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Under the Influence of Genetics: How Transdisciplinarity Leads Us to Rethink Social Pathways to Illness

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Abstract

To extend our understanding of how social structures and social processes impact behavior, sociologists have been challenged to incorporate the potential explanatory role of genetics in their models. Here, we draw propositions from three major understandings of illness causation offered by social theory – fundamental causes, social stress processes, and social safety net theories. We tailor hypotheses to the case of alcohol dependence, long considered a multifaceted problem, defying simple explanation and having both biological and social roots. After briefly reviewing current appeals for transdisciplinary research, we describe both sociological and genetic theories, and derive propositions expected under each and under a transdisciplinary theoretical frame. Analyses of a later wave of the preeminent medical science study, the Collaborative Study on the Genetics of Alcoholism (COGA), reveals a complex interplay of how the GABRA2 gene works with and against social structural factors to produce cases meeting DSM/ICD diagnoses. When both genetic and social factors are controlled, virtually equivalent effects of each remain; and, only modest evidence suggests that genetic influence works through social structural conditions and experiences. Further exploratory analyses using multiplicative terms reveal enhanced gene-environment interactions: 1) women are largely unaffected in their risk for alcohol dependence by allele status at this candidate gene; 2) family support attenuates genetic influence; 3) childhood deprivation exacerbates genetic predispositions. We discuss how these findings lead us to consider the essential ***intradisciplinary*** tension in sociological theories (i.e., the role of proximal and distal influences in social processes). Overall, our findings point to the promise of theories blending social and genetic influences by focusing directly on dynamic, networked sequences that produce different pathways to health and illness.

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INTRODUCTION

Historically, problems with alcohol have attracted the attention of both social and biological scientists. While some contend that the idea of the heritability of alcoholism is over a century old (Murray and Stabenau (1982), others maintain that it dates to ancient times (Hesselbrock et al. 2001). Medical studies which searched for genetic influences through family, adoption, and twin studies (e.g., Hesselbrock 1995) provided confirmatory evidence for leading candidates. Sociologists and other social scientists studying alcoholism have depended on social influence models (e.g., social learning theory, White, Bates, and Johnson 1991) and theories on the strength of normative structures to mitigate against the development of alcohol dependence (Roman 1981). Ironically, as genetic studies picked up in the 1980s, sociological attention lagged, likely due to a combination of courtesy stigma within the discipline, a political climate which discouraged investigation of social factors in illness, and the medicalization of alcohol problems under a growing biomedical dominance in research (Roman 1982).

Perhaps there is no better marker of that dominance than the Human Genome Project, completed ahead of schedule and under budget in 2003, that ushered in the “Genomic Era” (Bonham, Warshauer-Baker, and Collins 2005). Yet, the irony underlying one of the most significant medical science achievements of the twentieth century lies its’ accompanying conclusion: The environment – from chemical toxin exposure to national structures of inequality – plays a critical role, particularly in more complex health and illness problems. Indeed, calls for research agendas that target “cells to society” (Abrams 1999) or “neurons to neighborhoods” (Shonkoff and Phillips 2000) have been issued by the most prestigious arbiters of medical science in American society (Pescosolido 2006a).

Notions of epigenetic modification and gene-environment interactions theorize the intermingling and mutual influence of biological/genetic and social factors to produce complex health problems. From a sociological perspective, these new directions in the medical sciences agenda raise questions about the power of social structure and the role of social processes. Does the inclusion of genetics dampen, heighten, or otherwise change the influence of social factors in the onset of medical problems? Do genetic theories of the development of individual problems, defined as medical in nature, alter sociological theories of illness and disease?

Here, we attempt to offer some preliminary insight into these questions by focusing on one case, alcoholism, where social structure shapes the definition, determinants, and outcomes of drinking patterns, as well as the medical response to these problems. Similarly, as noted above, genetic predispositions, as well as physiological processes, have been implicated in the probability that casual drinking will translate into abuse or dependence as a result of biochemical variations in the way that different groups react to alcohol (e.g., Asians, women; Goodwin 1991).

Using data from one of the premier, multi-site, medical studies of alcoholism, the Collaborative Study of the Genetics of Alcoholism (COGA), we consider both sociological and genetic views of disease. We develop and test a set of direct and interactive hypotheses

about the influence of social and genetic factors in the hope of setting sociological challenges for the transdisciplinary agenda.

THEORETICAL BACKGROUND: CLASSIC AND CONTEMPORARY THEORIES OF ILLNESS AND DISEASE

The Call for Transdisciplinarity

In *New Horizons in Health*, a report from the National Research Council of the National Academy of Sciences, one priority for this "new era of research" lists understanding "environmentally induced genetic expression and its connection to positive and negative health outcomes" (Singer and Ryff 2001, pp. 17, 3, respectively). Debates about the primacy of genetics/biology versus society/culture have been declared "scientifically obsolete," replaced instead by a view of "their inseparability and complementarity", and characterized by "deliberate efforts to forge ongoing interaction among scientists" (Shonkoff and Phillips 2000, pp. 6, 41, 14, respectively; Hernandez and Blazer 2006; see also Horwitz et al. 2003; Guo and Stearns 2002).

At the heart of these arguments lies the notion that social and genetic factors are interconnected. To date, three basic theoretical approaches have been offered: 1) Genetic factors shape social processes, i.e., genetic inheritance influences social achievement via an influence on educational attainment and human capital acquisition (Guo and Stearns 2002), or shapes the social safety net via a tendency to develop affiliations such as marriage (Social Mediators Option; Dick et al. 2006a); 2) Injurious social factors "trigger" or "suppress" gene expression, i.e., poverty or other stressful life circumstances "turn on" particular disease genes (Social Trigger/Suppressor Option; Singer and Ryff 2001); or 3) Genes attenuate or exacerbate the effects of social stressors and negative life events, i.e., sensitivity to child abuse is reduced among children with protective genotypes (Caspi et al. 2002); or family disruptions are more likely to result in psychopathology among children with high-risk genotypes (Genetic Attenuation/Exacerbation Option; Silberg et al. 2001). Although not necessarily analytically distinct, these alternative perspectives comprise the basic, transdisciplinary theoretical approaches underlying the contemporary push to integrate social and genetic influences on illness and disease.

THE CASE OF ALCOHOL

Early and often, alcoholism has been singled out as a particularly rich case for integrative investigation (e.g., Bearman and Brueckner 2002; Guo 2006). Indeed, the precursors of alcoholism such as stress, socialization, and coping styles have been described as being driven by broad social structural influences, linked to gene expression, and to multiple pathophysiological systems (e.g., Singer and Ryff 2001: 130). As a result, some argue that behavioral disorders, psychopathology and anti-social behavior represent the prime candidates and leading edge for environmental-genetic studies (Merikangas and Avenevoli 2000).

Figure 1 presents the general theoretical framework derived from the discussion above that guides our analyses. This figure posits direct effects of the three streams of sociological

theory, genetic models, and a basic gene-environment interaction. We develop propositions and then narrow to hypotheses matching available operational measures.

THE SOCIOLOGICAL VIEW

We believe that the essence of the sociological contribution can best be captured through a conceptualization of three traditions that represent persistent themes in sociological inquiry -- The Theory of Fundamental Causes, Stress Process Theory, and Social Safety Net Theories.

The Theory of Fundamental Causes

Social inequality and its impact on health, illness, and disease represents one of the most enduring concerns of health-focused social science, as well as social medicine, social work and public health (Robert and House 2000). Indeed, the frequently offered observation that each of the founders of sociology focused, to one extent or another, on the social gradient of life and death as a window into general social processes and power differentials is hardly novel (Lutfey and Freese 2005; Pescosolido, McLeod, and Avison 2007). This realization notwithstanding, a recently-elaborated individual-focused lifestyle-based approach (e.g., emphasizing health-related choices made by individual actors relative to diet, exercise, smoking, etc.), has come to dominate public and professional discourse, often pushing social factors to the background.

In 1995, Link and Phelan reminded sociologists of the complexities of the relationship between social inequalities and the onset of illness and disease. The Theory of Fundamental Causes questioned the dominant focus of risk-factor epidemiology on proximate causes. Rather, they argued that the larger social context shapes access to economic resources, cultural norms, and social meanings that underlie lifestyle and biological mechanisms. At each point in time and place, social context determines links between social structure and disease; and, as those larger conditions change, so do the mechanisms that connect inequality and life chances (see Lutfey and Freese 2005 for an elaboration). Consequently, this basic sociological theory posits:

> *P1: Factors locating individuals on the social fault lines of society that denote power differentials will shape negative health, illness and disease outcomes*.

With regard to the Theory of Fundamental Causes, McLeod and Nonemaker (1999) clarify that the components of social stratification (resources, power) are made up of structures (e.g., poverty, segregation) and status characteristics (race, gender and age). We focus on five socio-demographic characteristics that directly measure or tap into social inequality:

> *H1: Income, education, race, gender and age will be associated with a diagnosis of alcohol dependence.*

The Stress Process

Stress theories focus on social experiences in terms of discrete events (e.g., divorce, abuse), pressures (e.g., job stress, marital discord) and enduring social conditions (e.g., economic strains, discrimination). As Wheaton (1999a) notes, this conceptualization laid out both the

rooting (social origins, contingencies, and types of stress) and well as the *routing* (sequences and coping responses) of stress. Over time, stress research has included a focus on life events, daily hassles, non-events, traumas, and ecological stressors which are conditions of "threat, demand or structure constraint" that call into question the "operating integrity of the organism" (defined as "a condition of threat, demand, or a structure constraint that"…"calls into question the operating integrity of the organism," Wheaton 1999a, p. 281, 278, respectively). Eventually, this led to a two-way classification defined by whether the stress is discrete or continuous and by the social level from which the stress emanates, i.e., micro, meso, or macro (Wheaton 1999b). What is key, according to Pearlin (1999), is that the stress process connects individuals to their inner selves (e.g., identity), to the rhythms of their daily lives, and to the larger social contexts in which they are embedded.

In sum, the Theory of the Stress Process holds that:

> *P2: Social stressors, whether chronic or episodic, current or past, influence negative health, illness and disease outcomes*.

Theories of the Stress Process focus on the health-related impacts of both the immediate set of stressful social experiences and the legacy of historical traumas. To that end, we hypothesize:

> *H2: Experiences of childhood maltreatment and daily hassles will be positively associated with a diagnosis of alcohol dependence*.

Social Safety Net Theories

The role of network-based resources available from family, friends, organizations, and even geographical areas in the social epidemiology of health, illness and disease has become a mainstay of sociological and behavioral research (Pescosolido and Levy 2002). Tracing their roots back to Durkheim (1951 [1897]), social support theories that came into vogue in the 1970s tended to focus on the power of social structure to help defend against social, biological or genetic insults to individuals (Meyers, Lindenthal, and Pepper 1975). While the presence of strong social ties has been found to mitigate against negative health outcomes, social ties have also been shown to be the vectors of morbidity and mortality (tuberculosis, Klovdahl, Graviss, and Musser 2002; obesity, Christakis and Fowler 2007; and suicide, Pescosolido and Georgianna 1989).

The difference in traditions (e.g., social support, social network, or social capital perspectives) found in the various historical and subfield roots led to divergent theoretical conceptualizations (Pescosolido 2006b). On the one hand, according to Turner (1999), social support is comprised of support network resources, supportive behavior, and perceived social support. In this social psychology-based approach, social networks represent one component of social support and the focus is on the sustaining qualities of social relationships (Haines, Beggs, and Hurlburt 2002). Support may be perceived (i.e., the belief that love, caring and assistance are potentially available from others) or received (i.e., the actual use of others for caring, assistance, appraisal; Thoits 1995; activated networks in the structural tradition; Knoke 1990). On the other hand, the more structurally-oriented social network approach sees social networks as the web of social relations that offer opportunities

through which resources such as social support may or may not be provided and invoked (Faber and Wasserman 2001).

Despite conceptual differences, we expect:

> *P3: Social relationships will be associated with health, illness and disease. Specifically, negatives ties will predispose individuals to health problems while positive ties will protect individuals*.

Traditionally, social supports that make up the social safety net have included both socio-demographics considered to be proxies for the existence of positive ties, along with direct measures of the actual and perceived availability of support from families and individuals in the community. These ties provide the kinds of emotional and instrumental assistance that have been hypothesized to decrease the occurrence of negative stressors or to lessen their impact:

> *H3: Being married and having greater support from family and friends will be negatively associated with a diagnosis of alcohol dependence*.

THE GENETIC VIEW

Simple Heritability Arguments

Genetic research is primarily inductive in nature, searching for "candidate genes" (e.g., serotonin transporter gene 5-HTT implicated in depression, Caspi et al. 2003). Initially, genetic linkage studies involved searching pedigrees in families that display high prevalence of a disorder and/or have remained relatively genetically isolated.[1] In recent years, association methods have located some single genes responsible for the linkage peaks in these chromosomal areas. They allow the interrogation of virtually every gene in the human genome at once. A basic proposition of genetic research posits:

> *P4: Genetic profiles, particularly candidate genes or suspicious gene clusters, discovered through an inductive process, will be associated with negative health, disease, and illness outcomes*.

Research on alcohol dependence implicates a dozen or more genes, each with only a modest effect on phenotype (Dick and Foroud 2003). The most promising candidate gene implicated in alcohol dependence, and documented in earlier analyses of the COGA data, is GABRA2, located on chromosome 4 (Edenberg et al. 2004; Whitfield et al. 2004). The protein product of the GABRA2 gene is the alpha 2 subunit of the GABA-A receptor protein. Single nucleotide variants in the GABRA2 gene are associated with a modest elevated risk of alcohol dependence (Hesselbrock 1995; Reich et al. 1998; Edenberg et al. 2004). The gene variants thus far identified are not associated with differences in the amino acid composition of the protein, but are presumed to participate in the regulation of the amount of protein produced.

[1]The Old Order Amish are a classic example. This unique community was considered ideal for "data mining" because Old Order Amish allow neither conversion nor marriage to non-group members. Genetic isolation both limits the possible genes involved and amplifies their effects, making them easier to detect. Analyses did isolate a gene candidate for bipolar depression, a disorder with a polygenic mode of inheritance. However, even as this finding continues to be cited, replicating these findings in other family lines has proven problematic (Levin 2005; Ginns et al. 1996).

GABA is the major inhibitory neurotransmitter in the mammalian brain. Changes in GABA receptor regulation may be associated with decreased effectiveness of inhibitory processes in the brain, which may in turn be associated with central nervous system hyperexcitability and various behavioral disorders such as substance abuse (Begleiter and Porjesz 2000). GABA-A receptors appear to mediate some of the subjective effects of alcohol and other drugs, including benzodiazepines (Koob 2004). More specifically, individuals with certain variants of GABRA2 have a low level of response (LR) to the intoxicating effects of alcohol (Pierucci-Lagha et al. 2005), a trait that has been linked to the development of alcohol dependence. LR individuals must consume more alcohol to achieve anxiolysis, or anxiety-reducing sedation, which may initiate a cycle of increasing tolerance and consumption. At least two other GABA receptor genes, GABRA1 and GABRG3 (Dick and Foroud 2003) have been associated with alcohol dependence.

We focus on GABRA2 for two reasons: 1) Since previous COGA analyses found a predisposing effect of GABRA2, it sets up the possibility of exploring gene × environment interactions; and, 2) not using the same paradigm of data analysis that established this effect we are able to provide information on the robustness of GABRA2's influence. This GABA-related gene variant is quite prevalent. About 55–60% of the general population carry one or more copies of the risk allele and about 33–35% carry two (dbSNP). The relative risk associated with homozygosity is about 1.2–1.4 (Dick et al. 2006a) and the amount of genetic variance explained by GABRA2 variation is estimated to be 6–12% (assuming an overall relative risk due to genetic factors at 2.0). This type of estimate will be more precise when large samples of cases and controls are genotyped at this locus, as may be expected as part of genome-wide association studies now in progress) (Nurnberger Jr. et al. 2004).

Thus, following from Proposition 4, we set a replicating hypothesis:

> *H4: GABRA2 will be associated with a modest, but significant increase in risk for a diagnosis of alcohol dependence.*

THE CROSS-CUTTING VIEW

Epigenetic Modification: Genes-Environment Interactions

Many of the most commonly cited behavioral-genetic findings are based on an earlier traditional model that pits genetic and social or environmental contributions to disease against one another. This approach is, in part, a function of the previously popular methodology of twin and adoption studies, utilized to support notions of the importance of heredity (Collins et al. 2000). For some time now, behavioral geneticists have supplemented this simplistic additive model with a more complex "multifactorial" model of disease. The contemporary view suggests that numerous genes and environmental stimuli interact, are mediated in the brain, and change over the life course to produce any of a set of multiple potential outcomes (Singer and Ryff 2001). Most heritable medical problems are assumed to be attributable to varying degrees of genetic and environmental influence; are encoded by not one gene but a set of polygenes; and demonstrate genetic heterogeneity (i.e., many genetic paths to the same outcome; e.g., hypertension). Diseases once thought to operate under a clear and simple recessive genetic model are now presumed to be shaped by polygenic complexities (e.g., cystic fibrosis; muscular dystrophy) and susceptible to

environmental influence (e.g., Fragile X syndrome), resulting in significant variation in severity, treatment response, and prognosis (Hamer 2002).

Thus, contemporary transdisciplinary theory proposes a more nuanced process:

> *P5: Genetic predispositions and environmental context, including social structures and social experiences, exist in a complex and mutually dependent relationship, interacting to influence health, illness and disease outcomes.*

Regarding the GABRA2 gene effects on alcohol dependence, interactions with age (around 20) and marital status (married) have been identified. High risk genotype on GABRA2 is expressed more strongly in currently married individuals and among those in stable marriages (Dick et al. 2006b). However, GABRA2 is associated with symptoms of childhood conduct disorder, suggesting that GABRA2 may shape patterns of uninhibited behavior that manifest in unique ways at different developmental stages (Dick et al. 2006b). The authors speculate that the overall rate of alcohol dependence in individuals who are unstably married or never married is sufficiently high that the risk associated with GABRA2 is undetectable.

In addition, gender often conditions social opportunities and the effect of genes implicated in behavioral disorders (Horwitz et al. 2003; Martin, Blum, and Roman 1989). Gene-environment interactions have also been suggested in analyses regarding childhood abuse (Caspi et al. 2002) and social supports (Fox et al. 2005). Finally, the issue of race has consistently presented problems for geneticists (Bonham, Warshauer-Baker, and Collins 2005); and, to some extent for sociologists, since the effects of race on drinking are also conditioned by gender, i.e., black women, perhaps more than any group, are likely to abstain from alcohol use or drink only infrequently (Martin 2000).

We do not offer a firm set of non-additive hypotheses. Rather, we empirically explore the general idea that the effects of the sociological influences will vary by the level of the candidate gene. Stressors, inequality, and supports will be examined to see if their effects differ depending on GABRA2 allele status:

> *H5: Factors that reflect disadvantaged social status will produce greater genetic effects while those that tap advantaged social positions will lessen genetic influence*.

Endogeneity: Gene-Environment Correlations

The identification of gene-environment interactions is further complicated by the Social Mediator Option discussed earlier. Also referred to in genetics research as “gene-environment correlations” or in sociological/social science language as “the endogeneity problem,” genes are theorized to shape the degree to which individuals are exposed to certain social conditions, how they interpret or react to those experiences, and the extent to which social conditions affect health and other outcomes (Rutter 1997). For example, the GABRA2 gene is associated with marital status, and not simply as a reflection of the effects of alcohol dependence on marriage and divorce (Guo and Stearns 2002; Dick et al. 2006a). Individuals with and without alcohol dependence who carry the high-risk genotype are less likely to be currently married, to ever have been married, and to be involved in a stable

marriage, suggesting that GABRA2 may shape personality characteristics that influence the likelihood of marriage and divorce. In addition to interacting with social variables to produce health outcomes, genetic heritability may be working *through* social structural conditions, making it difficult to tease out genetic and social influences. Within data limits, we explore Dick et al.'s (2006a) alternative conceptualization, examining gene-environment correlations and endogeneity issues, which essentially posit a classic mediating model whereby genetic factors shape *both* social structural conditions and illness.

H6: The effects of social factors will be associated with and attenuated in the presence of genetic influence.

Limitations

Both genetic and sociological theories are more nuanced and inter-connected than Figure 1 allows. Our purpose is to explore how genetic and sociological factors meet (i.e., in essence illustrating if, where, and how they interact) as a platform for understanding the implications for sociological theory and the transdisciplinary agenda. Given these unexplored complexities, the aims of the COGA Study and the methodological approaches used in medical studies that do not match traditional social science designs, a more conservative approach and parsimonious modeling seems judicious.

DATA, MEASURES AND METHODS

Sample

Data come from the Collaborative Study of the Genetics of Alcoholism. COGA is a National Institute on Alcohol Abuse and Alcoholism (NIAAA) funded study designed to identify and map predisposing and protective genes for diagnosis of alcohol dependence and related maladaptive patterns of drinking. Data collection took place at nine venues and in two phases. An initial assessment was conducted between 1989–1999, and a follow-up assessment was conducted between 1997–2004 (Edenberg et al. 2004). Since the measures of stress and support used here were not collected until Phase 2, we limit our analyses accordingly. As such, our analyses do not simply replicate earlier studies.

COGA utilizes a case-control methodology that relies on a complex, availability-based, family selection strategy that collected data from three groups of subjects (Agarwal and Seitz 2001). Two groups of families, referred to as Stage I or Stage II families, included persons diagnosed with alcohol dependence who were systematically recruited from consecutive admissions to both inpatient and outpatient alcohol treatment facilities. Stage I families were comprised of a focal respondent (FR) who met criteria for alcohol dependence and who had at least two first-degree relatives living within a 150 mile radius of the COGA catchment area. Stage I FRs and their biological relatives over age 6 who agreed to participate completed a structured psychiatric interview, provided psychiatric information on other family members, and completed a battery of standardized personality trait measures. Potential Stage I FRs were ineligible to participate if they were an intravenous-drug user, had a life-threatening illness unrelated to alcohol use, were non-English speaking, or identified as HIV positive. Stage I families where the FR had two or more first-degree relatives who also met criteria for a diagnosis of alcoholism were designated as Stage II

families. In these families, all first-, second-, and third-degree relatives who agreed to participate completed the battery of Stage I assessments and provided blood samples for biochemical analysis and the extraction of DNA.

A third group of families, designated as community controls, were selected from dental clinics, driver's license bureaus, health maintenance organizations, church congregations, or large corporations. All control families had two parents and at least three biological children over the age of 14. All family members over the age of 6 were evaluated using Stage II protocol. Control FRs were deemed ineligible if they had a life-threatening illness, had a history of serious head injury or neurological disease, were non-English speaking, or were known to be HIV positive.

Informed consent was obtained from all adult subjects and minor children provided informed assent and parental consent. A Certificate of Confidentiality was also provided by NIAAA. All subjects received financial compensation for participation.

At the completion of the Phase 2 follow-up assessment, these selection procedures yielded a sample of 10,330 subjects. We eliminated the children and adolescents (N=2,537). Among adults, we excluded those without genetic information (N=4,853) and in addition those with missing data on other study variables (N=424). This yielded a final sample of 2,516 adult subjects from 502 families, with an average of 5.0 respondents per family.

Given the non-random selection of the alcohol dependent cases and the "community controls," the final sample could have problems of selection bias. COGA's highly selected sample of families with alcoholic pedigrees raises concerns about generalizability. While there are methods to adjust for selection bias (Winship and Mare 1992), they cannot be addressed with the data at hand. As an alternative, we construct different subsamples to explore the robustness of our findings by manipulating the alcohol dependent and non-dependent "treatment" groups. We re-estimated all models after omitting alcohol dependent focal respondents from the sample (N=2,367), and again using only control families (N=828).

Variables

Alcohol Dependence—The dependent variable is indexed by the assignment of subjects who concurrently meet DSM-IV (American Psychiatric Association 1994) and ICD-10 (World Health Organization 1992–1994) criteria for alcohol dependence/alcoholism. These diagnostic classifications define alcohol dependence as a *long-term pattern* of maladaptive use with clinically significant behavioral, cognitive and/or physiological impairment. Impairment is assessed by some combination of increasing levels of tolerance; physical withdrawal symptoms; increasing levels of consumption; unsuccessful attempts to control consumption; increasing amounts of time spent obtaining, using, or recovering from drinking; reduction or termination of social, occupational, or recreational activities; and continued use despite knowledge of adverse physical or psychological effects. Alcohol dependence was coded 1 (35% of subset) if the FR was classified as dependent according to both criteria, else 0.

We are aware that diagnoses and classification of phenomena such as “alcohol dependence” are social constructions (Horwitz et al. 2003). Our theoretical, transdisciplinary project requires addressing the concerns of two audiences. We use the dichotomy but attempt to avoid terms such as “being alcoholic.”

Genetic Risk—*Genetic risk* is indexed by a single item, high risk on the GABRA2 gene, identified via SNP genotyping and association analyses as being linked to alcohol dependence (Edenberg et al. 2004; Reich et al. 1998).[2] Increased risk for a clinical diagnosis of alcohol dependence is associated with carrying two copies of the high risk allele A at the SNP rs279871 on GABRA2 (Dick et al. 2006a; Edenberg et al. 2004). Participants are classified as having a high risk genotype (coded 1) if they are homozygous for the A allele, and 0 if they carry one or zero copies of this allele.

Indicators of Fundamental Causes—*Gender* is coded 1 for women, else 0. *Race is* coded 1 for black and 0 otherwise. *Education* is coded as a series of dummy variables indicating less than high school, high school, less than college, and college plus. *Income* is measured as the log of household income in tens of thousands of dollars. *Age* is measured in years.

Stress Process Indicators—Having experienced *Deprivation During Childhood* is coded 1 if subjects agreed with the question “When you were 6–13, did you or anyone in your family ever not have enough to eat because your family was poor?”, else 0. *Daily Stressors* are measured by the 53-item Delongis Daily Hassles Scale. This measure is comprised of items indexing how much of a hassle a particular activity/venue/person (e.g., work, children, spouse, friends, clients, sex) had been in the last week (Weinberger, Hiner, and Tierney 1987). Response categories range from none or not applicable, coded 0, to a great deal, coded 3. We computed the square root of the sum of all items with missing data coded as 0.[3]

Indicators of Social Safety Net Protections—*Marital Status* is coded 1 for currently married; 0 otherwise. Family social support and friends social support, based on the social support index (Procidano and Heller 1983), uses 20 items reflecting perceived support. Sample items include: “My family (friends) provide the moral support I need;” or “I rely on my family (friends) for emotional support.” Response categories are 1=generally false, 2=more false than true, 3=more true than false, and 4=generally true. Items are coded so higher scores indicate more perceived support. Two measures sum all non-missing items, rescaling to the original range of 20 to 80.

Analytic Approach

The effects of GABRA2 and social factors on alcohol dependence are modeled with a population-average logit model (Rabe-Hesketh and Skrondal 2005: 120–124; Fitzmaurice,

[2]In preliminary analyses, we explored the effects of CHRM2 and ADH. However, we could not replicate significant associations from earlier studies. These empirical findings reinforced our decision to focus solely on GABRA2.

[3]COGA data do not distinguish between “no stress” and “not applicable.” We cleaned these data using social category variables (e.g., marital status) to recode individual responses to “missing” (e.g., marital stress).

Laird, and Ware 2004: 297–299) estimated with StataCorp's (2005) xtlogit command. This model adjusts for the lack of independence among observations from having multiple individuals from the same family. Given that our sample is not random, tests of significance should be interpreted cautiously.

A series of models is estimated (Table 2). Model 1 includes only GABRA2 as a predictor of alcohol dependence. Model 2 includes only social variables but does not include GABRA2. Model 3 includes both GABRA2 and the social variables. Because of the nonlinearity of the logit model, the effects of social variables on alcohol dependence can differ by the level of GABRA2. Given our fundamental interest in whether the effect of social variables differ by genotype on GABRA2, we also ran a series of exploratory models that added to a single multiplicative term for GABRA with a social variable (e.g., GABRA2*female added to Model 3). A separate model was estimated for each variable. We computed the predicted probability (i.e., marginal probabilities) of alcohol dependence (Rabe-Hesketh and Skrondal 2005: 120–124) at specific levels of independent variables to examine how the effects of the social variables vary by GABRA2.[4] We also examine "gene-environment correlations" by testing the association between GABRA2 and each social variable using a chi-square test of independence.

While the case-control methods employed in the COGA study are well-suited to studies of relatively rare events that are the result of a lengthy developmental process (like alcohol dependence), this design does have limitations regarding generalizability and causality.[5]

RESULTS

Baseline Models

Genetics—The observed probability of alcohol dependence for individuals with a high risk genotype .39 compares to .33 for those at low risk. This difference is consistent in direction and magnitude with those found in studies using a different COGA sub-sample (Dick et al. 2006a). Supporting our H4, the robustness of the effect across waves and case mix is reassuring.

Population-average logistic regression model estimates are reported in Table 2. In Model 1, having the high risk genotype on GABRA2 increases the odds of being diagnosed with alcohol dependence by 26 percent (OR=1.26, $p<.05$). The GABRA2 effect is essentially unchanged after adding controls for social variables (Model 3). Similarly, the effects of social variables on alcohol dependence are nearly identical whether or not genotype is included (compare Models 2 and 3). Thus, not only do both genetic and social factors affect medically-defined alcohol dependence, but the inclusion of both in the same model specification does not change the effects of each to any great extent, an unexpected result under many transdisciplinary theories (e.g., Options 1 and 3). This same result was found

[4]In logit models, Chow-type tests of the equality of coefficients across groups (e.g., testing if the coefficient for GABRA2 is the same for males as it is for females) are inappropriate since they confound the magnitude of the effect for each group with group differences in residual variation (Allison 1999). Predicted probabilities across groups, however, are unaffected by the confounding of the slope coefficients and variance of the errors (Long 2006).

[5]Case-control studies are generally unable to address the sequence of events that are presumed to produce the condition of interest, and as such, can only suggest causality based on logical criteria (Coggan, Rose, and Barker 1997).

when we restricted our sample to exclude focal respondents and when including only control families (available on request).

Social Factors—As expected under our H1, social factors that tap fundamental causes have a significant effect. As income increases, the odds of alcohol dependence decrease (OR=.89, p<.01). Being female (OR=.25, p<.001) and being black (OR=.51, p<.001) both decrease the odds of dependence. However, with age and age-squared (X^2=70.4, p<.001), the predicted probability of dependence increases rapidly from the age of 18 to the mid-40s and then steadily decrease, holding all other variables at their mean. A challenge to theory of fundamental causes lies in how women and African Americans have lower alcohol dependence. Because these social groups are usually cast as having less social power, this inconsistency presents a key opportunity for future transdiciplinary research. Finally, the odds of alcohol dependence decrease for those with a high school education (OR=.60, p<.001), some college (OR=.64, p<.01), or a college degree or more (OR=.36, p<.001) compared to those with less than high school. In sum, social locations associated with greater power generally decrease alcohol dependence, while those marking less power increase it. In addition, a clear but curvilinear life course pattern is in evidence with middle age showing a peak in alcohol dependence.

We also find support for the stress process hypothesis (H2), with both current and past stressors at work. The more daily hassles people report, or for those reporting material deprivation in childhood, the greater the odds (OR=1.16, p<.001; OR=1.49, p<.05, respectively) of alcohol dependence. The social safety net hypothesis (H3) is also supported. Being married significantly reduces the odds of alcohol dependence (OR=.61, p<.001), as does perceived social support from family members (OR=.99, p<.001). Support from friends does not have a significant effect. Thus, kin-based networks appear to play an important ameliorative role, while current or past stress aggravates problem drinking.

Gene-Environment Correlations—We find modest evidence of relationships between genotype and two social variables (H6). Among individuals without alcohol dependence, those with a high-risk genotype on GABRA2 are less likely to be currently married (X^2(1)=3.98, p<.05) and have lower household incomes (X^2(3)=9.74, p<.05) than those with the low-risk genotype. Although GABRA2 may play a small part in shaping social conditions, the gene does not appear to work through the social environment. The effect of GABRA2 retains the same magnitude, direction, and significance after controlling for social factors (Table 2).

Gene-Environment Interaction—Theories of epigenetic modification and our theoretical frame suggest that the effects of social variables may differ by genotype. The nonlinearity of the logit model allows the effects of social variables to differ by the level of GABRA2 (Long 1997: 75–76). However, given the potential importance of gene-environment interactions, we also estimated a series of models in which a single multiplicative term is added to Model 3.[6]

Figure 2 shows predicted probabilities of alcohol dependence from a model that adds a multicative term for GABRA2 and gender to Model 3, holding other variables at their

means. Women who are high risk on GABRA2 and those who are low risk have the same predicted probability of alcohol dependence (.27). For men, however, those with a low risk genotype on GABRA2 have a predicted probability of alcohol dependence of .56, compared to a probability of .67 among those with high genetic risk. We find a similar genotype by gender interaction in the sub-sample without alcohol dependent FR's and in control families.[7] Across all analyses, being female means that genetic inheritance is virtually unoperative. Given bio-physiological studies suggesting lower tolerance in women, these findings implicate the power of social regulation on curbing the genetic predispositions to alcohol dependence (Goodwin 1991).

Figure 3 reveals that genotype has a much larger effect for individuals who experienced childhood deprivation than for those who did not. Among persons who experienced deprivation, the predicted probability for those carrying the high risk genotype is .62 compared to .43 for those at low risk. By contrast, the difference in predicted probabilities is only .43 versus .38, respectively, among individuals who were not materially deprived as children. Again, results were similar when using the sub-sample with alcohol dependent FR's omitted.[8] Early stressors may trigger the negative effects of the high risk GABRA2 genotype. Poverty has been implicated in the resort to risky behavior and "cheap" coping. Both suggest that "escapist drinking" (Martin 2000) may likely be a culturally and socially programmed response which, in turn, makes genetic predispositions for individuals from disadvantaged backgrounds more likely to find behavioral expression.

Figure 4 displays the effects of perceived family support by genotype. Differences in the predicted probability of alcohol dependence are larger at low levels of support (about .14 difference), suggesting that social support from family members may function as a buffering mechanism among those high risk on GABRA2. However, this steadily decreases as support increases. The difference in predicted probability at the highest levels of family support is only about .02. Results are similar for the sub-sample without alcohol dependent FR's and even more pronounced for control families.[9]

In total, empirical evidence suggests interactive findings on social stress and perceived support from family networks in line with social theory. Stress aggravates and network support protects. The support findings are stunning: while individuals reporting no family

[6]As noted in Footnote 4, standard tests of statistical significance of multiplicative terms are not appropriate for testing group differences. We used predicted probabilities to examine whether the effect of GABRA2 on alcohol dependence differed by the level of a social variable (e.g., being married or not). Unfortunately, a test for the difference of differences in probabilities is not available. Given the exploratory nature of these analyses, we rely on whether the differences in predicted probabilities are substantively meaningful.

[7]In the sample without alcohol dependent FRs, women who are high risk on GABRA2 have virtually equal predicted probability of alcohol dependence (.23) to low risk women (.24). For men, those with a low risk genotype vs. high risk on GABRA2 have a predicted probability of alcohol dependence (.51, compared to .61, respectively). In the control sample, the predicted probability of women at low vs. high genetic risk is .08 compared to .12. Men at low genetic risk have a predicted probability of alcohol dependence of .31 compared to .43.

[8]In the sub-sample without alcohol dependent FRs, the predicted probability of those at high vs. low genetic risk who experienced deprivation is .60, compared to .37 (compared to .37 versus .33, respectively, among individuals not materially deprived). In fact, the inclusion of the alcohol dependent FR's attenuates the magnitude of the interaction between genotype and childhood deprivation. Too few cases of childhood deprivation in control families prevented reanalysis.

[9]In the sub-sample without FRs, the difference in predicted probabilities of dependence among those at high and low genetic risk is virtually the same (.02, high support; .14, low support). In the control sample, the difference is magnified (.03, high support; .29, low support).

supports have the expected difference in the probability of alcohol dependence given their genetic inheritance, those reporting high levels of support do not. The monotonic decrease in the influence of genetic risk as social support increases implies that social ties can level the risk of genetic inheritance.

DISCUSSION AND CONCLUSION: THEORETICAL INSIGHTS, SOCIOLOGICAL CAUTIONS AND FUTURE DIRECTIONS

Pathways and Sequences to Clinical Diagnoses

Drawing data from the Collaborative Study of the Genetics of Alcoholism (COGA), we theoretically laid out the set of possible influences between GABRA2 and indicators of medical sociology's primary frameworks – the Theory of Fundamental Causes, Stress Process Theory and Social Safety Net Theories. Our basic findings replicate previous research. Genes matter. Social structures and experiences matter.

The candidate gene, GABRA2, is robust using a different wave of data with different case mixes, offering the same modest increase in the risk of alcohol dependence (about 6%) seen across medical studies. Of course, we explore only a fraction of the variance related to GABA receptor structure. GABA-related variance is, in turn, only one aspect of genetic variance related to alcohol dependence.[10] Further, variables tapping into societal fault lines of inequality (e.g., income, education, race and gender), the experience of stress (e.g., childhood material deprivation, daily hassles), and the presence of a social safety net (e.g., marital status, family-based social support) offer evidence for sociological hypotheses. Of course, we also explore only a fraction of the variance related to social structures and processes.

Importantly, our analyses offer provocative findings, both for the transdisciplinary agenda and for sociological theory. Genetic and social effects change little in the presence of the other. While it would be too strong to say that there is no endogeneity problem, these findings are nonetheless curious, suggesting that the effects of genes and society are not confounded. At least for the individuals in the COGA study, genetic inheritance does not push individuals into material deprivation, stressful situations, or alienation from family. However, both nature and nurture push certain individuals to become dependent on alcohol and to receive a clinical diagnosis.

More challenging, other findings demand further theorizing. While the non-linear models estimated here inherently reveal different effects in different parts of the data space; the introduction of two-way interaction terms indicates that sometimes genetic effects are triggered or suppressed. That is, under the "right" circumstances, genetics and social influences may play complimentary roles in the initiation and maintenance of patterns of alcohol-related behavior.

[10]Despite the strength of the social variables, it would be unwise to conclude that social factors predominate over genetics. We examine just one of the many genes implicated in alcohol dependence. Current polygenetic theory allows us to go no further. Other candidate genes implicated in alcohol dependence may confer risk via different physiological mechanisms.

Genetic predisposition to alcohol dependence on GABRA2 is operative in men but not women. Given the same genetic inheritance and similar social circumstances, men are more likely to become dependent on alcohol. It is no secret that drinking, especially in public, is more acceptable for men than women in American society. This greater cultural tolerance sets up American men to engage in a pattern of behavior that leads to "alcohol dependence," especially for those at high genetic risk. As Bearman and Bruckner (2002: 1201) contend: "genetic expression for alcoholism is impossible in cultures without alcohol."

Findings also point to the interplay of social and genetic factors under the Trigger/Suppression option. Social experiences, both positive and negative, affect whether and how genotypes translate into behavioral phenotypes. Specifically, a history of deprivation during childhood may trigger the genetic tendency, reinforcing the power of stress theory and previous transdisciplinary findings (Caspi et al. 2003). And, as Durkheim (1951 [1897]) long ago theorized, the existence of a social safety net, in this case the perceived availability of family-based social support, counters the influence of negative genetic tendencies. Support from family, apparently even those that have a history of alcohol dependence, decrease the power of genetic predisposition and/or, perhaps "caseness" (recognition and identification as a medical problem).

Critically, the family, but *not* the friendship, network is at work in alcohol dependence. That is, greater support from family networks decrease problematic drinking behavior but the influence of friend support is equivocal. Family, friends and even co-workers are, according to White et al. (1991: 177), "powerful agents of social influence" regarding drinking because, "like other acquired human behaviors, [drinking] is learned and usually performed in a social context." Social networks provide motivation for drinking, prescribe when, why, where and how much to drink, and reinforce or punish certain drinking behaviors by example, attitude, and behavior (Martin 1990).

Taken together, our findings suggest central theoretical roles for network specificity (tie type or context), homophily, and a dynamics of social selection. Network structures can support drinking as entertainment and solution or discourage it as problematic or offensive. "Spillover effects" of drinking may result in problems in existing networks; and selection may determine whether or not individuals continue their drinking patterns or how some network ties can be reconfigured to 'fit' continued drinking. That is, a person who engages in significant drinking will likely face exclusion from non-drinking "chosen" networks (i.e., those outside the family's ascribed ties), and will seek out networks more in line with their own drinking preferences, even in the workplace (Kandel 1985; Trice 1965). The cultural context of the support structures, often ignored in network theory in favor of a simple focus on perceived numbers or levels, determines the impact of friendship on drinking, as Sutherland (1955) theorized long ago in the Theory of Differential Association regarding other behaviors defined as "deviant." Thus, if a network selection process that produces homophily operates for drinking, as recently documented for eating (Christakis and Fowler 2007), then the structure, content and dynamics of social ties together predispose individuals to drinking. Our equivocal findings for friendship networks suggest the power of content and dynamics of less ascribed ties. Without these variables, the effects of supportive networks may cancel each other out. While some friendship networks support, or even

demand sobriety, others may encourage social or even heavy drinking. Social network cultures and network dynamics become a central component of an integrative theory of alcohol use and abuse, indeed of *any* human behavior, and may be the most promising multi-level perspective to emerge to date.

In sum, our findings suggest a compelling mechanism underlying these gene-environment interactions. If the GABRA2 gene is expressed exclusively or more strongly in men, those who have experienced stressful life circumstances (childhood deprivation), and those who perceive no social safety net in the form of a supportive family, then those social circumstances likely encourage individuals to turn to alcohol as a coping mechanism ("escapist" or "instrumental drinking"; Martin, Blum, and Roman 1989). Indeed, perceptual and metabolic effects of alcohol consumption have been shown to alleviate the stress associated with negative life events and circumstances (Pearlin and Radabaugh 1976), with men more frequently using alcohol in this way than women (Nurnberger Jr. et al. 2004). Combined with a high risk genotype on GABRA2, more alcohol may be required to experience its stress-relieving effects. In turn, this low level of response to the anxiolytic properties of alcohol precipitates the development of heavier consumption and a clinical diagnosis of alcohol dependence (Pierucci-Lagha et al. 2005). Stress, and an absence of social support initiate coping behaviors (e.g., drinking), which set in motion a social process that becomes medically problematic in the face of a genetically inherited propensity to drink excessively. These issues are even more critical for genetic/medical research designed, not simply to understand disease, but to develop treatment strategies. If individuals diagnosed and treated for alcohol problems return to social networks in which drinking is a usual social activity, then “rehabilitation treatment” is not likely to “take.” In the end, cultural context may be more powerful than medical solutions (Glisson and Hemmelgarn 1998).

Further, while Dick and her colleagues (2006a) suggest that high levels of alcohol dependence among the never-married and divorced masks the relatively small effect of genotype, we suggest an alternative. We find that GABRA2 exerts influence among those *most likely* to be diagnosed with alcohol dependence. These interactions may not simply be an artifact of the weak influence of GABRA2. Rather, if correct, this epidemiological process represents a true blending of sociological and genetic causes: *Social conditions shape initial behavior, while genetic predisposition increases the likelihood that this behavior becomes habitual, maladaptive, and constructed as a disorder in contemporary society. Thus, social structure sets in motion a social process of coping, negatively spurred on by genetic predisposition and abetted by an absence of positive family network supports, resulting in a diagnosis of alcohol dependence*.

The Challenge to Sociological Theory in Pursuing Complex Pathways

We began by asking if and how the inclusion of genetics might change sociological theories. Our analyses suggest that the disease process is characterized by direct influence of genes and society complicated by interactions between physiological systems and the multiple levels at which social factors shape health outcomes, from culture and social systems to maladaptive behavior. Social factors operating at three different levels — individual stressors, dyadic and small group interaction, and social structural location — increase the

likelihood that drinking behavior triggers a physiological response. In short, while medical sociology's theories work as anticipated, our findings suggest that identifying causal pathways requires an examination of points of intersection between and among sociological and genetic mechanisms. This demands an integrative perspective that is dynamic, interdisciplinary, multi-level, and importantly, *intradisciplinary*.

The sociological theories examined here are not independent, nor have they ignored each other as they have developed over time. As Pearlin (1999: 397) indicates, the stress process is not unconnected to individuals' social and economic statuses. In fact, their consideration makes the stress process model "quintessentially sociological." Furthermore, its buffering hypothesis draws directly from the social support tradition (Pearlin and Aneshensel 1986). McLeod and Nonnemaker (1999) go further to suggest that the reason that status characteristics are linked to mental health is because they define important differences in stress exposure. Finally, resources, like social support, are not equally available to all individuals but are differentially distributed across groups in society (Lin 2000). In short, sociological theories themselves are nuanced and inter-connected. While we earlier noted the limitations in our own theoretical model and in the analytic strategy that the available data allow, the issue for sociological theory we raise goes far beyond this point.

Essentially, the sociological theories that we laid out differ on the issue of distal versus proximate causes that often overlap with levels of analysis. Emerging research suggests that social and biological factors interact at every level of analysis. The 'chain' metaphor and the distal/proximal distinction (Krieger 1990; Link and Phelan 1995) that dominated the decade-long debate surrounding risk factor epidemiology and fundamental social causes of disease may be counterproductive. Although certain social and individual causes of disease may be "fundamental" in that they persist in a dynamic system, researchers in any discipline have yet to identify a risk factor with a one-to-one relationship to health outcomes. The degree and even the direction of the impact of any one risk factor is inevitably contingent in part on social and biological conditions at different levels of analysis. Our findings suggest that a consideration of the interplay between social-structural and individual-level mechanisms is necessary to identify even one of many causal pathways to a particular disease or disorder.

Blending sociological theories would suggest, for example, that the influence of the GABRA2 gene would be even further amplified as men who experience high levels of stress also become socially isolated. While this approach requires attention to the ways in which sociological mechanisms attenuate or exacerbate one another, the task of identifying causal pathways becomes even more complex when physiological response levels are introduced. In the case of the pathway to alcohol dependence examined here, various social and genetic influences seem to converge at the point of individual behavior. We know, for example, that social structure and stressors can increase the likelihood of behavior that suppresses the immune system (i.e., smoking, drinking, and poor diet), increases exposure to pathogens (i.e., not seeking out social support), and determines the course and prognosis of disease and illness (i.e., healthcare utilization and compliance; Cohen and Williamson 1991). Conversely, genetic factors can influence partnering behavior, including one's tendency to become and remain married or to cohabit, which has important implications for the development of substance abuse and other mental illnesses (Dick et al. 2006a). Finally,

those who are available as research subjects in traditionally-designed, treatment-based medical studies, are already at the end of a social process influenced, in part, by biology and, in part, by social networks (Pescosolido, Brooks-Gardner, and Lubell 1998; McAlpine and Boyer 2007).[11]

As our results suggest, the identification of complex causal pathways requires a perspective that bridges multiple levels of analysis, as well as disciplinary traditions in theory and method. Individuals (and the total of their psychological and biological competencies, limitations, tendencies, and predispositions) are embedded in dynamic, social relationships which provide a basis for network structures, upon which communities, social institutions, and cultures are built (Lin and Peek 1999; Pescosolido 2006a). Moreover, because networks have recently been used to describe phenomena at virtually every level of analysis, from cellular to organizational, across disciplines as diverse as neurology and public health, they are broadly resonant (Pescosolido 2006a; Weiner 1998; Wellman and Frank 2001). Given that stress and social networks (or support) have been linked in countless studies to various heritable physical and mental health problems and health-related behaviors (Pescosolido and Levy 2002; Singer and Ryff 2001), pursuing a dynamic, network-structured approach to theory and modeling of sequence pathways to illness and disease seems promising.

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[11]Biomedicine's general reliance on non-representative, clinical samples poses a major problem in the ability to understand the dynamic pathways to illness, treatment, and to ultimate outcome. To be sure, genetic epidemiologists like Collins (Collins et al. 2003) have been aware of these difficulties.

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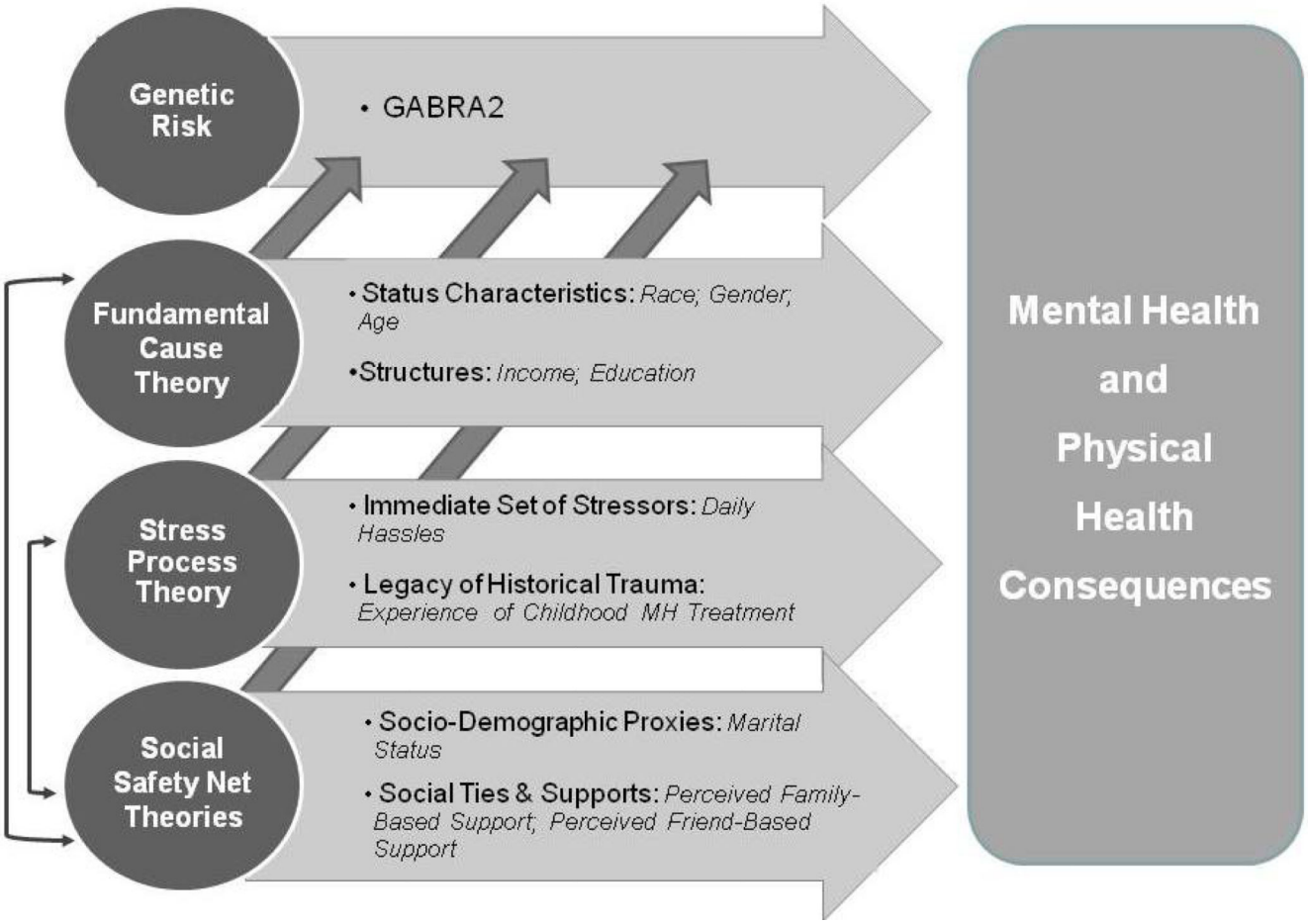

Figure 1.
Socio-Genetic Model (Simplified)

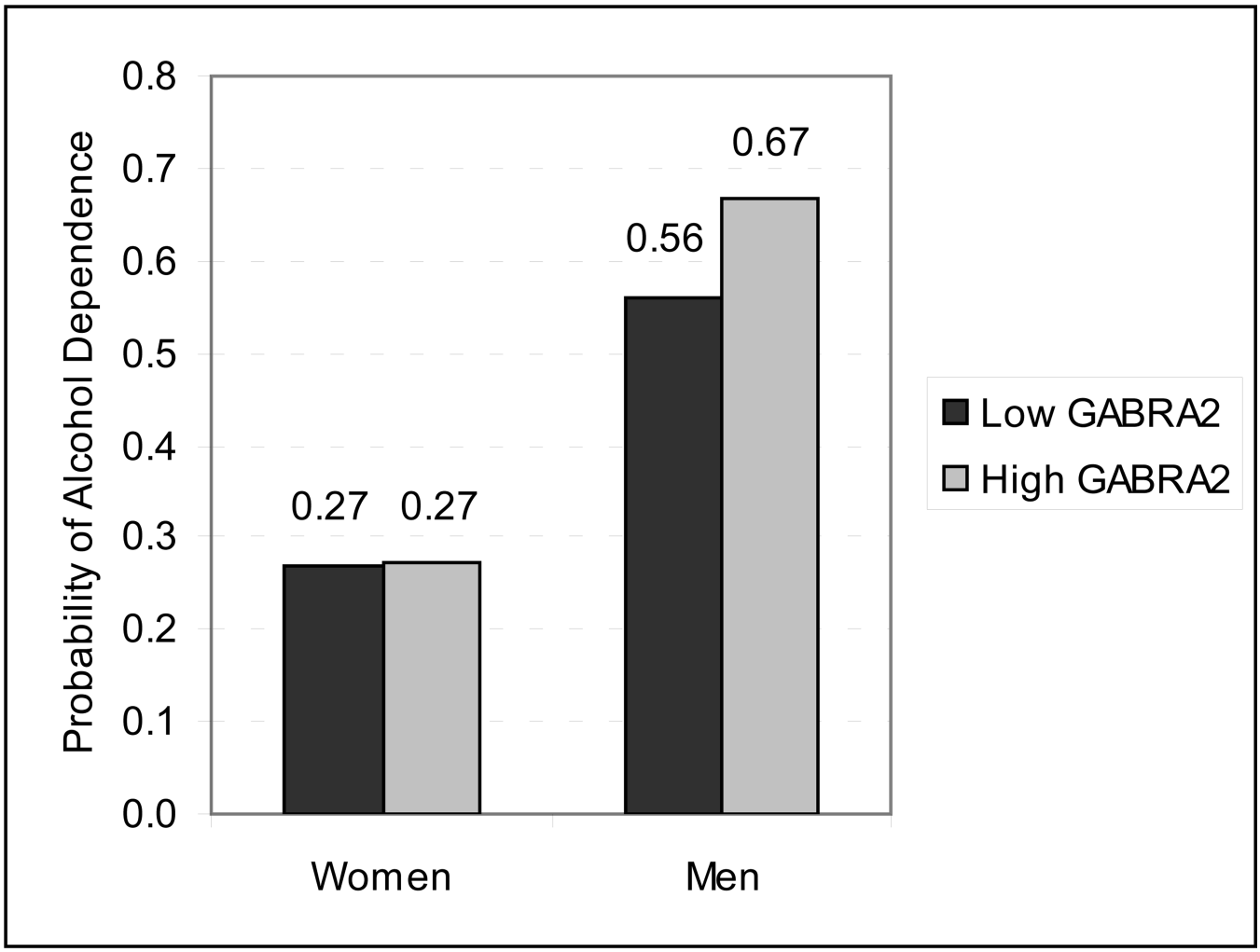

Figure 2.
Predicted Probabilities for Alcohol Dependence by Gender and Genetic Risk, COGA Study (N= 2,516).

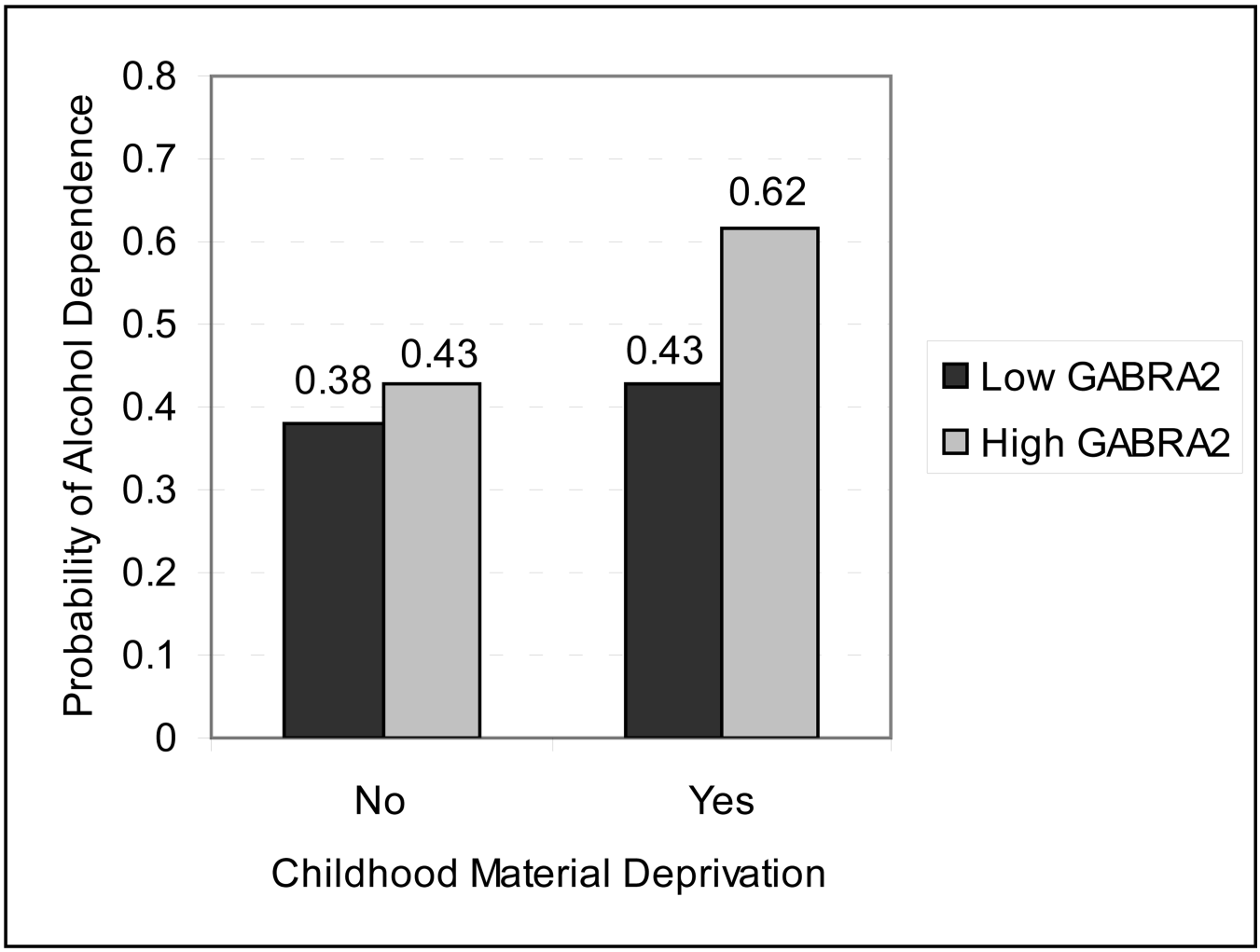

Figure 3.
Predicted Probabilities for Alcohol Dependence by Childhood Material Deprivation and Genetic Risk, COGA Study (N= 2,516).

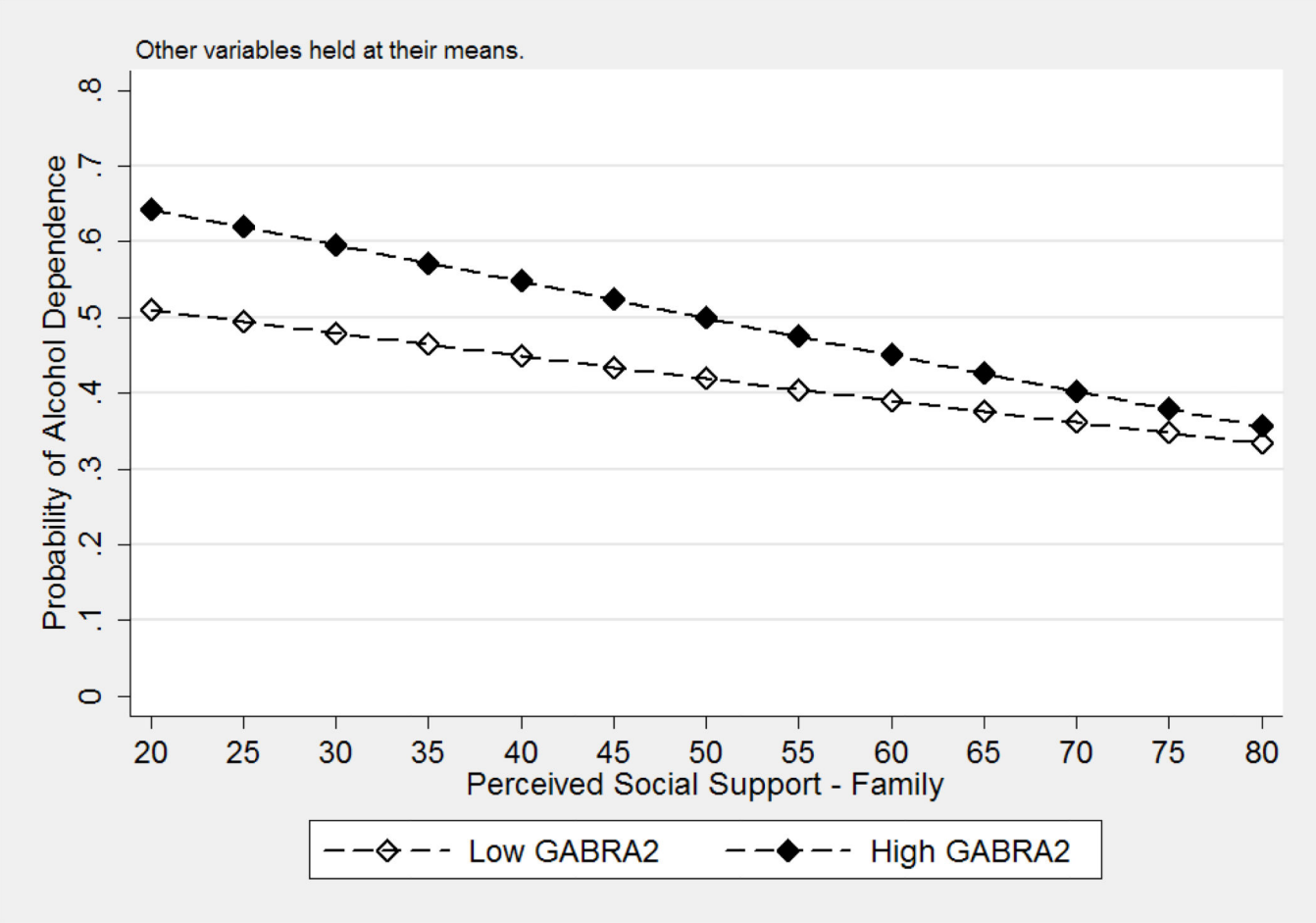

Figure 4.
Predicted Probabilities of Alcohol Dependence by Perceived Family Support – GABRA2 Interaction, COGA Study (N=2, 516).

Table 1

Means, Standard Deviations, and Ranges on Study Variables, COGA Study (N=2,516)

	Mean	Sth.Dev.	Range
Dependent Variable			
Alcohol Dependence (1=Dependent; 0=not)	0.35	0.48	
Independent Variables			
Genetic Risk on GABRA2 (1=at risk; 0=not at risk)	0.34	0.47	
Gender (1=female; 0=male)	0.56	0.50	
Race (1=black; 0=non-black)	0.11	0.31	
Marital Status (1=currently married; 0=not)	0.54	0.50	
Age in years	40.30	14.60	18–84
Education in years	13.46	2.33	4–17
Household income (in $10,000s)	5.11	4.04	0.05–17.50
Childhood Deprivation (1=yes; 0=no)	0.07	0.26	
Daily ‘Hassles’ (low to high)	35.17	20.30	0–120
Social Support-Family (low to high)	61.77	13.01	20–80
Social Support-Friends	60.03	11.12	20–80

Table 2

Population-Average Logistic Regression Models for the Effects of Genotype, Fundamental Causes, the Stress Process, and Social Safety Net Theories on Alcohol Dependence, COGA Study (N=2,516).

	Model 1 OR	Model 2 OR	Model 3 OR
Genotype			
High risk on GABRA2	1.26** (2.55)	—	1.27* (2.41)
Fundamental causes			
Female	—	0.25*** (−14.44)	0.25*** (−14.43)
Black	—	0.53*** (−3.36)	0.51*** (−3.58)
Age	—	1.18*** (8.39)	1.18*** (8.39)
Age-squared	—	0.998*** (−8.30)	0.998*** (−8.30)
Education[2]			
High school	—	0.60*** (−3.38)	0.60*** (−3.40)
Less than college	—	0.65** (−2.94)	0.64** (−3.01)
College degree or more	—	0.36*** (−6.36)	0.36*** (−6.36)
Log of household income (in tens of thousands)	—	0.89** (−3.07)	0.89** (−2.96)
Stress Process			
Square root of daily hassles	—	1.16*** (5.49)	1.16*** (5.40)
Childhood deprivation	—	1.48* (2.25)	1.49* (2.26)
Social Support			
Married	—	0.61*** (−4.42)	0.61*** (−4.44)
Social Support – Family	—	0.99*** (−3.62)	0.99*** (−3.67)
Social Support – Friends	—	1.00 (0.90)	1.00 (0.91)
Test that all effects are 0:			
X^2	6.49	375.89	378.99
df	1	13	14
p	0.00	0.00	0.00

[1] Table presents odds ratios; z-values in parentheses

[2] Comparison group is “Less than high school”