGY

The epidemiologic approach involved 9 steps (6): 1) (most important) Is there an epidemic? 2) If yes, what is the population at risk? 3) What is the mode of transmission? 4) What are the possible etiological agents? 5) What is the attack rate (i.e., incidence)? 6) What is the gradation of disease (i.e., subclinical to clinical disease)? 7) What is the incubation period? 8) What are the best methods to control the epidemic? For example, should clinical trials be conducted? 9) How effective are the control procedures? For example, should effectiveness studies be conducted? In a paper in the *American Journal of Epidemiology* (3), on the 100th anniversary of the Johns Hopkins School of Public Health, I discussed some of these components of epidemiology and therefore have restricted this article to a few important issues for the future.

## AGENTS OF DISEASE (ETIOLOGY)

Etiology of disease (i.e., the study of causal pathways) has been a major concern of chronic disease epidemiologists (14, 15). Chronic disease epidemiologic research was severely criticized because none of the etiological observations met the traditional requirements of the Koch's postulates of infectious disease (5, 16). For example, lung cancer did not develop in most cigarette smokers and cases of lung cancer occurred among nonsmokers. Lilienfeld (17) suggested that many of the variables associated with increasing incidence of chronic diseases were "vectors" in the pathway to the specific etiological agent(s). In 1976, Alfred Evans, professor of Epidemiology at Yale, proposed guidelines for investigation of etiology for infectious and chronic disease epidemiology (18). Cervical cancer epidemiology was a good example. The vectors included low socioeconomic status, early age at first intercourse, and then multiple sex partners. Ultimately, low risk for cervical cancer was identified in certain populations, such as Jewish women and nuns. Vectors pointed to a venereal disease with the ultimate success of identifying human papillomavirus virus, specific types of human papillomavirus as the causal agent, and then the development of an effective vaccine (19–21). Epidemiologic studies evolved from descriptive, observational, case-control, longitudinal to clinical trials, and finally, efficacy studies, now often referred to as "pragmatic trials."

## CAUSAL PATHWAYS OF DISEASE

### The biology approach

There are 3 current approaches to identifying causal pathways. First, the physical and social factors are vectors in the causal pathway of disease leading to exposure to biological agents, such as unique environmental toxins or micronutrients, or living organisms, such as viruses. Epidemiology is a biological science. New epidemiologic research methods, such as Mendelian randomization (22), personalized monitoring of exposures, and epigenetic and RNA analyses (23, 24), to evaluate biological responses of the individual to the agents are some of the important new technologies. Also, better data analysis and monitoring very large sample sizes (i.e., "big data") are of potential great value (25).

### Physical and social factors as causal factors

Second, the interrelationships of physical and social environmental factors and host susceptibility are the primary pathways of disease (26, 27). Education, housing, and social factors, such as racism, religious practices, occupation, marital status, social stressors, and family structure, are powerful predictors of disease. Epidemiology is a social science. Most observations of the strong association of social class and education variables to disease are well recognized by most individuals in the community, irrespective of whether they are epidemiologists. Many epidemiologists are strong advocates and leaders for social changes to improve health. A very important component of this approach is the study of the social and physical environmental interactions that determine the distribution and rate of transmission of the epidemic in populations. New biostatistical modeling that originally was used primarily for infectious diseases with a short incubation period but now also is used for diseases requiring long incubation periods is valuable in studying the transmission of these diseases in the population and especially the interrelationship of social and behavioral dynamics of disease transmission within and between populations (28).

### -Omics as causal pathway (phenomenology)

The third approach assumes that epidemiology is primarily a data collection and analysis discipline. New areas of research focus on biological pathways (i.e., so-called -omics) with little interest in the external (i.e., environment or causal agents of disease). I previously described this as "phenomenology" (29). The approach includes identifying genomic risk, then using epigenetic and RNA analysis as markers of environmental exposures and "molecular pathology epidemiology" (30) and applicable -omics to identify pathways of disease (31). There are no specific hypotheses, agnostic approach, or attempts to identify epidemics. Many epidemiologists have joined this approach by applying the new biomarker technologies to current longitudinal epidemiology studies—"pseudopod" epidemiology (32, 33). The primary role of the epidemiologist in this third approach is as a data collector and analyst.

## EPIDEMIOLOGIC METHODS AND NEW TECHNOLOGIES ARE THE WINNERS

Today, the traditional epidemiologic approaches to studying epidemics, combined with modern scientific technology, have had a bigger impact than the phenomenological approach. This may change if, as suggested, all the low-hanging fruit from epidemiologic studies has been culled (which is doubtful). Will the future of epidemiology be based on the -omics ladder to reach the high-risk fruits or are there just a lot of "lemons" waiting to be picked at a very high cost?

To date, most diseases in the population are determined by a relatively few well-defined epidemics, as shown in Table 1. The big problem is, given an epidemic and causal pathways

**Table 1.** Examples of Epidemics (Not Inclusive)

| Epidemic | Type | Measurement | Outcome |
|---|---|---|---|
| CHD | Common source<br>Diet, saturated, polyunsaturated, monounsaturated fat | Change in blood cholesterol level | Trends in CHD death in those <65 years of age |
| Lung cancer, COPD, other smoking-related cancers | Person-to-person | Change in cigarette smoking | Trends in lung cancer in young people |
| Drug deaths | Person-to-person<br>Common source | Change in opioid drug use | Drug overdose deaths: total death rate |
| Accidental deaths | Common source<br>Person-to-person | Change in alcohol, drug consumption | Accidental death rate |
| Suicide | Common source | Changes in alcohol and drug use. Guns? | Suicide death rates |
| Homicide | Common source<br>Person-to-person | Alcohol, drugs, guns | Homicide death rate |
| Obesity-related diabetes | Common source<br>Kilocalorie intake, energy expenditure | Change in BMI, percent obesity | Incidence of type 2 diabetes, hypertension, other diseases |
| HIV | Person-to-person | Change in incidence of HIV | HIV death rate, some cancers |
| Cirrhosis and liver cancer | Common source<br>Person-to-person<br>Alcohol, hepatitis viruses (especially B in the United States), obesity | Change in alcohol consumption, obesity, immunization | Cirrhosis death rate |
| Stroke | Common source | Salt consumption, change in BP levels, hypertension control | Stroke death rates in those <65 years of age |
| Autism and related neurological diseases in children | Person-to-person<br>Common source? | Brain MRI, PET, exposure to neurotoxins, viruses? | Rates of autism and other neurological disease, cognition, IQ, developmental abnormalities |
| Poor cognition (in part) | Common source<br>Lead in environment | Lead levels in blood | Decreased lead levels, IQ |
| Stomach cancer | Person-to-person | Exposure to *Helicobacter pylori*, gastric atrophy | Decreased stomach cancer in middle age, decreased antibody titers |
| Cervical cancer | Person-to-person | Carcinogenic HPV levels | Decreased cervical cancer, vaccine uptick |
| Small brain size, Zika virus | Vector borne | Antibody titers, virus, mosquitos | Malformations, cognition |
| COPD, CHD | Common source<br>Pollution, air | Air pollution levels, fine particulates, ozone, pulmonary function | Reduction of pollution, decreased COPD, CHD |
| Lyme disease | Vector borne | Antibody titers, Lyme arthritis | Vaccine, reduced tick exposures, antibody levels |
| Influenza | Person-to-person | Vaccine coverage, antibody levels | Death totals, CHD incidence, pneumonia |

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HPV, human papillomavirus; IQ, intelligence quotient; MRI, magnetic resonance imaging; PET, positron emission tomography.

to disease, how to control it—whether by lifestyle or environmental changes, new drugs, surgical procedures (e.g., bariatric surgery for the obesity epidemic) (34–40).

The phenomenology approach assumes we can identify all the genes and their variations in the genome, all the proteins associated with the genes through proteomics, and secondary metabolic pathways (e.g., metabolomics, lipidomics), and then the biological abnormalities associated with exposure, let us say, to Ebola virus or excess use of opiates will be identified and new pharmacological therapies will be immediately available. Until this fantasy becomes a reality, epidemiology may still have an important role in controlling epidemics (41).

## IDENTIFY AND CONTROL NEW EPIDEMICS

New epidemics due to exposures to changes in physical and social environments or lifestyles are on the horizon. Most of these epidemics will begin in the upper and middle social classes because of the greater likelihood for exposure to new environments, technologies, and lifestyles. However, almost all epidemics move rapidly from the middle and upper classes to the lower social classes, and by the time large epidemiologic studies are underway, there is usually a higher rate of disease in the lower social class. We will need a large cadre of epidemiologists to at least monitor evolving epidemics and their causal pathways

before they become pandemic. Hopefully, through clinical trials and other studies, approaches for prevention can be identified (42–49).

Epidemiologists have also done a relatively poor job of identifying new epidemics. A major reason for this failure, as Rothman noted (50), is that epidemiologists have lost touch with the original data sources and primarily focus on applying complex statistical analysis to existing data sets without an understanding of the basic structure of the data set (51). For example, epidemiologic studies missed the opiate epidemic because much of their analysis was restricted to age and a variety of other adjustments to the original morbidity and death data without evaluation of the age- and regional-specific data. The recent opiate epidemic resulted in an actual increase in the US death rates and life shortening for the first time in many generations, especially among middle-aged white people and those in rural areas (52). I have proposed the original unadjusted data sets for published papers in epidemiology journals be available as a supplement.

The loss of the close linkage between academic epidemiology, public health, and preventive medicine is of greatest concern. Public health and preventive medicine efforts to reduce morbidity and death in recent years have been relatively unsuccessful except for the continued decline in cigarette smoking and decrease in lung cancer (53–56). A primary cause of this failure may be the lack of application of good epidemiologic methods to control of epidemics, especially 1) understanding the modes of disease transmission (i.e., common source, vector, or person-to-person) and 2) focusing on vectors distant from the causal agents that require individual changes for many people to prevent a few events as compared to a community population approach. For example, having families in low-income old housing use bottled water to reduce lead exposure versus checking lead in the houses and modifying the environment (e.g., pipes, paint, water supply).

The control of most common-source epidemics, such as the opioid epidemic, requires identification and reduction or elimination of the agent (e.g., opioids, salt in the food chain, kilocalorie-dense foods, air pollutants, carcinogens in food chain), and/or reduction of exposure to agent, especially for susceptible individuals, such as taxes on cigarettes, control of alcohol distribution systems, better food labeling, or recreational facilities in the community. The approach to control common-source epidemics at the individual level often does not work and results in high-cost medical care to reduce case-fatality rates.

Identification of the almost-certain new epidemics around the world provides the initial clue for new epidemiologic studies and can help identify specific genetic and agent interactions, and new causal pathways (57–61). For example, the epidemic of chikungunya virus in the Caribbean was associated with chronic arthritis and may be a marker for the infectious etiology of autoimmune arthritis (i.e., rheumatoid arthritis) (62).

## TRAINING EPIDEMIOLOGISTS OF THE FUTURE

Epidemiologic studies in the past have been greatly enhanced by the development of new technologies and their application to epidemiologic methods. I do not believe, therefore, that epidemiologic methodology is old hat and that these new technologies will replace epidemiology; rather, I think the epidemiologic methods have to combine with these new technologies to improve the methods of studying epidemics. This will require different types of training of epidemiologists, with the stronger emphasis on biology and on understanding the use of these new technologies as applied to epidemiologic studies (33).

However, good epidemiologic research requires skills from many disciplines, including basic biological and social sciences, biostatistics, medicine, and other health-related fields. What is badly needed is new training for the individuals whose initial doctorate was in epidemiology, so their career is more than secondary analyses of large data sets or, worse, they become "meta analysts" (63).

The methods of infectious and chronic disease epidemiology are not very different except for the incubation period. Epidemiology remains the study of epidemics in populations, not individuals. Observational epidemiology remains a powerful approach for identifying and determining the causal pathways for many new and existing epidemics. Epidemiology must reinsert itself as the primary science of public health and preventive medicine (33, 34, 64).

## ACKNOWLEDGMENTS

Author affiliation: Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania (Lewis H. Kuller).

Conflict of interest: none declared.

## REFERENCES

1. Terris M. The Society for Epidemiologic Research (SER) and the future of epidemiology. *Am J Epidemiol*. 1992;136(8):909–915.
2. Liu DJ, Peloso GM, Yu H, et al. Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet*. 2017;49(12):1758–1766.
3. Kuller LH. Epidemiology: then and now. *Am J Epidemiol*. 2016;183(5):372–380.
4. Galea S. An argument for a consequentialist epidemiology. *Am J Epidemiol*. 2013;178(8):1185–1191.
5. Lilienfeld AM. On the methodology of investigations of etiologic factors in chronic diseases: some comments. *J Chronic Dis*. 1959;10(1):41–46.
6. Kuller LH. Relationship between acute and chronic disease epidemiology. *Yale J Biol Med*. 1987;60(4):363–377.
7. Ogino S, King EE, Beck AH, et al. Interdisciplinary education to integrate pathology and epidemiology: towards molecular and population-level health science. *Am J Epidemiol*. 2012;176(8):659–667.
8. Kuller LH. A new era for dementia epidemiology: Alzheimer's disease, hardening of arteries, or just old age? *Eur J Epidemiol*. 2018;33(7):613–616.
9. Kitzman DW, Upadhya B. Heart failure with preserved ejection fraction: a heterogenous disorder with multifactorial pathophysiology. *J Am Coll Cardiol*. 2014;63(5):457–459.
10. Greenland P, Lloyd-Jones DM. Defining the new normal in cardiovascular risk factors. *JAMA Cardiol*. 2018;3(9):789–790.
11. Institute of Medicine. *A Nationwide Framework for Surveillance of Cardiovascular and Chronic Lung Diseases*. Washington, DC: National Academy of Sciences; 2011.

12. Franceschini N, Kopp JB, Barac A, et al. Association of APOL1 with heart failure with preserved ejection fraction in postmenopausal African American women. *JAMA Cardiol*. 2018;3(8):712–720.
13. Dolley S. Big data's role in precision public health. *Front Public Health*. 2018;6:68.
14. Susser M, Susser E. Choosing a future for epidemiology: I. Eras and paradigms. *Am J Public Health*. 1996;86(5):668–673.
15. Ebrahim S, Lau E. Commentary: sick populations and sick individuals. *Int J Epidemiol*. 2001;30(3):433–434.
16. Byrd AL, Segre JA. Infectious disease. Adapting Koch's postulates. *Science*. 2016;351(6270):224–226.
17. Lilienfeld AM. Epidemiology of infectious and non-infectious disease: some comparisons. *Am J Epidemiol*. 1973;97(3): 135–147.
18. Evans AS. Causation and disease: the Henle-Koch postulates revisited. *Yale J Biol Med*. 1976;49(2):175–195.
19. Pridan H, Lilienfeld AM. Carcinoma of the cervix in Jewish women in Israel, 1960–67. An epidemiological study. *Isr J Med Sci*. 1971;7(12):1465–1470.
20. Ogilvie GS, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical hpv testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA*. 2018; 320(1):43–52.
21. Clifford GM, Gallus S, Herrero R, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet*. 2005;366(9490):991–998.
22. Hindy G, Engström G, Larsson SC, et al. Role of blood lipids in the development of ischemic stroke and its subtypes: a Mendelian randomization study. *Stroke*. 2018;49(4):820–827.
23. Richard MA, Huan T, Ligthart S, et al. DNA methylation analysis identifies loci for blood pressure regulation. *Am J Hum Genet*. 2017;101(6):888–902.
24. Hang D, Nan H, Kværner AS, et al. Longitudinal associations of lifetime adiposity with leukocyte telomere length and mitochondrial DNA copy number. *Eur J Epidemiol*. 2018; 33(5):485–495.
25. Saracci R. Epidemiology in wonderland: big data and precision medicine. *Eur J Epidemiol*. 2018;33(3):245–257.
26. Marmot M, Wilkinson R. *Social Determinants of Health*. New York, NY: Oxford University Press; 1999.
27. Stringhini S, Sabia S, Shipley M, et al. Association of socioeconomic position with health behaviors and mortality. *JAMA*. 2010;303(12):1159–1166.
28. Fang D, Thomsen MR, Nayga RM Jr., et al. Association of neighborhood geographic spatial factors wtih rates of childhood obesity. *JAMA Netw Open*. 2018;1(4):e180954.
29. Kuller L. Is phenomenology the best approach to health research? *Am J Epidemiol*. 2007;166(10):1109–1115.
30. Price ND, Magis AT, Earls JC, et al. A wellness study of 108 individuals using personal, dense, dynamic data clouds. *Nat Biotechnol*. 2017;35(8):747–756.
31. Gustafsson M, Nestor CE, Zhang H, et al. Modules, networks and systems medicine for understanding disease and aiding diagnosis. *Genome Med*. 2014;6(10):82.
32. Wurtz P, Kangas AJ, Soininen P, et al. Quantitative serum nuclear magnetic resonance metabolomics in large-scale epidemiology: a primer on -omic technologies. *Am J Epidemiol*. 2017;186(9):1084–1096.
33. Kuller LH. The limitations of opportunistic epidemiology, pseudopod epidemiology. *Eur J Epidemiol*. 2016;31(10):957–966.
34. Adami HO, Nyrén O. Enigmas, priorities and opportunities in cancer epidemiology. *Eur J Epidemiol*. 2016;31(12): 1161–1171.
35. Gomes T, Greaves S, Tadrous M, et al. Measuring the burden of opioid-related mortality in Ontario, Canada. *J Addict Med*. 2018;12(5):418–419.
36. Naimi TS, Xuan Z, Sarda V, et al. Association of state alcohol policies with alcohol-related motor vehicle crash fatalities among US adults. *JAMA Intern Med*. 2018;178(7):894–901.
37. Toy M, Hutton DW, So S. Population health and economic impacts of reaching chronic hepatitis B diagnosis and treatment targets in the US. *Health Aff (Millwood)*. 2018;37(7): 1033–1040.
38. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of *Helicobacter pylori*, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst*. 2012; 104(6):488–492.
39. de Oliveira WK, de França GVA, Carmo EH, et al. Infection-related microcephaly after the 2015 and 2016 Zika virus outbreaks in Brazil: a surveillance-based analysis. *Lancet*. 2017;390(10097):861–870.
40. Sidney S, Quesenberry CP, Jr., Jaffe MG, et al. Recent trends in cardiovascular mortality in the United States and public health goals. *JAMA Cardiol*. 2016;1(5):594–599.
41. Kuller LH, Bracken MB, Ogino S, et al. The role of epidemiology in the era of molecular epidemiology and genomics: summary of the 2013 AJE-sponsored Society of Epidemiologic Research Symposium. *Am J Epidemiol*. 2013; 178(9):1350–1354.
42. Gates B. Innovation for pandemics. *N Engl J Med*. 2018; 378(22):2057–2060.
43. McClelland A, Frieden TR. Understanding, preventing, and stopping epidemics. *Lancet*. 2018;391(10139):2489–2490.
44. Jacobson MF, Krieger J, Brownell KD. Potential policy approaches to address diet-related diseases. *JAMA*. 2018; 320(4):341–342.
45. Liu G, Li Y, Hu Y, et al. Influence of lifestyle on incident cardiovascular disease and mortality in patients with diabetes mellitus. *J Am Coll Cardiol*. 2018;71(25):2867–2876.
46. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank Study. *JAMA Cardiol*. 2018;3(8):693–702.
47. Di Q, Dai L, Wang Y, et al. Association of short-term exposure to air pollution with mortality in older adults. *JAMA*. 2017; 318(24):2446–2456.
48. Yang J, Siri JG, Remais JV, et al. The Tsinghua-Lancet Commission on Healthy Cities in China: unlocking the power of cities for a healthy China. *Lancet*. 2018;391(10135): 2140–2184.
49. Neta G, Brownson RC, Chambers DA. Opportunities for epidemiologists in implementation science: a primer. *Am J Epidemiol*. 2018;187(5):899–910.
50. Rothman KJ. The growing rift between epidemiologists and their data. *Eur J Epidemiol*. 2017;32(10):863–865.
51. Stang A, Deckert M, Poole C, et al. Statistical inference in abstracts of major medical and epidemiology journals 1975–2014: a systematic review. *Eur J Epidemiol*. 2017;32(1): 21–29.
52. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci U S A*. 2015;112(49):15078–15083.
53. Bound J, Geronimus AT, Rodriguez JM, et al. Measuring recent apparent declines in longevity: the role of increasing

educational attainment. *Health Aff (Millwood)*. 2015;34(12): 2167–2173.
54. Global Burden of Cardiovascular Diseases Collaboration, Roth GA, Johnson CO, et al. The burden of cardiovascular diseases among US states, 1990–2016. *JAMA Cardiol*. 2018;3(5):375–389.
55. Jemal A, Miller KD, Ma J, et al. Higher lung cancer incidence in young women than young men in the United States. *N Engl J Med*. 2018;378(21):1999–2009.
56. Chetty R, Stepner M, Abraham S, et al. The association between income and life expectancy in the United States, 2001–2014. *JAMA*. 2016;315(16):1750–1766.
57. Abbasi J. Call to action on neurotoxin exposure in pregnant women and children. *JAMA*. 2016;316(14):1436–1437.
58. Fauci AS, Morens DM. Zika virus in the Americas–yet another arbovirus threat. *N Engl J Med*. 2016;374(7):601–604.
59. Apovian CM. The obesity epidemic–understanding the disease and the treatment. *N Engl J Med*. 2016;374(2):177–179.
60. Stone DM, Simon TR, Fowler KA, et al. Vital signs: trends in state suicide rates - United States, 1999–2016 and circumstances contributing to suicide - 27 states, 2015. *MMWR Morb Mortal Wkly Rep*. 2018;67(22):617–624.
61. Lee LK, Mannix R. Increasing fatality rates from preventable deaths in teenagers and young adults. *JAMA*. 2018;320(6): 543–544.
62. Chang AY, Martins KAO, Encinales L, et al. Chikungunya arthritis mechanisms in the Americas: a cross-sectional analysis of chikungunya arthritis patients twenty-two months after infection demonstrating no detectable viral persistence in synovial fluid. *Arthritis Rheumatol*. 2018;70(4):585–593.
63. Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Q*. 2016;94(3):485–514.
64. Galea S. On the potential of academic epidemiology. *Eur J Epidemiol*. 2017;32(3):169–171.