Defining the Environment in Gene–Environment Research: Lessons From Social Epidemiology

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In this article, we make the case that social epidemiology provides a useful framework to define the environment within gene–environment (G×E) research. We describe the environment in a multilevel, multidomain, longitudinal framework that accounts for upstream processes influencing health outcomes. We then illustrate the utility of this approach by describing how intermediate levels of social organization, such as neighborhoods or schools, are key environmental components of G×E research. We discuss different models of G×E research and encourage public health researchers to consider the value of including genetic information from their study participants. We also encourage researchers interested in G×E interplay to consider the merits of the social epidemiology model when defining the environment. (*Am J Public Health.* 2013;103:S64–S72. doi:10.2105/AJPH.2013.301355)

Inquiry into the complex relationships between genetic and environmental influences on behavioral traits has increased substantially in the past decade,[1,2] and this trend is particularly pronounced in health research.[3–6] A PubMed search yielded 42 articles published in 2000 that contained the expression "gene–environment interaction" in the title, abstract, or keywords, and this number increased to 704 by 2012. Although new and important findings have emerged from this body of work, there are also strong criticisms of the existing gene–environment (G×E) interaction studies from researchers across health, psychological, and social sciences.[2,7–10] There has been a weak replication record for "established" G×E interaction results,[11,12] there are concerns about statistical power for G×E associations,[8] and few researchers articulate plausible biological pathways for G×E associations.[7] Each of these factors has reduced the potential impact of many candidate G×E studies.

To date, however, there has been very little discussion about one of the key shortcomings in the existing G×E research. Specifically, there is no real consensus about the nature and scope of the environment within G×E studies.[13] Because the "E" is one half of the G×E framework, it is critical to define the environment in a manner that maximizes the contributions from both social and biological sciences and improves our understanding about the health of populations. This need for cross-disciplinary discussions is echoed in the current efforts of the National Coalition for Health Profession Education in Genetics (http://www.nchpeg.org/bssr). This group, with support from the Office of Behavioral and Social Science Research with the National Institutes of Health (NIH), has developed a project entitled "Genetics and Social Science" with the explicit goal to "create an educational program that will improve social scientists' genetics literacy." This project points to a variety of collaboration opportunities within the area of G×E interplay and states that "geneticists may be less familiar with measures used to quantify the observable external environments, and can benefit from the guidance of social and behavioral researchers."[14] The goal of this article is to address this comment by offering guidance for operationalizing and measuring the social environment in G×E studies. Consensus regarding the definition of the social environment will help to guide future work and locate G×E evidence in a more coherent framework.

We make 3 contributions toward this goal. First, we discuss the importance of existing social epidemiological and sociological theory for understanding the environment in a multilevel, multidomain, longitudinal framework that accounts for upstream processes influencing health outcomes. In particular, this approach draws a sharp distinction between individual and family attributes and the broader social contexts in and through which they arise. Second, and relatedly, we emphasize the potentially important role that characteristics of intermediate levels of social organization, such as neighborhoods, schools, and the workplace, have to play in a more thoughtful account of the environment in G×E interplay research. Finally, we discuss different forms and models of G×E interplay with frequent reference to previous published research.

DEFINING THE ENVIRONMENT FROM A SOCIAL EPIDEMIOLOGICAL PERSPECTIVE

In one of the first articles to describe a general framework for G×E associations in epidemiological research, Ottman defined the environment as follows:

> The environmental risk factor can be an exposure, either physical (e.g., radiation, temperature), chemical (e.g., polycyclic aromatic hydrocarbons), or biological (e.g., a virus); a behavior pattern (e.g., late age at first pregnancy); or a "life event" (e.g., job loss, injury).[15(p764)]

Although this statement accurately summarizes how most G×E research approaches the environment, it is limited in at least 2 respects. First, each of the factors that are described may be thought of as proximate environmental moderators of genetic associations. This same characterization of the environment is evident in the Gene Environment Association Studies consortium, which is led by NIH and National Human Genome Research Institute through the Gene, Environment, and Health Initiative. The list of published articles from this group includes "environments" such as obesity[16] and

maternal smoking,[17] which are far downstream from social environmental factors that structure exposure in the first place. By contrast, the fundamental cause perspective argues that

> individually-based [sic] risk factors must be contextualized, by examining what puts people at risk of risks, if we are to craft effective interventions and improve the nation's health.[18(p80)]

Full understanding of the determinants of a health outcome requires understanding the social structure from which proximate risks and exposures arise.

Second, emphasis on individual environments does not account for group-level behavioral, normative, and cultural processes that shape individual health and behavior. To illustrate the importance of these issues within G×E research, a recent article in the *American Journal of Epidemiology*[19] examined the interaction between single nucleotide polymorphisms (SNPs) within 38 genes and specific health behaviors (e.g., smoking, drinking, exercise, and nutrition) on body mass index (BMI) among White and Black adults. They provided evidence for gene–behavior interactions (G×B) by demonstrating that the association between each health behavior and BMI depended on the genotype of individuals. By labeling these G×Bs as G×Es, this approach, which was also evident in other research,[20] took a narrow view of the environment. Understanding how genes moderate the consequences of specific behaviors is an important component of a genetic epidemiological understanding of health, but as others have made clear,[21] it is distinct from G×E research. Individuals do help shape environments through their behaviors, but it is nevertheless important to distinguish between the actions of people and the circumstances in which these actions occur. The latter incorporates a much more comprehensive approach to the environment for G×E interplay research.

This distinction conforms to the social epidemiological emphasis on the upstream sources of risk exposure. Social epidemiology explicitly reframes traditional epidemiological paradigms by emphasizing the role played by an individual's location within a particular social structure as a fundamental determinant of vulnerability and exposure.[22] Accordingly, we conceptualize the social environment as an external, multilevel, and multidimensional feature that determines an individual's exposure to risks and access to resources and constrains or enables people to engage in healthy lifestyles at different stages of the life course. A unique contribution of social epidemiology is the emphasis on the embodiment of social arrangements, or "how we literally incorporate, biologically, the material and social world in which we live, from conception to death."[23(p672),24] Sociologists' contribution to this idea is the explication of pathways of embodiment that constrain and enable individuals' capacities to live healthy lives, including social structures.[25–27] These pathways are multilevel, multidomain, and multi-time-scaled. Multilevel pathways incorporate contextual dynamics at supraindividual, often nested, levels of analysis (e.g., families, schools, neighborhoods, states, countries). Multidomain pathways span different spheres of people's lives (e.g., social, economic, physical, and institutional). Multi–time-scaled pathways encompass both change within individuals over the life course and historical changes in populations. Importantly, Krieger[23(p672)] wrote that embodiment provides a "biological expression of social relations," and as such, the complex, dynamic, and transactional nature of the social environment becomes a critical input into basic biological processes.

One important aspect of this perspective is that environmental risk factors are not characterized as independent of one another. For instance, the joint distribution of collective efficacy, socioeconomic status (SES), and crime rates across neighborhoods in Chicago, Illinois, makes it difficult to consider each of these factors as independent variables in traditional multivariate models.[28] Just as the "fundamental cause" perspective focuses on an individual location within the social order as relative factors rather than an objective indicator of "exposure," the clustering of social characteristics within geographically defined neighborhoods and schools provides important evidence about the relative position of a particular social context along a continuum of privilege and disadvantage. Identifying the mechanisms through which this allocation system affects measured phenotypes is critical, but exclusive focus on downstream processes like stressful life events and behaviors loses sight of the possibility that ill health and social risks will often be derived from the same source.

This understanding is very important because it helps to contextualize findings from genetic epidemiology studies in which genetic associations are shown to be different for members of different racial, ethnic, and socioeconomic groups. Environmental factors may fundamentally alter the way in which genes are associated with health outcomes because in some residential areas, health may be driven exclusively by the physical and social features of the neighborhood, and genes have virtually nothing to do with individual differences in health within these communities. For example, using data from the Chicago Health and Aging Project, researchers have shown that the association between the apolipoprotein E-ε4 allele and change in cognitive function is the strongest in the most socially organized neighborhoods in the Chicago area.[29] Consistent with the "social distinction" model we describe in the following, these researchers argue that the comparably small influence of genotype is further muted by social factors that may profoundly influence cognitive decline in the most disorganized communities.

This understanding is also in line with the social construction perspective on racial and ethnic identity[30] that is shared by most social scientists. This includes research that focuses on features of the social environment that are amenable to policy interventions and are precursors to the observable behavior, rather than emphasizing racial identification as a cause. Without reliable and valid measures of the environment and theory linking environmental factors to health behaviors, results from genetic association studies may, at times, provide misleading conclusions. In an influential example, Turkheimer et al.[31] provided convincing evidence that the heritability of cognitive test scores was virtually zero for those who were raised in the most disadvantaged homes but increased dramatically as the level of socioeconomic resources increased. Others have reported similar results,[32] and together this research indicates that genetic factors linked to cognitive performance may not be fully realized for those in the most disadvantaged communities.

The social epidemiological focus on pathways from social structure to health is critical

because it better clarifies the factors that structure both differential exposure and mitigating resources. Nevertheless, this approach is limited by its inattention to G×E interplay. Consider health-related behaviors such as exercise, nutrition, substance use, and adherence to medical treatments. All of these are necessarily linked to the ecosocial precursors, but, just as importantly, people from comparable ecosocial environments respond differently to similar environmental conditions. The links between social structure, the physical and social environment, health behaviors, and morbidities are well established, and yet it is increasingly clear that genotype may factor into this conceptual orientation at each stage of the process.

In this respect, G×E interplay provides a great opportunity for the elaboration of the social epidemiological perspective in public health. Advances in molecular technology have made it possible for researchers to incorporate genotypic information into this traditional social epidemiological framework to ask new and important questions that involve genetic differences yet remain true to core principles of social epidemiology. The notion of embodiment as both an indicator of social location and a cause of future health trajectories becomes more, not less, relevant as we learn more about the human genome. As others have made clear, understanding both social and genetic risks at each developmental stage is critical to understanding specific pathways to divergent health outcomes throughout the life course.[33–35]

The ecosocial perspective emphasizes the role of places in which individuals reside, work, interact, and attend school, and life course theory emphasizes that the environments that are most important change in predictable ways across the life course. During gestation, the uterine environment and determinants of maternal health are the most important environmental influences on health outcomes. During childhood and adolescence, one's parents, neighborhood, school, and social networks are the most influential. In adulthood, the workplace becomes an increasingly important environment, and one's formed family and home become increasingly important from young adulthood to old age. Each of these social environments provide a conceptual bridge from individuals' place in the broader social structure to the way in which they live their lives and embody their relative status in a particular social context. Measures exist for several well-established social environmental factors related to health, including social integration,[36] collective efficacy,[28] social capital,[37–39] psychosocial stressors,[40] behavioral norms,[41] and segregation.[42]

We argue that genetic influences should be incorporated into this model, as they potentially influence all of these connections.[43] Genetic differences influence how individuals end up in different types of environments.[44] Genetic differences moderate how particular environments translate into environmental risks, resources, and health behaviors. Finally, genetic differences also likely moderate how these risks, resources, and behaviors all influence embodied health outcomes.

To summarize, we argue that previous G×E research has adopted an improperly atomistic view of the social environment, often even treating behaviors as environmental characteristics. By contrast, a social epidemiological perspective contextualizes individual actions and attributes within the broader organization of society into institutions and meaningful social groups, to which health risks and resources are systematically and jointly distributed. Taking the nature of this allocation system seriously in G×E interplay research entails a move away from mere risk factor epidemiology and toward a focus on environmental pathways to embodiment of social conditions from macro to micro levels. This joint distribution of health-relevant features of the social environment means that genetic influences on health may be far more important in some contexts than others, in some stages of the life course than others, and for some socially meaningful groups than others. Finally, it may frequently be the case that specific genetic loci serve to modify the effects of these environmental risks and resources on health outcomes, as is discussed presently.

TYPES OF GENE–ENVIRONMENT INTERPLAY

The social epidemiological perspective provides a useful framework to delineate meaningful social environments for research on G×E interplay. Most broadly, this interplay encompasses a combination of G×E interactions and gene-environment correlations (rGE). G×E interactions are cases in which genetic and environmental influences on a particular trait are conditional upon the level of the other. Such interactions can be usefully subdivided into 2 distinct types. A heritability–environment (H×E) interaction is a population-based model that estimates the relative contribution of genetic influences to overall phenotypic variance across different environments.[33,45] As with the bulk of the G×E research, much of this work focuses on proximate environmental influences at the individual and family levels. For example, Silventoinen et al.[46] used samples of twins from Denmark and Finland to examine the heritability of body size, showing that genetic associations for body mass were lower for those who exercised more and those whose diets contained a larger portion of protein compared with those who did not exercise and ate less protein. Likewise, Gottlieb et al.[47] used data from the Framingham Heart Study to demonstrate that the heritability of lung function (forced expiratory volume in 1 second) increased from 0.05 in the entire population to 0.18 when they only considered current smokers. In this case, some genetic differences that can otherwise be inconsequential for lung function may influence lung function among those who smoke.

This same emphasis on proximate environmental determinants is also evident in studies that rely upon candidate G×E research designs. Because these studies focus on environmental moderation of the association between a specific allele and a health outcome, this type of G×E association can be referred to as an allele-by-environment (A×E) interaction (the distinction between H×E and A×E is also referred to as the difference between "latent" and "measured" G×E[48]). The most widely cited A×E interaction, despite a fairly weak replication record,[8,49] is found in the work of Caspi et al.,[50] who showed that carriers of the short allele in a gene that codes for serotonin (*5HTTLPR*) are particularly sensitive to individual-specific stressful life events, but that the carriers of 2 long alleles at this loci are fairly immune to the deleterious effects of regular exposure to strain and stress. In a similar manner, Mitchell et al.[51] reported 2

genetic polymorphisms that are associated with a crossover in the relationship between SES and postpartum depression: the genotypes that conferred more risk for poor mothers conferred less risk for wealthier ones. There are countless examples of A×E research in the psychological, social scientific, and health literatures, but the overwhelming share of these findings operationalize and measure environmental exposure as a proximate- and individual-level characteristic (see Duncan and Keller[8] for a review).

This body of work is critical to public health research because it signals a need to consider specific environmental contingencies that may mask or illuminate genetic influences on health and well-being. However, it is limited because the environmental factors are typically either behaviors (e.g., smoking) or family characteristics (e.g., SES). In the past decade, a body of research has emerged that focuses on exogenous and more broadly defined social environments such as neighborhoods,[52] schools,[45,53] states of residence,[54] and historical periods[3,55,56] as important environmental moderators of genetic effects on health and health behaviors. The focus on these broad social environments is important because it delineates a range of social contexts in which individuals are socialized about health-related behaviors that are pegged to key developmental periods. These environments also provide socially and geographically meaningful boundaries for policymakers to implement specific public health initiatives.

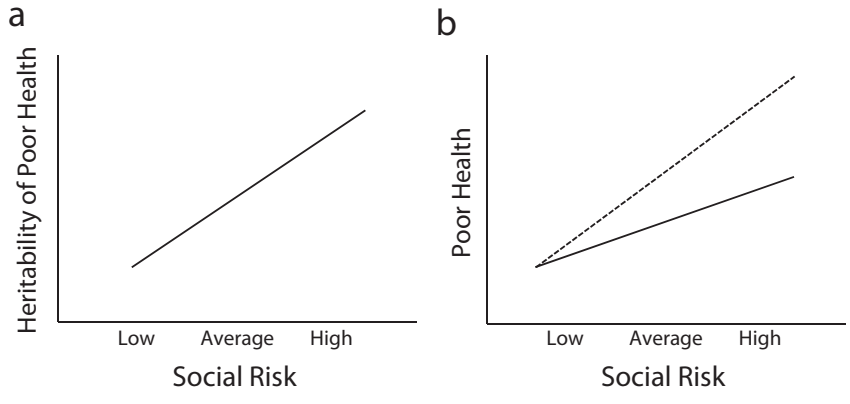
The limited examples of this work have provided important substantive and methodological contributions to the G×E research. For example, a recent article showed that the magnitude of the association between one SNP (rs1801282) and metabolic syndrome varies depending on the availability of exercise facilities.[57] In other words, changes to the structure and aspects of built environments can affect the association between specific genetic variants and specific health outcomes.

G×E interactions can also be distinguished by the functional forms of the relationship between genotype, environment, and outcome. Figures 1 through 4 distinguish 4 models implied by a G×E typology that is used by researchers,[33,58] differentiated by their H×E formulation or A×E formulation. Figures 1 and 2 depict the diathesis-stress and differential susceptibility models.[59–62] Both propose that individuals with long-term exposure to socially risky environments are more likely to display poor health. The diathesis-stress model suggests that the genetic differences that are associated with negative outcomes in risky environments will have either an attenuated or entirely muted relationship in low-risk environments. This is best characterized by the work of Caspi et al.[50,63] As shown in Figure 1, a diathesis-stress model implies increasing heritability in negative environments, and an allelic divergence as adversity increases.

A complement to the diathesis-stress model is one that calls attention to how genetic associations can be attenuated by social control.[64] As an H×E example, previous research has shown that the heritability of regular smoking is significantly reduced in states that have the most restrictive policies regarding the sale of cigarettes and in states that have the highest taxes per pack on cigarettes.[54] An A×E counterpart is shown in the work of Fletcher,[65] who found that the association between an SNP in the *CHRNA6* gene (rs2304297) and tobacco use described by others[66] was significantly reduced for those who lived in states with the highest levels of tax on tobacco products.

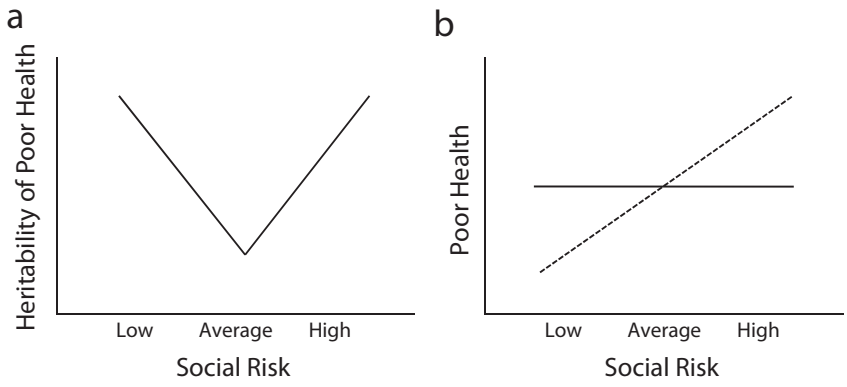
By contrast, the differential susceptibility hypothesis implies that alleles associated with negative outcomes in adverse environments may be associated with positive outcomes in the most salutary environments. The previously discussed study by Mitchell et al.[51] serves as an illustration. This is shown with the u-shaped H×E association and the crossover A×E association in Figure 2. As another example, Simons et al.[62] showed that individuals with a higher number of plasticity alleles (the 7R allele in *DRD4* and the S allele in *5HTTLPR*) were the most aggressive in the most adverse social environments and least aggressive in the least adverse social environments. Their study is an important extension to the G×E research because it employed an inherently multilevel perspective emphasizing social resources from the respondent's neighborhood, school, and family levels of social support.

At the same time, the approach to the environment in this study does not contain any information describing the behavioral expectations, a description of the sanctions for violating norms, or a description of the mechanisms in place to enforce these norms. This difference is shown in the work of Daw et al.[67] who examined the link between school-level smoking behaviors and the likelihood that individuals will smoke themselves. They showed that increasing copies of the short allele in the *5HTTLPR* gene increased the likelihood that individuals will adopt the smoking norms of their school. The association was even stronger for the drinking phenotype, and the differential susceptibility model seems to best characterize the link between school-level drinking patterns and individual risks of



Note. The dashed line corresponds to the presence of "risk" (or responsive in the case of differential susceptibility) allele.

FIGURE 1—Diathesis-stress model of gene–environment interaction differentiated by (a) heritability-by-environment specifications and (b) allele-by-environment specifications.



Note. The dashed line corresponds to the presence of "risk" (or responsive in the case of differential susceptibility) allele.

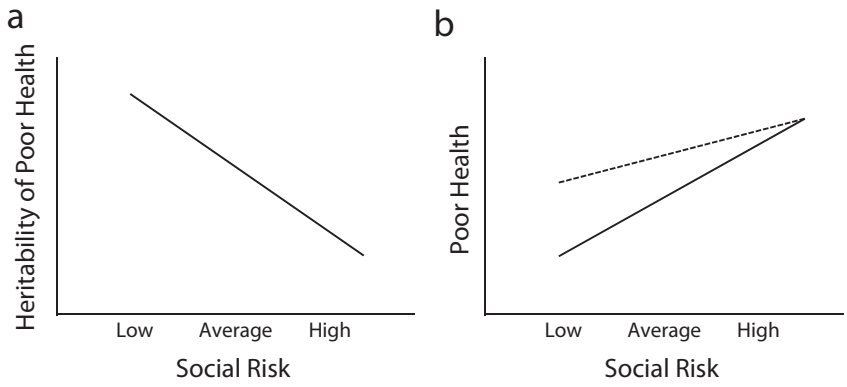
FIGURE 2—Differential susceptibility model of gene–environment interaction differentiated by (a) heritability-by-environment specifications and (b) allele-by-environment specifications.

drinking. Specifically, in the schools that have the lowest drinking rates, those with the short allele drank the least, but the same allele is associated with the highest alcohol consumption in schools that have higher than average drinking levels. This is important because without this type of specification, one cannot see an association between genotype and phenotype. This has been discussed recently in the debates regarding the power of candidate G×E associations,[68] but it is also important because it suggests that normative factors that limit or enable specific behaviors should be considered as potentially important moderators of genetic effects.

This example also highlights the critical need to consider the full continuum of environmental conditions rather than simply exposure. Having a representative sample of the population has long been a concern of researchers in the social demographic community, but this concern is particularly relevant in G×E research. Consider a study in which differential susceptibility loci are the key elements placing individuals at risk for smoking cigarettes. If this study is done in communities in which very few people smoke cigarettes, researchers may conclude that allele A confers a benefit (those with the A allele smoke the least). However, if this same study is done in a community in which smoking is very popular, those with the A allele may actually smoke the most. Finally, if the same study is done in typical environments, researchers cannot observe any association. Without a complete representation of the individuals across the full range of environments, researchers can only tell one part of the story.

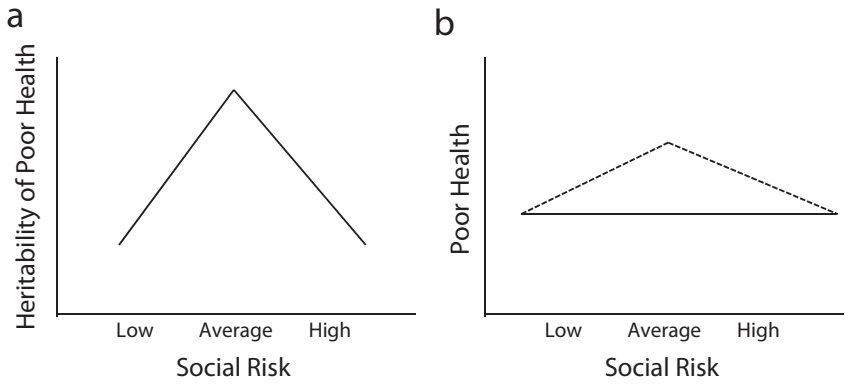
Characterizing the environment across the full continuum is also important because it allows one to examine the social push and social distinction G×E models. The social push model differentiates between typical and extreme social contexts and hypothesizes that genetic factors will be the most important within typical environments, whereas social influences dominate within extreme environments. In these extreme environments, social factors so strongly influence the phenotype that ordinary genotypic differences have little room to differentiate individuals from one another. However, environments that have fewer social factors that limit individual differences allow for "biology to shine through."[69] The social distinction model is very similar to the social push model, but it anticipates that the highest social risk environments will have the lowest heritability and lowest measured genetic associations.

The social push and social distinction models are not necessarily causal G×E models in the biological sense of genes actually functioning differently in different environments. To illustrate the issue, researchers showed that genetic factors related to smoking were virtually nonexistent in the early 1960s, but then became increasingly important for smoking initiation following the Surgeon General's report on the dangers of smoking.[3] The researchers argued that those for whom smoking was driven by social factors were far less likely to initiate smoking, as well as more likely to successfully quit smoking, after the 1964 report, compared with those for whom smoking was largely a result of genetic factors related to nicotine metabolism. In other words, this important scientific announcement had significantly less influence on the future smoking patterns for individuals with specific genetic risk profiles because it affected the social costs and benefits of smoking, rather than any moderation of the role of genetic differences in nicotine metabolism itself. To the extent that



Note. The dashed line corresponds to the presence of "risk" (or responsive in the case of differential susceptibility) allele.

FIGURE 3—Social distinction model of gene–environment interaction differentiated by (a) heritability-by-environment specifications and (b) allele-by-environment specifications.



Note. The dashed line corresponds to the presence of "risk" (or responsive in the case of differential susceptibility) allele.

FIGURE 4—Social push model of gene–environment interaction differentiated by (a) heritability-by-environment specifications and (b) allele-by-environment specifications.

reduction of overall smoking rates might have occurred largely among those for whom smoking was intrinsically less rewarding, public health campaigns against smoking might have changed the actual allelic composition of the population of smokers while reducing the number of smokers overall.[55]

Evidence for the social push and distinction models can be found in the public health and problem behavior literatures, such as the previously described work on apolipoprotein E.[29] A similar result can be seen in the work of Tuvblad et al.[70] who examined antisocial behavior in 1133 Swedish twin pairs (ages 16–17 years). The study used a broad indicator of the social, economic, and behavioral context of the neighborhoods and found that the heritability of antisocial behavior was significantly higher for those who resided in the most socioeconomically advantaged neighborhoods. As a last example, Boardman et al.[45] used the school-based design of the National Longitudinal Study of Adolescent Health to show that social understandings of body size substantially moderated the estimated influence of genetic differences on BMI. They examined the average BMI for those who said that they were "normal weight" to calculate a school-level norm about body size. In line with the social push models, they showed that the heritability of BMI was highest in schools with body size norms in the average range but lowest in schools in which the norm was very low or very high.

As noted earlier, G×E interplay encompasses not only G×E interaction but also rGE, in which genotypes are associated with causally relevant aspects of the environments to which an individual is exposed.[71] This type of correlation may create the appearance of a direct gene–health relationship where none exists. Passive rGE are perhaps the most common and are a result of the obvious fact that children inherit both genes and their environments from their parents; parents who smoke because of genetic reasons pass these genes to their children but also raise their children in a household in which cigarettes are available and where they model smoking behavior. Price and Jaffee[72] also described work in which parents with lower verbal ability raised children in environments that had more disorganization in the home, and that this disorganization had a causal effect on the child's verbal ability. This has the side consequence of creating a spurious association between children's genes and verbal ability.

Alternatively, genetically influenced individual traits can influence the environments that an individual may experience. Thus, genetic factors are an indirect cause of whatever other traits these environments may influence. The key distinction often drawn here is between traits influencing their selection of environments (active rGE) and environments responding differently to individuals based on observable traits (evocative rGE). As an example of the latter, if differences in skin color lead to differential treatment and experiences of discrimination, then pathways from discrimination to health outcomes could induce a correlation between genetic causes of skin color variation and health.[73] In this way, evocative rGE closely corresponds to the sociological notion of ascription,[74–76] insofar as the latter is based on genetic foundations. Active rGEs encompass genetic influences on the environments that individuals seek out. For instance, Cleveland et al.[77] found evidence for genetic influence on whether one has friends who smoke and drink. If these friendships, in turn, influence whether adolescents smoke and drink themselves, then friendship selection mediates a relationship between genes and these health behaviors.

rGE is very important for the G×E research described previously because a key assumption of G×E research is that the environmental exposure is assumed to be independent of genotype. Others have shown that violations of this assumption can have important implications for the interpretation of the G×E estimates.[78] The most effective strategy to deal with the possibility of rGE in G×E studies is to consider environmental factors that are exogenous to genetic characteristics of individuals.[79] This further highlights the importance of the ecosocial perspective because the emphasis on large environmental contexts such as schools, neighborhoods, or counties reduces the likelihood that genetic and environmental factors are correlated.

IMPLICATIONS

Although researchers have given much attention to G×E interplay, this work has thus far focused on a fairly narrow characterization of the environment. As social epidemiology and sociological research has shown, the social environment is more than a set of independent risk factors and protective influences. Instead, society and its major institutions and contexts are jointly distributed in a manner that disproportionately channels health-promoting resources to the wealthy and powerful at the expense of the poor and powerless. Thus, good schools and safe neighborhoods,[80] opportunities for good careers,[81] and access to nutritious food, health care, and conditions amenable to

exercise[82] are disproportionately available to higher SES families. Equally important, the distribution of resources and risks obviously has substantial consequences for health inequality,[83] and genetic epidemiology has heretofore paid limited attention to these lessons from social epidemiology. To be sure, researchers have expressed valid concern regarding the blind enthusiasm for the marriage between genetic and social explanations for behaviors.[84] However, as others have pointed out,[26] sociological explanations become far more relevant when the genetic influences on social forces are made clear. Advancing understanding of these processes should therefore be a high priority for both sociology and public health.

However, much work remains to be done in this area of research. Perhaps the most important limitations are a limited conceptualization of the nature and scope of the environment and its interaction with the genome; limited sample sizes available to study this topic in a biologically informative manner; the weak replication record for some of the most widely cited G×E associations[8,49]; and the lack of analytical strategies that offer causally satisfying interpretations. In this article, we have sought to address the first limitation, and the second is increasingly being addressed by efforts to genotype long-standing, large-sample, population-representative social science data sets such as the Health and Retirement Study, the National Longitudinal Study of Adolescent Health, and the Wisconsin Longitudinal Study. The incorporation of genetic samples into moderately sized and representative data sources may help to clarify the salience of the G×E perspective, and it will certainly help stabilize the G×E parameter estimates that show a great deal of variation across different, and at times, fairly small studies.[11] However, the sample sizes of these studies still fall well short of the nearly 100 000 observations that some have argued are needed to identify true G×E associations.[85] The presence of statistically significant G×E associations within the literature has led some to assert that the bulk of these associations are likely to be false positives and appear in scholarly journals because of publication bias.[8]

Concerning the last limitation, most research on G×E interplay in public health and elsewhere is primarily correlative, providing evidence on interactive associations but not necessarily causal ones. Population stratification[86] and rGE[78,87] are strong potential challenges to any claim of exogenous environmental exposure. For instance, residential segregation by race and ethnicity remains a fundamental feature of social life in the United States.[88] Small differences among socially defined racial and ethnic differences in allele frequencies for genes that are related to specific health behaviors is the primary concern of population stratification, but these same small differences may be correlated with neighborhood characteristics that we are describing as exogenous. As such, we encourage researchers to employ one of the many standard statistical approaches to adjust for the possibility that environmental exposure and genotype are independent above and beyond population differences across the genome. These methods include ancestrally informative markers,[89] principal components,[90,91] and sibling fixed effects or family-based studies to reduce this influence of this form of rGE.[67,92,93]

CONCLUSIONS

Our discussion offers 3 primary lessons for G×E interplay research within public health. These lessons are derived from the demonstration that most health behaviors of interest to public health researchers have a heritable component, but that the relative influence of genes is often contingent upon environmental factors. First, we advocate taking the multilevel, multidomain, and longitudinal nature of the environment seriously in G×E interplay research. We believe that the social epidemiological framework offers the best approach to do so because of its focus on the upstream processes of social organization that lead to the joint allocation of health risks, resources, and norms within society. This offers a fuller understanding of the environment than has been seen in most research on this topic. This approach emphasizes that behaviors are not environments, that individual and familial environmental influences are best understood in their broader social contexts, and that proximate risks and rewards in the pathway between social structure and health are often systematically and jointly distributed.

Second, we emphasize the role of intermediate levels of social organization, such as neighborhoods, schools, workplaces, and social networks, as important features of the social environment for understanding gene–environment interplay and health. These units of organization provide important linkages between the broader social structure and individual lives, and have the benefit of providing plausibly exogenous sources of environmental variation for models of G×E interplay. Which of these units of social organization are most consequential varies systematically through the life course. In addition, the specific ways that these intermediate levels influence individuals' lives are highly variegated, but assessing their comparative importance can provide important clues toward identifying their key etiologic attributes.

Third, we highlight different basic forms of G×E interactions and rGEs with examples that have been observed. The differences between these forms affect our ability to predict the health of populations in light of current and anticipated environmental changes. Most importantly, distinguishing among the different models requires information on the full range of social environments. Articulating the models also provides an opportunity to emphasize the difference between biological and statistical interaction, because changing social conditions can influence the observed population association between a gene and an outcome without at all moderating the biological effect of genes.

It is our hope that the research will continue to provide new insights for public health research from the simultaneous consideration of genetic and social factors. We hope that this framework and language will help to organize the otherwise atomized results from the large body of G×E research. We stress the need to consider social components of the environment that provide cues about specific health behaviors in specific social contexts and specific times in the life course—environmental risks involve shared understandings about the meaning of risks that are critically related to norm formation and enforcement across different contexts.[94] Treating risk as a characteristic of an individual may be a very useful model for the medical sciences, but it does very little to advance our understanding of public health because we lose sight of the social origins of

individual beliefs and behaviors. This point has been made clearly by others,[95] but we believe that this is particularly salient to research involving G×E interactions. In this manner, it is our hope that social scientists recognize that processes of G×E interplay are an important subsequence of the class of generic social processes, whereby features of the environment and the individual recursively influence health. ■

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References

1. Bearman P. Exploring genetics and social structure: introduction. *Am J Sociol.* 2008;114(suppl 1):v–x.

2. Freese J, Shostak S. Genetics and social inquiry. *Annu Rev Sociol.* 2009;35(1):107–128.

3. Boardman JD, Blalock CL, Pampel FC. Trends in the genetic influences on smoking. *J Health Soc Behav.* 2010;51(1):108–123.

4. Schnittker J. Happiness and success: genes, families, and the psychological effects of socioeconomic position and social support. *Am J Sociol.* 2008;114(suppl):S233–S259.

5. Guo G, Roettger EM, Cai T. The integration of genetic propensities into social control models of delinquency and violence among male youths. *Am Sociol Rev.* 2008;73(4):543–568.

6. Seabrook JA, Avison WR. Genotype-environment interaction and sociology: contributions and complexities. *Soc Sci Med.* 2010;70(9):1277–1284.

7. Charney E, English W. Candidate genes and political behavior. *Am Polit Sci Rev.* 2012;106(1):1–34.

8. Duncan LE, Keller MC. A critical review of the first ten years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry.* 2011;168 (10):1041–1049.

9. Eaves LJ. Genotype x environment interaction in psychopathology: fact or artifact? *Twin Res Hum Genet.* 2006;9(1):1–8.

10. North KE, Martin LJ. The importance of gene-environment interaction implications for social scientists. *Sociol Methods Res.* 2008;37(2):164–200.

11. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis. *JAMA.* 2009;301(23):2462–2471.

12. Munafò MR, Durrant C, Lewis G, Flint J. Gene x environment interactions at the serotonin transporter locus. *Biol Psychiatry.* 2009;65(3):211–219.

13. Perrin AJ, Lee H. The undertheorized environment: sociological theory and the ontology of behavioral genetics. *Sociol Perspect.* 2007;50(2):303–322.

14. National Coalition for Health Profession Education in Genetics. Environmental continuum. Available at: http://www.nchpeg.org/bssr/index.php?option=com_k2&view=item&id=94:environmental-continuum&Itemid=131. Accessed July 18, 2013.

15. Ottman R. Gene-environment interaction: definitions and study designs. *Prev Med.* 1996;25(6):764–770.

16. Cornelis MC, Tchetgen EJT, Liang LM, et al. Gene-environment interactions in genome-wide association studies: a comparative study of tests applied to empirical studies of type 2 diabetes. *Am J Epidemiol.* 2012;175 (3):191–202.

17. Beaty TH, Ruczinski I, Murray JC, et al. Evidence for gene-environment interaction in a genome wide study of nonsyndromic cleft palate. *Genet Epidemiol.* 2011;35 (6):469–478.

18. Link BG, Phelan J. Social conditions as fundamental causes of disease. *J Health Soc Behav.* 1995;35(extra issue):80–94.

19. Edwards TL, Edwards DRV, Villegas R, et al. HTR1B, ADIPOR1, PPARGC1A, and CYP19A1 and obesity in a cohort of Caucasians and African Americans: an evaluation of gene-environment interactions and candidate genes. *Am J Epidemiol.* 2012;175(1):11–21; erratum 2012;175(7):732.

20. Wareham NJ, Young EH, Loos RJF. Epidemiological study designs to investigate gene-behavior interactions in the context of human obesity. *Obesity (Silver Spring).* 2008;16(suppl 3):S66–S71.

21. Bouchard C, Agurs-Collins T. Studying gene-behavior interactions: summary of recommendations. *Obesity (Silver Spring).* 2008;16(suppl 3):S95–S96.

22. Berkman LF, Kawachi I. *Social Epidemiology.* Oxford, UK: Oxford University Press; 2000.

23. Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. *Int J Epidemiol.* 2001;30(4):668–677.

24. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? *Soc Sci Med.* 1994;39 (7):887–903.

25. Williams GH. The determinants of health: structure, context and agency. *Sociol Health Illn.* 2003;25(3):131–154.

26. Harden KP, Hill JE, Turkheimer E, Emery RE. Gene–environment correlation and interaction in peer effects on adolescent alcohol and tobacco use. *Behav Genet.* 2008;38(4):339–347.

27. Link BG. Epidemiological sociology and the social shaping of population health. *J Health Soc Behav.* 2008;49(4):367–384.

28. Sampson RJ, Raudenbush SW, Earls F. Neighborhoods and violent crime: a multilevel study of collective efficacy. *Science.* 1997;277(5328):918–924.

29. Boardman JD, Barnes LL, Wilson RS, Evans DA, de Leon CFM. Social disorder, APOE-E4 genotype, and change in cognitive function among older adults living in Chicago. *Soc Sci Med.* 2012;74(10):1584–1590.

30. Omi M, Winant H. *Racial Formation in the United States: From the 1960s to the 1990s.* London, UK: Routledge; 1994.

31. Turkheimer E, Haley A, Waldron M, D'Onofrio B, Gottesman II. Socioeconomic status modifies heritability of IQ in young children. *Psychol Sci.* 2003;14(6):623–628.

32. Rowe DC, Jacobson KC, Van den Oord E. Genetic and environmental influences on vocabulary IQ: parental education level as moderator. *Child Dev.* 1999;70(5): 1151–1162.

33. Shanahan MJ, Boardman JD. Genetics and behavior in the life course: a promising frontier. In: Elder GH Jr, Giele JZ, eds. *The Craft of Life Course Research.* New York, NY: The Guilford Press; 2009.

34. Burt A. Some key issues in the study of gene-environment interplay: activation, deactivation, and the role of development. *Res Hum Dev.* 2011;8(3-4): 192–210.

35. Wanke KL, Spittel ML. Advancing research in gene-environment interplay: can developmental science lead the way? *Res Hum Dev.* 2011;8(3-4):165–172.

36. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. *Soc Sci Med.* 2000;51(6):843–857.

37. Portes A. Social capital: its origins and applications in modern sociology. *Annu Rev Sociol.* 1998;24(1):1–24.

38. Coleman JS. Social capital in the creation of human-capital. *Am J Sociol.* 1988;94(suppl):S95–S120.

39. Kawachi I, Kennedy BP, Lochner K, Prothrow-Stith D. Social capital, income inequality, and mortality. *Am J Public Health.* 1997;87(9):1491–1498.

40. Boardman JD, Finch BK, Ellison CG, Williams DR, Jackson JS. Neighborhood disadvantage, stress, and drug use among adults. *J Health Soc Behav.* 2001;42(2):151–165.

41. Boardman JD, Saint Onge JM, Rogers RG, Denney JT. Race differentials in obesity: the impact of place. *J Health Soc Behav.* 2005;46(3):229–243.

42. Massey DS, Denton NA. The dimensions of residential segregation. *Soc Forces.* 1988;67(2):281–315.

43. Dick DM. Gene-environment interaction in psychological traits and disorders. *Annu Rev Clin Psychol.* 2011;7(1):383–409.

44. Dick DM, Agrawal A, Schuckit MA, et al. Marital status, alcohol dependence, and GABRA2: evidence for gene-environment correlation and interaction. *J Stud Alcohol.* 2006;67(2):185–194.

45. Boardman JD, Roettger ME, Domingue BW, McQueen MB, Haberstick BC, Harris KM. Gene-environment interactions related to body mass: school policies and social context as environmental moderators. *J Theor Polit.* 2012;24(3):370–388.

46. Silventoinen K, Hasselbalch AL, Lallukka T, et al. Modification effects of physical activity and protein intake on heritability of body size and composition. *Am J Clin Nutr.* 2009;90(4):1096–1103.

47. Gottlieb DJ, Wilk JB, Harmon M, et al. Heritability of longitudinal change in lung function. The Framingham Study. *Am J Respir Crit Care Med.* 2001;164(9):1655–1659.

48. Dick DM. An interdisciplinary approach to studying gene-environment interactions: from twin studies to gene identification and back. *Res Hum Dev.* 2011;8(3-4):211–226.

49. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (*5-HTTLPR*), stress, and depression meta-analysis revisited. *Arch Gen Psychiatry.* 2011;68(5):444–454.

50. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301(5631):386–389.

51. Mitchell C, Notterman D, Brooks-Gunn J, et al. Role of mother's genes and environment in postpartum depression. *Proc Natl Acad Sci U S A.* 2011;108(20):8189–8193.

52. Cleveland HH. Disadvantaged neighborhoods and adolescent aggression: behavioral genetic evidence of contextual effects. *J Res Adolesc.* 2003;13(2):211–238.

53. Boardman JD, Saint Onge JM, Haberstick BC, Timberlake DS, Hewitt JK. Do schools moderate the genetic determinants of smoking? *Behav Genet.* 2008;38(3):234–246.

54. Boardman JD. State-level moderation of genetic tendencies to smoke. *Am J Public Health.* 2009;99(3):480–486.

55. Boardman JD, Blalock CL, Pampel FC, Hatemi PK, Heath AC, Eaves LJ. Population composition, public policy, and the genetics of smoking. *Demography.* 2011;48(4):1517–1533.

56. Adkins DE, Guo G. Societal development and shifting influence of the genome on status attainment. *Res Soc Stratification Mobility.* 2008;26(3):235–256.

57. Wang SH, Chen WJ, Chuang LM, Hsiao PC, Liu PH, Hsiao CK. Inference of cross-level interaction between genes and contextual factors in a matched case-control metabolic syndrome study: a Bayesian approach. *PLoS ONE.* 2013;8(2):e56693.

58. Shanahan MJ, Hofer SM. Social context in gene-environment interactions: retrospect and prospect. *J Gerontol B Psychol Sci Soc Sci.* 2005;60(special no 1):65–76.

59. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull.* 2009;135(6):885–908.

60. Belsky J, Pluess M. The nature (and nurture?) of plasticity in early human development. *Perspect Psychol Sci.* 2009;4(4):345–351.

61. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary-neurodevelopmental theory. *Dev Psychopathol.* 2011;23(1):7–28.

62. Simons RL, Lei MK, Beach SRH, Brody GH, Philibert RA, Gibbons FX. Social environment, genes, and aggression: evidence supporting the differential susceptibility perspective. *Am Sociol Rev.* 2011;76(6):883–912.

63. Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. *Science.* 2002;297(5582):851–854.

64. Koopmans JR, Slutske WS, van Baal GCM, Boomsma DI. The influence of religion on alcohol use initiation: evidence for genotype x environment interaction. *Behav Genet.* 1999;29(6):445–453.

65. Fletcher JM. Why have tobacco control policies stalled? Using genetic moderation to examine policy impacts. *PLoS ONE.* 2012;7(12):e50576.

66. Saccone SF, Hinrichs AL, Saccone NL, et al. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Hum Mol Genet.* 2007;16(1):36–49.

67. Daw J, Shanahan M, Harris KM, Smolen A, Haberstick B, Boardman JD. Genetic sensitivity to peer behaviors: 5HTTLPR, smoking, and alcohol consumption. *J Health Soc Behav.* 2013;54(1):92–108.

68. Pluess M, Belsky J. Conceptual issues in psychiatric gene-environment interaction research. *Am J Psychiatry.* 2012;169(2):222–223.

69. Raine A. Biosocial studies of antisocial and violent behavior in children and adults: a review. *J Abnorm Child Psychol.* 2002;30(4):311–326.

70. Tuvblad C, Grann M, Lichtenstein P. Heritability for adolescent antisocial behavior differs with socioeconomic status: gene-environment interaction. *J Child Psychol Psychiatry.* 2006;47(7):734–743.

71. Plomin R, Defries JC, Loehlin JC. Genotype-environment interaction and correlation in analysis of human-behavior. *Psychol Bull.* 1977;84(2):309–322.

72. Price TS, Jaffee SR. Effects of the family environment: gene-environment interaction and passive gene-environment correlation. *Dev Psychol.* 2008;44(2):305–315.

73. Branigan AR, Freese J, Patir A, McDade TW, Liu K, Kiefe C. Skin color, sex, and educational attainment in the post-civil-rights era. Presented at: The Meeting of the Research Committee on Social Stratification and Mobility (RC28) of the International Sociological Association; April 15, 2011; Colchester, UK.

74. Stovel K, Savage M, Bearman P. Ascription into achievement: models of career systems at Lloyds Bank, 1890-1970. *Am J Sociol.* 1996;102(2):358–399.

75. Reskin BF, McBrier DB. Why not ascription? Organizations' employment of male and female managers. *Am Sociol Rev.* 2000;65(2):210–233.

76. Nielsen F. Achievement and ascription in educational attainment: genetic and environmental influences on adolescent schooling. *Soc Forces.* 2006;85(1):193–216.

77. Cleveland HH, Wiebe RP, Rowe DC. Sources of exposure to smoking and drinking friends among adolescents: a behavioral-genetic evaluation. *J Genet Psychol.* 2005;166(2):153–169.

78. Jaffee SR, Price TS. Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Mol Psychiatry.* 2007;12(5):432–442.

79. Fletcher JM. enhancing the gene-environment interaction framework: evidence from differential responses to September 11th. Presented at: The 76th Annual Meeting of the Population Association of America; March 31–April 2, 2011; Washington, DC.

80. Sampson RJ, Morenoff JD, Gannon-Rowley T. Assessing "neighborhood effects": social processes and new directions in research. *Annu Rev Sociol.* 2002;28(1):443–478.

81. Theorell T. Working conditions and health. In: Berkman LF, Kawachi I, eds. *Social Epidemiology.* New York, NY: Oxford University Press; 2000:95–117.

82. Reidpath DD, Burns C, Garrard J, Mahoney M, Townsend M. An ecological study of the relationship between socioeconomic status and obesogenic environments. *Health Place.* 2002;8(2):141–145.

83. Williams DR, Collins C. US socioeconomic and racial-differences in health: patterns and explanations. *Annu Rev Sociol.* 1995;21(1):349–386.

84. Duster T. Comparative perspectives and competing explanations: taking on the newly configured reductionist challenge to sociology. *Am Sociol Rev.* 2006;71(1):1–15.

85. Hartz SM, Short SE, Saccone NL, et al. Increased genetic vulnerability to smoking at CHRNA5 in early-onset smokers. *Arch Gen Psychiatry.* 2012;69(8):854–860.

86. Cardon LR, Palmer LJ. Population stratification and spurious allelic association. *Lancet.* 2003;361(9357):598–604.

87. Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatry.* 2006;47(3-4):226–261.

88. Massey DS, Rothwell J, Domina T. The changing bases of segregation in the United States. *Ann Am Acad Pol Soc Sci.* 2009;626(1):74–90.

89. Pritchard JK, Stephens M, Rosenberg NA, Donnelly P. Association mapping in structured populations. *Am J Hum Genet.* 2000;67(1):170–181.

90. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet.* 2006;38(8):904–909.

91. Daw J, Guo G. The influence of three genes on whether adolescents use contraception, USA 1994–-2002. *Popul Stud (Camb).* 2011;65(3):253–271.

92. Fletcher JM, Lehrer SF. Genetic lotteries within families. *J Health Econ.* 2011;30(4):647–659.

93. Wang KS, Liu XF, Aragam N, et al. Family-based association analysis of alcohol dependence in the COGA sample and replication in the Australian twin-family study. *J Neural Transm.* 2011;118(9):1293–1299.

94. Blumer H. *Symbolic Interactionism: Perspective and Method.* Englewood Cliffs, NJ: Prentice-Hall; 1969.

95. Barnett E, Casper M. A definition of "social environment." *Am J Public Health.* 2001;91(3):465.