REVIEW

Translational Epidemiology in Psychiatry

Linking Population to Clinical and Basic Sciences

Myrna M. Weissman, PhD; Alan S. Brown, MD, MPH; Ardesheer Talati, PhD

Translational research generally refers to the application of knowledge generated by advances in basic sciences research translated into new approaches for diagnosis, prevention, and treatment of disease. This direction is called *bench-to-bedside*. Psychiatry has similarly emphasized the basic sciences as the starting point of translational research. This article introduces the term *translational epidemiology* for psychiatry research as a bidirectional concept in which the knowledge generated from the bedside or the population can also be translated to the benches of laboratory science. Epidemiologic studies are primarily observational but can generate representative samples, novel designs, and hypotheses that can be translated into more tractable experimental approaches in the clinical and basic sciences. This bedside-to-bench concept has not been explicated in psychiatry, although there are an increasing number of examples in the research literature. This article describes selected epidemiologic designs, providing examples and opportunities for translational research from community surveys and prospective, birth cohort, and family-based designs. Rapid developments in informatics, emphases on large sample collection for genetic and biomarker studies, and interest in personalized medicine—which requires information on relative and absolute risk factors—make this topic timely. The approach described has implications for providing fresh metaphors to communicate complex issues in interdisciplinary collaborations and for training in epidemiology and other sciences in psychiatry.

Arch Gen Psychiatry. 2011;68(6):600-608

Translational research generally refers to the application of knowledge generated by advances in basic sciences research translated into new approaches for prevention, diagnosis, and treatment of disease, followed by the introduction of innovations into clinical practice and health policy.[1] This direction is called *bench-to-bedside*. Translational research has received increasing priority in recent years, by means of the National Institutes of Health's Road Map Plan,[2] newly launched scientific journals (eg, http://www.sciencetranslationalmedicine.org), new career programs,[3] and the Clinical and Translational Science Award program. This emphasis is not just within the United States: the British Medical Research Council in 2007 established 6 new translational medicine centers, one of which is devoted to translational epidemiology, and translational research has served as a centerpiece of the European Commission health budget.[1]

Psychiatry has similarly emphasized the basic sciences as the starting point of translational research. Wang et al,[4] in an explicit application of translation research to psychiatry, applied the Institute of Medicine's recommendations for translational research[5] to schizophrenia and other psychotic disorders. They describe the application of 2 translational blocks. The first block, called *T1*, translates discoveries from the basic sciences into new diagnostic and preventive interventions, including early identification of high-risk individuals and

Author Affiliations: Department of Psychiatry, Columbia University College of Physicians and Surgeons (Drs Weissman, Brown, and Talati); Division of Epidemiology, New York State Psychiatric Institute (Drs Weissman, Brown, and Talati); and Department of Epidemiology, Mailman School of Public Health, Columbia University (Drs Weissman and Brown).

new methods for testing interventions. In the second block, called *T2*, resulting clinical developments are received in clinical practice in comparative effectiveness studies, bridging the gap between diagnosis and actual treatment, providing health education, and changing prescribing practices. Within this bench-to-bedside framework, Wang et al argue, clinical epidemiology has played an important role in the design of clinical trials, prevention, health education, and service delivery.

The purpose of this article is to expand the term *translational epidemiology* into psychiatric research as a bidirectional concept in which the *bedside,* ie, the population, can also be translated into the *benches* of laboratory science. This approach uses epidemiologic designs and findings to facilitate or to partner with basic science research. We will apply this concept of translational epidemiology to psychiatry and demonstrate that the representative samples, novel designs, and hypotheses offered by epidemiology can be translated into more tractable experimental approaches in the clinical and basic sciences.[6,7] Because the validity, interpretation, and generalizability of findings vary by design, we provide a brief overview of core epidemiologic designs and provide illustrations of translational applications with each design. The discussion of design is not intended as a substitute for an exhaustive review of epidemiologic design, for which we direct the reader to one of many excellent textbooks.[8-10] We also do not intend to appropriate bedside-to-bench as a novel direction. There are a number of classic examples in medicine, such as the epidemiologic observation of the relationship between smoking and lung cancer, which led to animal studies demonstrating the carcinogenic effect of nicotine and other cigarette toxins.[11]

This approach does not contradict the literature on bench-to-bedside translation; rather, it is complementary and iterative. The use of epidemiology in bedside-to-bench translational research in psychiatry has not been fully explicated, even though a number of studies appearing in the psychiatric literature have indirectly used epidemiologic designs.[12,13] It is useful to make this idea explicit because epidemiology can provide hypotheses, designs, and samples for basic research, and the failure to avail oneself of these resources can lead to lost opportunities. Furthermore, different epidemiologic designs answer different questions, and inappropriate designs or inferences, particularly generalization of findings across designs, can confound results.

COMMUNITY SURVEYS

The goal of obtaining community-based epidemiologic rates of psychiatric disorder in the United States has been achieved during the past 30 years. The Epidemiologic Catchment Area, launched in the 1980s with a probability sample of 18 000 adults living in 5 cities in the United States, was the first to use structured diagnostic assessments and clinical diagnostic criteria.[14] A series of epidemiologic studies in the United States, begun in the 1990s, included national samples.[15] These studies were followed by more focused surveys targeting African Americans, Latinos, and Asians[16-18] and a worldwide study (in 27 countries).[19] The largest US epidemiologic survey ever conducted, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), involved more than 45 000 persons and added detailed assessments on substance use.[20] Similar but less extensive efforts have been undertaken on the epidemiology of child and adolescent psychiatric disorders.[21] Information from these studies on rates and their variation by sex, age, racial and ethnic groups, and geographic location, as well as age at onset and comorbidity, have provided an empirical foundation for much research.

There are at least 3 ways in which community surveys can assist translational research[1]: by direct incorporation of blood or saliva samples for collection of DNA or, increasingly, for biomarkers such as cortisol or C-reactive proteins[22]; by providing samples for future case-control studies[2]; and by hypothesis generation.[3] These ways are explored in the following sections.

Genetic Studies

In terms of DNA sample collection, general population surveys have been underused in the United States, and their utility for the generation of large, ethnically varied samples has been unrealized. These samples could be important for use as cases or controls in genome-wide association studies, which require DNA from large, well-characterized samples. Currently, the National Institute of Mental Health stores a valuable resource consisting of more than 4000 control samples with DNA in a repository (http://www.nimhgenetics.org).[23] These samples are population representative but not population based, and diagnoses were generated by Internet-based self-report screening instruments. Any of the community samples might have provided a large, directly interviewed sample. Furthermore, African American study participants were particularly difficult to recruit in the National Institute of Mental Health sample and required a separate recruitment strategy using Web-based advertisements.[23] The African Americans recruited in that study had an overrepresentation of educated participants relative to their representation in the general population. Recruitment for DNA samples from the community samples of African Americans[17,18] might have included comprehensive assessments, such as direct interviews and a more representative sample of African Americans.

Brief methods suitable for quickly collecting family history data in surveys have been developed and could be a valuable resource for defining or refining phenotypes.[24,25] For cases, requiring family history in a first-degree relative may make the phenotype more genetically robust and may minimize the likelihood of including spurious cases. For controls, it could be used to weed out study participants who may be asymptomatic at recruitment but who still have high familial rates of the disorder and may not be appropriate controls in genetic studies. The use of community samples in genetic studies may be increasing because some genetic studies are now including blood or saliva sample collection in population-based samples.[26] The community samples for biomarker studies have potential for translational studies, and applications are beginning to appear.[22,27]

The use of large community surveys for DNA or biomarker collections requires a number of ethical considerations.[28] If the material is not collected at the time of the survey and while covered by informed consent, the investigator may not be allowed to return to collect the material. Participants must be notified at the time of the original interview that they may be recontacted and have to give permission. If the participant agrees to provide DNA or other biomarkers, the potential uses of the sample, including deposit in a repository for use by accredited investigators, must be part of the consent procedure. These procedures are new and until recently have not been incorporated into surveys. There are also scientific considerations. A community sample is not a sample of healthy controls. As has been shown,[29] individuals with symptoms or disorders under study need to be segregated out for association and other studies—or they will confound the comparison. The specific disorders to allow among the controls need to be carefully considered.[30]

Selection of Samples for Case-Control Studies

Community surveys can be used to select samples for follow-up studies by identifying risk factors of interest. For instance, a sample of adolescents identified from community survey as being at high risk for adversity (on the basis of parental psychiatric history or other predefined risk factors) were followed up to determine the relationship between serotonin transporter gene promoter (5HTTLPR) genotype, cortisol levels, and onset of major depressive disorder.[31] The authors found that carriers of the short allele had higher levels of salivary cortisol and that the *ss* genotype and high cortisol levels together increased the likelihood of a subsequent episode of depression. In another example, a Netherlands population-based study (the Rotterdam Scan Study)[32,33] of dementia-free individuals (aged 60-90 years) was used to power one of the largest ($n > 500$) magnetic resonance imaging case-control studies to date. The purpose of that study was to examine the role of macrostructural white matter changes in cognitive decline. The epidemiologic source population allowed the recruitment of participants in the desired age range who were free of dementia at the time but who had varying levels of cognition. By scanning the subjects at baseline and then approximately 5 and 10 years later, the researchers were able to show that a decrease in hippocampal volume predicted dementia, even after controlling for baseline hippocampal volume and other measures of executive function.[32]

Hypothesis Generation

There are numerous examples of hypotheses generated from epidemiologic surveys that have informed basic research. Using schizophrenia as a prototype example, a number of animal and neuroscience studies have been spawned by the epidemiologic observation of risk factors, such as maternal prenatal infection, prenatal famine, and parental age.[7]

Paternal age, in particular, has been one of the most robustly observed risk factors in current epidemiology, with a number of independent community and cohort studies from different parts of the world (eg, Canada, Greece, Israel, Sweden, the United Kingdom, and the United States) showing advanced paternal age to increase the risk for offspring schizophrenia and autism,[34] as well as impaired neurocognition in infancy and childhood.[35] Although precise mechanisms remain unknown, these observations led to postulation of a genetic model based on increased risk for de novo germline mutations and methylation changes among men, compared with the corresponding risk for women, as they age.[36] These observations have been translated to animal models: mice sired by aging males have now been shown to display increased anxiety-related behaviors and decreased learned helplessness, as well as thinner cortical volumes at birth.[37] At the human counterpart, a recent family study reported that the risk for schizophrenia substantially increased among sister-pairs with advancing paternal age,[38] suggesting a mechanism possibly involving paternally expressed genes on the X chromosome. This can now lead to a new round of animal models and genetic studies.

PROSPECTIVE COHORT STUDIES

Prospective cohort studies (also referred to as *longitudinal studies*) follow a defined population over time. Birth cohort studies are typically prospective cohort studies, but we discuss them separately because of their unique potential contribution to translational work. Prospective cohorts can examine developmental trajectories and risk factors that give rise to illness and early phenomenologic predictors of later psychiatric outcomes. Prospective cohort studies involve initial selection of a cohort from the population, which is then followed up over time to determine whether end points of interest (eg, incidence of a disorder or change in a particular score) vary across subgroups. Because the assessments are conducted prospectively over time, these studies reduce biases stemming from retrospective recall. The sequential assessment allows for separation of risk factors (which must precede the outcome of interest) from other factors that may be concurrent with or may arise from the disorder, thereby improving the capacity to identify causal risk factors that can then be tested in basic science studies.

The Dunedin Multidisciplinary Health and Development Study[39] from New Zealand provides an excellent illustration. In this study, a representative cohort of more than 1000 children was recruited at age 3 years and followed up approximately every 2 years until age 32, with low attrition rates. The cohort was assessed on common medical and psychiatric disorders, as well as childhood environmental exposures related to parenting, maltreatment, and early stresses. Because of the repeated assessments, the investigators were able to follow both stressors and health outcomes, including psychiatric symptoms and disorders, as they emerged. Among the best-known findings from this cohort is that a polymorphism within the promoter region of the serotonin transporter (5HTTLPR) moderated the effects of early life stress on subsequent depression.[39] The longitudinal design and systematic assessment of stress enabled the investigators to hone in on the interaction with the serotonin trans-

porter. Intriguingly, smaller prospective studies that followed have replicated the original findings with greater fidelity than much larger cross-sectional studies. Although a meta-analysis including many of these examples found no overall interaction effect,[40,41] the meta-analysis focused on genetic measures while not fully taking into account variability in the epidemiologic designs. As a result, prospective and retrospective studies were grouped together in the analysis, along with varying measures of stress.

Regardless of the meta-analysis, the original findings from the Dunedin study were based on observational epidemiology and required translation in the laboratory. Studies that followed have targeted biological pathways underlying the serotonin transporter polymorphism by stress, as well as other gene × environmental interactive effects.[42] For example, rhesus monkeys subjected to deleterious early maternal rearing were shown to have different cerebrospinal fluid concentrations of serotonergic metabolites that were moderated by 5HTTLPR genotype.[43] At the human level, imaging genetics has tethered neural circuitry to the genetic study of the serotonin transporter. Reports of direct effects of 5HTTLPR genotype on amygdala activation[44,45] and negative emotionality[46] were followed by studies showing that the genotype moderated cortical connectivity (between the amygdala and the executive cortex),[47] suggesting a model by which gene variation can influence behavioral regulation and ultimately psychiatric outcomes.

Similar translational approaches have been applied to study the gateway hypothesis of substance use. Epidemiologic studies had noted a sequence of illicit drug use beginning with experimentation with alcohol and tobacco in adolescence and progressing to heroin and/or cocaine abuse.[48,49] A 30-year prospective population study showed that the teenage rather than adult initiation of marijuana was the "gateway" (ie, predictor) of more dangerous or addictive drugs.[50] The epidemiologic findings on the timing of initiation of marijuana use are now being translated into numerous laboratory studies. Exposure to cannabis in adolescence has been found to have an enduring effect on hedonic processing in the rat and a corresponding enduring increase in opiate intake.[51] The authors speculate that this may be mediated by means of alterations in opioid neurons in limbic regions. The gateway hypothesis is now also being tested at the molecular level[52] using a mouse model of long-term memory that is based on evidence that chronic exposure to nicotine enhances long-term potentiation selectively in the amygdala but not in other regions.[53] These investigators have capitalized on gene-chip analysis to examine messenger RNA in the striatum and to examine signal transduction pathways that could mediate the way that early exposure to nicotine might prime the mouse to subsequent cocaine use.

Birth Cohort Studies

Birth cohort studies are a subset of prospective cohort studies and have only recently come to be fully appreciated in psychiatry. A birth cohort is a population of individuals born in a defined time and place but studied first in utero or at the time of birth.[8] The goal is to examine whether risk factors from birth and/or during pregnancy predict the occurrence of later disease outcomes. Birth cohort studies can be either prospective or retrospective. In a prospective birth cohort study, participants are ascertained from the time of birth or during pregnancy. Exposure and demographic data are obtained during this period and often at later times as well. In certain studies, biological specimens (eg, biomarkers of infections and immune activation, including cytokines) can be collected for concurrent analysis of risk exposures. These specimens may be stored for later assays. The individuals are then followed up at various points in the life course for outcomes of interest. In a retrospective design, information on the exposures, the outcomes, or both, are obtained either on the basis of previously collected data that were not obtained specifically for the intention of a risk factor study or by anamnestic report. The following discussion focuses on prospective birth cohort studies.

Birth cohort studies offer the potential to prospectively identify risk factors of interest from as early as conception (if based on recruitment of women before they become pregnant) until onset of the outcome. Unique questions in developmental biology, such as the effects of exposures during critical periods of development on outcomes from as early as infancy to as late as death, and the elaboration of developmental trajectories can be addressed.[54] Such studies feature a population in which the circumstances of time and place of birth are constrained but offer the additional advantage that the initial selection of subjects is not predicated on characteristics of the offspring that are identified after birth. If the recruitment strategy is based on a population, which is the case in most birth cohort studies, such cohorts are representative of the source population from which they were derived, thereby increasing generalizability and mitigating the effects of ascertainment bias.

Some of the most prolific birth cohort studies include the Medical Research Council National Survey of Health and Development (also known as the British 1946 birth cohort),[55] the Northern Finland Birth Cohort Study,[56] the Copenhagen Perinatal Cohort,[57] the California Child Health and Development Study,[58] and the National Collaborative Perinatal Project.[59] Several new initiatives have been launched toward improving on the limitations of earlier birth cohort studies, including data collection for molecular genetic studies and of other biological measures in offspring and parents. These include the Mother and Child Cohort Study in Norway,[60] the Danish National Birth Cohort,[61] and the National Children's Study[62] in the United States. The Finnish Prenatal Studies (FIPS) is the most recent of the birth cohort studies to be initiated with respect to follow-up for psychiatric disorders. The advantage of many birth cohort studies outside the United States is the ability to follow up patients and their offspring over time through medical record linkage or repositories and to follow outcomes related to prenatal exposures or other early life antecedents through long-term critical periods of brain development.

One important finding to emerge from birth cohort studies of psychiatric disorders is the demonstration that in utero exposure to infectious microbes and excessive

activation of the immune response are associated with an increased risk of schizophrenia.[63-65] Studies that were derived from the Child Health and Development Study and National Collaborative Perinatal Project cohorts have yielded some of the more prominent findings in this area of work, in that biomarkers of infection in prospectively collected archived maternal serum samples were tested for these exposures by assay for specific antibodies. As reviewed by Patterson,[66] this work provided a major impetus for translational research on animal models of schizophrenia that involved maternal immune activation of pregnant rodents and experimental paradigms conducted on offspring. These studies have demonstrated that maternal immune activation results in behavioral and brain phenotypes in animals that resemble those observed in neuroimaging and postmortem studies of patients with schizophrenia.[66,67] In one type of maternal immune activation model, pregnant rodents are administered polyinosinic:polycytidylic acid, which stimulates the secretion of proinflammatory cytokines. Rodent offspring of dams exposed to maternal immune activation during pregnancy evidence behavioral abnormalities analogous to those observed in schizophrenia, including excessive responses to dopaminergic and glutamatergic stimulation, social and working memory deficits, and electrophysiologic abnormalities, including disturbances of prepulse inhibition. Extensive translational work suggests that interleukin 6, a cytokine, plays a significant role in these deficits.[68]

FAMILY STUDIES

In a family study, well-characterized probands (index cases) and matched controls are identified. Usually, the biological first-degree relatives are also assessed, either directly or by history from relatives. For greatest validity, assessors of family members should be blind to the clinical status of the index case or controls. For relatives who refuse to participate or are unreachable, family history from multiple relatives, which can then be integrated to derive a consensus diagnosis, can approximate a direct interview.[69]

Family studies were popular in psychiatry in the 1980s and 1990s but became less so in the past decade as attention turned to direct molecular genetic studies.[70-72] Increasing evidence demonstrating high familial loading and specificity of diagnosis for schizophrenia, depression, alcoholism, and anxiety disorders[69] has now provided an empirical basis for use of family designs in genetic and imaging studies.[73] Information on transmission, comorbidity spectrum, subgroups (eg, early-onset recurrent depressions as a possible subtype[74]), and early risk factors of later disease (eg, prepubertal anxiety predicting later depression[75]) can also be gleaned from family designs.

High-Risk Designs

High-risk studies (ie, studies identifying offspring at increased risk for a disorder, usually by virtue of the presence of the same disorder in one or more parents) allow follow-up to begin in the high-risk offspring before the onset of symptoms and therefore identify risk factors that are premorbid to, rather than concomitant with, the disorder or a particular manifestation of it.[76,77] High-risk designs can reduce the sample size necessary to yield sufficient incidence rates for meaningful analysis and are particularly apt for rare disorders. Because they are populated with non-ill but at-risk individuals, the high-risk design is well-suited for discovering endophenotypes (ie, heritable phenotypes associated with the diseases but that can be measured independently of the disease state).

High-risk designs have been extensively used in studies of depression, anxiety, and schizophrenia. The Edinburgh High Risk Study is an excellent such example. The study initially recruited non-ill individuals who had a family history of schizophrenia (to ensure a robust phenotype, they required the proband to have ≥2 relatives with the full disorder) who were then followed up over time, comparing those who remained symptom-free with those who developed symptoms. With the progressive incorporation of measures of brain structure, function, and cognition, a number of provocative reports attributing structural and functional brain differences to the onset of the disorder have emerged,[78-80] and addition of genetic markers has further revealed gene × circuitry interactions (eg, D-amino acid oxidase activator gene moderating hippocampal function in subjects at high risk for schizophrenia[81]).

Another example is a 3-generation cohort at high and low risk for depression.[82,83] This cohort includes probands with or without a lifetime history of major depression and their biological children and later grandchildren, who were characterized and followed up blindly for 20 years. Some of the major findings of the study were that depression was transmitted across the generations, that there was a similarity of the age-at-onset pattern across generations—with anxiety disorders beginning before puberty and mood disorders emerging at puberty, especially in girls, and that high-risk individuals were beginning to report an increase in cardiovascular disorders as they entered their sixth decade of life.[82] Subjects from families with 2 generations previously affected were at greatest risk.[83] At the 20-year follow-up, magnetic resonance imaging measures were added to examine whether abnormalities in brain structure or function contributed to the familial transmission of depression. A robust association of familial risk for major depressive disorder with asymmetries in cortical thickness, including a 30% reduction in thickness observed in the lateral parietal, temporal, and frontal cortices of the right hemisphere of the high-risk group, was found.[84] These magnetic resonance imaging findings were consistent with earlier electroencephalographic results that also demonstrated reduced activity over the posterior cortices of the right cerebral hemisphere.[85,86] Both the magnetic resonance imaging and electroencephalographic findings were present in high-risk individuals who never had major depressive disorder in their lifetimes, suggesting that these abnormalities could not be simply a consequence of previously having been depressed or treated for depression. Thinning of the cortical mantle and reduced electrophysiologic activity in the right hemisphere may constitute related endophenotypes for familial vulnerability to developing major depressive disorder.

The take-home message is that, in each of the examples just mentioned, these observations would not have been detectable without the use of the family high-risk design that permitted the identification of individuals who were not ill initially but at high risk for the outcomes being studied. Conversely, only neuroscience methods are equipped to directly target underlying brain circuits and to address the neurobiological pathways by which genetic abnormalities lead to psychiatric phenotypes.[87]

Twin Designs

Disorders that are highly familial are likely genetic, but nongenetic risks can also run in families. Twin studies allow partitioning of genetic and environmental variances. The Virginia Twin Study of Adolescent Behavioral Development,[88-90] a large longitudinally followed epidemiologic cohort, has been instrumental in partitioning the unique and shared genetic and environmental influences not only for major psychiatric disorders but also for personality and behavioral traits. A number of studies have tethered the twin design to molecular and imaging studies. In a landmark 1990 study,[91] 15 sets of monozygotic twins, in which one twin had schizophrenia but the other did not, were imaged. Differences in cerebrospinal fluid, smaller hippocampal volume, and larger ventricular volume were found among affected twins compared with those of unaffected twins. Further follow-up revealed that the hippocampal differences were related to differences in verbal memory that differentiated the case from the noncase twin.[92] More recent studies have used the discordant twin design to report schizophrenia-attributable differences in dopamine D1 receptor binding,[93] working memory,[94] verbal recall and recognition,[95] and electroencephalographic alpha synchrony.[96]

CONCLUSIONS

We have provided examples of how results from various epidemiologic designs can be translated into a wide range of bench science, including molecular genetics, neuroimaging, electrophysiology, neurocognition, and animal models. These examples have used epidemiologic findings to draw hypotheses (eg, mouse models to test the gateway hypothesis of substance use) and, in some cases (eg, the Netherlands scan study), have directly used the epidemiologic source populations. Many more such opportunities exist and should be leveraged.

Translational epidemiology, as discussed herein, comes at an opportune time. First, recent findings from the genome-wide association studies of complex psychiatric disorders have found only small percentages of variance to be accounted for by individual genes, underscoring the need to search for additional environmental factors and their interactions with the underlying genetic architecture.[97-99] Epidemiologic studies can identify environmental risks that take into account broadly defined exposures in representative populations (eg, paternal age and malnutrition during gestation for schizophrenia). Recent advances have led to much interest in using genetics and other biomarkers for personalized medicine. However, predicting individual response to treatment requires detailed epidemiologic information on known risk markers in the individual, as well as relative and absolute disease rates in the population.[100-102] Finally, the introduction of computerized medical records in the United States, coupled with rapid developments in informatics, could open a wealth of epidemiologic data on variations in patient risk, therapeutic response, and emerging disease. Epidemiologic data from such national registries—already well established in several countries outside the United States—can provide powerful data on environmental risks and on long-term patient outcomes. Protections for privacy of medical information, the lack of centralized and coordinated health care, the use of fully informed consent regarding future follow-up, and intended future use of acquired samples need to be addressed.

Each of the epidemiologic designs reviewed also has limitations, which are well described in standard epidemiologic textbooks. Some potential pitfalls include attrition, confounding, and geographic dispersion, which can complicate the acquisition of biomarkers. In studies spanning long periods, changes in technology, diagnostic classifications, and even society (eg, changes in smoking) can contribute to methodological problems. Moreover, different designs answer different questions, and generalization of results between designs may not be possible. Therefore, an understanding of the advantages and limitations of each design is important.

We recommend shifts in training approaches to facilitate the translational research described. Epidemiologic training in psychiatry, which has heavily emphasized environmental risks and the social sciences, might include training in the methods of clinical and basic neuroscience and molecular genetics. Training in novel methods for determining modifiable exposures, such as mendelian randomization, will offer new opportunities for using observational studies to examine causal effects of modifiable risk factors by measuring genetic variants of known functional effects.[103,104] Likewise, graduate students in the neurosciences and genetics should receive exposure to epidemiologic concepts and resources to help avoid design errors and to capitalize on available samples. Psychiatry could benefit in this regard from trends that are increasing in other biomedical disciplines.[105] For example, the University of Rochester has developed a new PhD training program that incorporates clinical science, public health, and basic biomedical research and is aimed to connect basic and social scientists (http://www.urmc.rochester.edu/ctsi/links). In another example, the Howard Hughes Medical Institute in 2006 initiated a new PhD program in translational medicine (http://www.hhmi.org/grants/institutions/medintograd.html). These approaches are not limited to training endeavors but can readily be incorporated into ongoing research. Reciprocal exposures by trainees in epidemiology and those in the neurosciences can begin to offer the potential for a plethora of creative and novel research and a generation of fresh metaphors to communicate complex issues that will benefit the neurosciences, epidemiology, and psychiatry.

Submitted for Publication: May 5, 2010; final revision received December 13, 2010; accepted December 15, 2010.

Correspondence: Myrna M. Weissman, PhD, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, 1051 Riverside Drive-Unit 24, New York, NY 10032 (mmw3@columbia.edu).

Author Contributions: *Study concept and design:* Weissman, Brown, and Talati. *Acquisition of data:* Weissman. Analysis and interpretation of data: Weissman. *Drafting of the manuscript:* Weissman, Brown, and Talati. *Critical revision of the manuscript for important intellectual content:* Brown and Talati. *Obtained funding:* Weissman and Talati. *Administrative, technical, and material support:* Weissman and Brown. *Study supervision:* Weissman.

Financial Disclosure: In the past 2 years, Dr Weissman reports receiving funding from the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Sackler Institute for Developmental Psychobiology, the Templeton Foundation, and the Interstitial Cystitis Association. She receives royalties from the Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems. Dr Brown reports receiving funding from the NIMH, National Institute of Environmental Health Sciences, and NARSAD and reports receiving funding from Merck for speaking engagements.

Funding/Support: Dr Weissman was funded in part by grant R01 MH36197 from the NIMH, which includes a supplement from the NIDA; grant 1P50MH090966 from the NIMH Conte Center; a NARSAD Distinguished Investigator Award; and the Sackler Institute for Developmental Psychobiology. Dr Brown was funded by grants K02 MH065422-06 and R01 MH082052-01 from the NIMH and a NARSAD Independent Investigator Award. Dr Talati was funded by grant K01 DA029598-01 from the NIDA, a NARSAD Young Investigator Award, and the Research Foundation for Mental Hygiene, Inc.

REFERENCES

1. Woolf SH. The meaning of translational research and why it matters. *JAMA*. 2008;299(2):211-213.
2. Insel TR. Translating scientific opportunity into public health impact: a strategic plan for research on mental illness. *Arch Gen Psychiatry*. 2009;66(2):128-133.
3. Andrews N, Burris JE, Cech TR, Coller BS, Crowley WF Jr, Gallin EK, Kelner KL, Kirch DG, Leshner AI, Morris CD, Nguyen FT, Oates J, Sung NS. Translational careers [editorial]. *Science*. 2009;324(5929):855.
4. Wang PS, Heinssen R, Oliveri M, Wagner A, Goodman W. Bridging bench and practice: translational research for schizophrenia and other psychotic disorders. *Neuropsychopharmacology*. 2009;34(1):204-212.
5. Sung NS, Crowley WF Jr, Genel M, Salber P, Sandy L, Sherwood LM, Johnson SB, Catanese V, Tilson H, Getz K, Larson EL, Scheinberg D, Reece EA, Slavkin H, Dobs A, Grebb J, Martinez RA, Korn A, Rimoin D. Central challenges facing the national clinical research enterprise. *JAMA*. 2003;289(10):1278-1287.
6. Cannon TD. Candidate gene studies in the GWAS era: the MET proto-oncogene, neurocognition, and schizophrenia. *Am J Psychiatry*. 2010;167(4):369-372.
7. McGrath JJ, Richards LJ. Why schizophrenia epidemiology needs neurobiology—and vice versa. *Schizophr Bull*. 2009;35(3):577-581.
8. Rothman K, Greenland S, Lash TL. *Modern Epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
9. Schwartz S, Susser E. *Psychiatric Epidemiology: Searching for the Causes of Mental Disorders*. New York, NY: Oxford University Press; 2006.
10. Tsuang M, Tohen M. *A Textbook of Psychiatric Epidemiology*. New York, NY: Wiley-Liss; 2002.
11. Rutter M, Plomin R. Pathways from science findings to health benefits. *Psychol Med*. 2009;39(4):529-542.
12. Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ. Early life programming and neurodevelopmental disorders. *Biol Psychiatry*. 2010;68(4):314-319.
13. Sen S, Kranzler HR, Krystal JH, Speller H, Chan G, Gelernter J, Guille C. A prospective cohort study investigating factors associated with depression during medical internship. *Arch Gen Psychiatry*. 2010;67(6):557-565.
14. Robins L, Regier DA. *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. New York, NY: Free Press; 1991.
15. Kessler RC, Berglund P, Chiu WT, Demler O, Heeringa S, Hiripi E, Jin R, Pennell BE, Walters EE, Zaslavsky A, Zheng H. The US National Comorbidity Survey Replication (NCS-R): design and field procedures. *Int J Methods Psychiatr Res*. 2004;13(2):69-92.
16. Alegría M, Mulvaney-Day N, Torres M, Polo A, Cao Z, Canino G. Prevalence of psychiatric disorders across Latino subgroups in the United States. *Am J Public Health*. 2007;97(1):68-75.
17. Gavin AR, Walton E, Chae DH, Alegria M, Jackson JS, Takeuchi D. The associations between socio-economic status and major depressive disorder among blacks, Latinos, Asians and non-Hispanic whites: findings from the Collaborative Psychiatric Epidemiology Studies. *Psychol Med*. 2010;40(1):51-61.
18. Jackson JS, Torres M, Caldwell CH, Neighbors HW, Nesse RM, Taylor RJ, Trierweiler SJ, Williams DR. The National Survey of American Life: a study of racial, ethnic and cultural influences on mental disorders and mental health. *Int J Methods Psychiatr Res*. 2004;13(4):196-207.
19. Kessler RC. *The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders*. New York, NY: Cambridge University Press; 2008.
20. Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in *DSM-IV* alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend*. 2004;74(3):223-234.
21. Szatmari P. More than counting: milestones in child and adolescent psychiatric epidemiology. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):353-355.
22. Pasco JA, Nicholson GC, Williams LJ, Jacka FN, Henry MJ, Kotowicz MA, Schneider HG, Leonard BE, Berk M. Association of high-sensitivity C-reactive protein with de novo major depression. *Br J Psychiatry*. 2010;197:372-377.
23. Sanders AR, Levinson DF, Duan J, Dennis JM, Li R, Kendler KS, Rice JP, Shi J, Mowry BJ, Amin F, Silverman JM, Buccola NG, Byerley WF, Black DW, Freedman R, Cloninger CR, Gejman PV. The Internet-based MGS2 control sample: self report of mental illness. *Am J Psychiatry*. 2010;167(7):854-865.
24. Milne BJ, Caspi A, Harrington H, Poulton R, Rutter M, Moffitt TE. Predictive value of family history on severity of illness: the case for depression, anxiety, alcohol dependence, and drug dependence. *Arch Gen Psychiatry*. 2009;66(7):738-747.
25. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry*. 2000;57(7):675-682.
26. Terracciano A, Balaci L, Thayer J, Scally M, Kokinos S, Ferrucci L, Tanaka T, Zonderman AB, Sanna S, Olla N, Zuncheddu MA, Naitza S, Busonero F, Uda M, Schlessinger D, Abecasis GR, Costa PT Jr. Variants of the serotonin transporter gene and NEO-PI-R neuroticism: no association in the BLSA and SardiNIA samples. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(8):1070-1077.
27. Singh I, Rose N. Biomarkers in psychiatry. *Nature*. 2009;460(7252):202-207.
28. Lakhan SE, Vieira K, Hamlat E. Biomarkers in psychiatry: drawbacks and potential for misuse. *Int Arch Med*. 2010;3:1. doi:10.1186/1755-7682-3-1.
29. Talati A, Fyer AJ, Weissman MM. A comparison between screened NIMH and clinically interviewed control samples on neuroticism and extraversion. *Mol Psychiatry*. 2008;13(2):122-130.
30. Schwartz S, Susser E. Genome-wide association studies: does only size matter? *Am J Psychiatry*. 2010;167(7):741-744.
31. Goodyer IM, Bacon A, Ban M, Croudace T, Herbert J. Serotonin transporter genotype, morning cortisol and subsequent depression in adolescents. *Br J Psychiatry*. 2009;195(1):39-45.
32. den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP, Niessen WJ, Breteler MM. A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain*. 2010;133(pt 4):1163-1172.
33. Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, Niessen WJ, Van der Lugt A, Breteler MM. White matter microstructural integrity and cognitive function in a general elderly population. *Arch Gen Psychiatry*. 2009;66(5):545-553.
34. Miller B, Messias E, Miettunen J, Alaraisanen A, Jarvelin MR, Koponen H, Rasanen P, Isohanni M, Kirkpatrick B. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring [published online February 25, 2010]. *Schizophr Bull*.

35. Saha S, Barnett AG, Foldi C, Burne TH, Eyles DW, Buka SL, McGrath JJ. Advanced paternal age is associated with impaired neurocognitive outcomes during infancy and childhood. *PLoS Med*. 2009;6(3):e40. doi:10.1371/journal.pmed.1000040.
36. Malaspina D, Reichenberg A, Weiser M, Fennig S, Davidson M, Harlap S, Wolitzky R, Rabinowitz J, Susser E, Knobler HY. Paternal age and intelligence: implications for age-related genomic changes in male germ cells. *Psychiatr Genet*. 2005;15(2):117-125.
37. Foldi CJ, Eyles DW, McGrath JJ, Burne TH. Advanced paternal age is associated with alterations in discrete behavioural domains and cortical neuroanatomy of C57BL/6J mice. *Eur J Neurosci*. 2010;31(3):556-564.
38. Perrin M, Harlap S, Kleinhaus K, Lichtenberg P, Manor O, Draiman B, Fennig S, Malaspina D. Older paternal age strongly increases the morbidity for schizophrenia in sisters of affected females. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153(7):1329-1335.
39. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.
40. Munafò MR, Freimer NB, Ng W, Ophoff R, Veijola J, Miettunen J, Järvelin MR, Taanila A, Flint J. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150(2):271-281.
41. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis [published correction appears in *JAMA*. 2009;302(5):492]. *JAMA*. 2009;301(23):2462-2471.
42. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010;167(5):509-527.
43. Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, Champoux M, Suomi SJ, Linnoila MV, Higley JD. Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry*. 2002;7(1):118-122.
44. Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR. A susceptibility gene for affective disorders and the response of the human amygdala. *Arch Gen Psychiatry*. 2005;62(2):146-152.
45. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297(5580):400-403.
46. Holmes A, Hariri AR. The serotonin transporter gene-linked polymorphism and negative emotionality: placing single gene effects in the context of genetic background and environment. *Genes Brain Behav*. 2003;2(6):332-335.
47. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005;8(6):828-834.
48. Mackesy-Amiti ME, Fendrich M, Goldstein PJ. Sequence of drug use among serious drug users: typical vs atypical progression. *Drug Alcohol Depend*. 1997;45(3):185-196.
49. Tarter RE, Vanyukov M, Kirisci L, Reynolds M, Clark DB. Predictors of marijuana use in adolescents before and after licit drug use: examination of the gateway hypothesis. *Am J Psychiatry*. 2006;163(12):2134-2140.
50. Chen K, Kandel DB. The natural history of drug use from adolescence to the mid-thirties in a general population sample. *Am J Public Health*. 1995;85(1):41-47.
51. Ellgren M, Spano SM, Hurd YL. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. *Neuropsychopharmacology*. 2007;32(3):607-615.
52. Kandel D, Kandel ER, Levine A. A molecular analysis of the gateway hypothesis in mice. Project No. 5R01DA024001-02. September 2007–August 2012. National Institute on Drug Abuse. http://projectreporter.nih.gov/project_info_description.cfm?aid=7502028&icde=0. Accessed November 2008.
53. Huang YY, Kandel ER, Levine A. Chronic nicotine exposure induces a long-lasting and pathway-specific facilitation of LTP in the amygdala. *Learn Mem*. 2008;15(8):603-610.
54. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health*. 2003;57(10):778-783.
55. Wadsworth ME. *The Imprint of Time: Childhood, History, and Adult Life*. Oxford, England: Clarendon Press; 1991.
56. Rantakallio P. Groups at risk in low birth weight infants and perinatal mortality. *Acta Paediatr Scand*. 1969;193(suppl 193):1.
57. Zachau-Christiansen B, Ross EM. *Babies: Human Development During the First Year*. Bristol, England: JW Arrowsmith Ltd; 1975.
58. Van den Berg BJ. *The California Child Health and Development Studies: Handbook of Longitudinal Research*. New York, NY: Praeger; 1984.
59. Buka SL, Tsuang MT, Lipsitt LP. Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. *Arch Gen Psychiatry*. 1993;50(2):151-156.
60. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C; MoBa Study Group. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2006;35(5):1146-1150.
61. Olsen J, Melbye M, Olsen SF, Sørensen TI, Aaby P, Andersen AM, Taxbøl D, Hansen KD, Juhl M, Schow TB, Sørensen HT, Andresen J, Mortensen EL, Olesen AW, Søndergaard C. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health*. 2001;29(4):300-307.
62. Landrigan PJ, Trasande L, Thorpe LE, Gwynn C, Lioy PJ, D'Alton ME, Lipkind HS, Swanson J, Wadhwa PD, Clark EB, Rauh VA, Perera FP, Susser E. The National Children's Study: a 21-year prospective study of 100,000 American children. *Pediatrics*. 2006;118(5):2173-2186.
63. Brown AS. Prenatal infection as a risk factor for schizophrenia. *Schizophr Bull*. 2006;32(2):200-202.
64. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004;61(8):774-780.
65. Brown AS, Schaefer CA, Quesenberry CP Jr, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry*. 2005;162(4):767-773.
66. Patterson PH. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav Brain Res*. 2009;204(2):313-321.
67. Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophr Bull*. 2009;35(5):959-972.
68. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. *J Neurosci*. 2007;27(40):10695-10702.
69. Weissman MM, Merikangas KR, John K, Wickramaratne P, Prusoff BA, Kidd KK. Family-genetic studies of psychiatric disorders: developing technologies. *Arch Gen Psychiatry*. 1986;43(11):1104-1116.
70. Kendler KS, Gruenberg AM, Tsuang MT. Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients: a family study using *DSM-III* criteria. *Arch Gen Psychiatry*. 1985;42(8):770-779.
71. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *Br J Psychiatry*. 1980;137:497-504.
72. Weissman MM, Wickramaratne P, Merikangas KR, Leckman JF, Prusoff BA, Caruso KA, Kidd KK, Gammon GD. Onset of major depression in early adulthood: increased familial loading and specificity. *Arch Gen Psychiatry*. 1984;41(12):1136-1143.
73. Hopper JL. Commentary: case-control-family designs: a paradigm for future epidemiology research? *Int J Epidemiol*. 2003;32(1):48-50.
74. Levinson DF, Zubenko GS, Crowe RR, DePaulo RJ, Scheftner WS, Weissman MM, Holmans P, Zubenko WN, Boutelle S, Murphy-Eberenz K, MacKinnon D, McInnis MG, Marta DH, Adams P, Sassoon S, Knowles JA, Thomas J, Chellis J. Genetics of recurrent early-onset depression (GenRED): design and preliminary clinical characteristics of a repository sample for genetic linkage studies. *Am J Med Genet B Neuropsychiatr Genet*. 2003;119B(1):118-130.
75. Warner V, Wickramaratne P, Weissman MM. The role of fear and anxiety in the familial risk for major depression: a three-generation study. *Psychol Med*. 2008;38(11):1543-1556.
76. Hammen C, Burge D, Burney E, Adrian C. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. *Arch Gen Psychiatry*. 1990;47(12):1112-1117.
77. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen HU. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*. 2002;59(4):365-374.
78. Lawrie SM, McIntosh AM, Hall J, Owens DG, Johnstone EC. Brain structure and function changes during the development of schizophrenia: the evidence from studies of subjects at increased genetic risk. *Schizophr Bull*. 2008;34(2):330-340.
79. Whalley HC, Mowatt L, Stanfield AC, Hall J, Johnstone EC, Lawrie SM, McIntosh AM. Hypofrontality in subjects at high genetic risk of schizophrenia with depressive symptoms. *J Affect Disord*. 2008;109(1-2):99-106.
80. Whalley HC, Simonotto E, Marshall I, Owens DG, Goddard NH, Johnstone EC, Lawrie SM. Functional disconnectivity in subjects at high genetic risk of schizophrenia. *Brain*. 2005;128(pt 9):2097-2108.
81. Hall J, Whalley HC, Moorhead TW, Baig BJ, McIntosh AM, Job DE, Owens DG, Lawrie SM, Johnstone EC. Genetic variation in the DAOA (G72) gene modulates hippocampal function in subjects at high risk of schizophrenia. *Biol Psychiatry*. 2008;64(5):428-433.

82. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. Offspring of depressed parents: 20 years later. *Am J Psychiatry*. 2006; 163(6):1001-1008.
83. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdeli H, Pilowsky DJ, Grillon C, Bruder G. Families at high and low risk for depression: a 3-generation study. *Arch Gen Psychiatry*. 2005;62(1):29-36.
84. Peterson BS, Warner V, Bansal R, Zhu H, Hao X, Liu J, Durkin K, Adams PB, Wickramaratne P, Weissman MM. Cortical thinning in persons at increased familial risk for major depression. *Proc Natl Acad Sci U S A*. 2009;106(15): 6273-6278.
85. Bruder GE, Tenke CE, Warner V, Nomura Y, Grillon C, Hille J, Leite P, Weissman MM. Electroencephalographic measures of regional hemispheric activity in offspring at risk for depressive disorders. *Biol Psychiatry*. 2005;57(4): 328-335.
86. Bruder GE, Tenke CE, Warner V, Weissman MM. Grandchildren at high and low risk for depression differ in EEG measures of regional brain asymmetry. *Biol Psychiatry*. 2007;62(11):1317-1323.
87. Akil H, Brenner S, Kandel E, Kendler KS, King MC, Scolnick E, Watson JD, Zoghbi HY. Medicine: the future of psychiatric research: genomes and neural circuits. *Science*. 2010;327(5973):1580-1581.
88. Fanous A, Gardner CO, Prescott CA, Cancro R, Kendler KS. Neuroticism, major depression and gender: a population-based twin study. *Psychol Med*. 2002; 32(4):719-728.
89. Gillespie NA, Neale MC, Kendler KS. Pathways to cannabis abuse: a multistage model from cannabis availability, cannabis initiation and progression to abuse. *Addiction*. 2009;104(3):430-438.
90. Kendler KS, Gardner CO, Lichtenstein P. A developmental twin study of symptoms of anxiety and depression: evidence for genetic innovation and attenuation. *Psychol Med*. 2008;38(11):1567-1575.
91. Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med*. 1990;322(12):789-794.
92. Goldberg TE, Torrey EF, Berman KF, Weinberger DR. Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. *Psychiatry Res*. 1994; 55(1):51-61.
93. Hirvonen J, van Erp TG, Huttunen J, Aalto S, Någren K, Huttunen M, Lönnqvist J, Kaprio J, Cannon TD, Hietala J. Brain dopamine D_1 receptors in twins discordant for schizophrenia. *Am J Psychiatry*. 2006;163(10):1747-1753.
94. Karlsgodt KH, Glahn DC, van Erp TG, Therman S, Huttunen M, Manninen M, Kaprio J, Cohen MS, Lönnqvist J, Cannon TD. The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects. *Schizophr Res*. 2007;89(1-3): 191-197.
95. van Erp TG, Therman S, Pirkola T, Tuulio-Henriksson A, Glahn DC, Bachman P, Huttunen MO, Lönnqvist J, Hietanen M, Kaprio J, Koskenvuo M, Cannon TD. Verbal recall and recognition in twins discordant for schizophrenia. *Psychiatry Res*. 2008;159(3):271-280.
96. Bachman P, Kim J, Yee CM, Therman S, Manninen M, Lönnqvist J, Kaprio J, Huttunen MO, Näätänen R, Cannon TD. Abnormally high EEG alpha synchrony during working memory maintenance in twins discordant for schizophrenia. *Schizophr Res*. 2008;103(1-3):293-297.
97. Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol*. 2011;93(1):23-58.
98. Dermitzakis ET, Clark AG. Genetics: life after GWA studies. *Science*. 2009;326 (5950):239-240.
99. Goldman D. Gene × environment interactions in complex behavior: first, build a telescope. *Biol Psychiatry*. 2010;67(4):295-296.
100. Gaziano JM. The evolution of population science: advent of the mega cohort. *JAMA*. 2010;304(20):2288-2289.
101. Manolio TA, Collins R. Enhancing the feasibility of large cohort studies. *JAMA*. 2010;304(20):2290-2291.
102. Ng PC, Murray SS, Levy S, Venter JC. An agenda for personalized medicine. *Nature*. 2009;461(7265):724-726.
103. Qi L. Mendelian randomization in nutritional epidemiology. *Nutr Rev*. 2009;67 (8):439-450.
104. Smith GD. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol*. 2008;102(2):245-256.
105. Seminara D, Khoury MJ, O'Brien TR, Manolio T, Gwinn ML, Little J, Higgins JP, Bernstein JL, Boffetta P, Bondy M, Bray MS, Brenchley PE, Buffler PA, Casas JP, Chokkalingam AP, Danesh J, Davey Smith G, Dolan S, Duncan R, Gruis NA, Hashibe M, Hunter D, Jarvelin MR, Malmer B, Maraganore DM, Newton-Bishop JA, Riboli E, Salanti G, Taioli E, Timpson N, Uitterlinden AG, Vineis P, Wareham N, Winn DM, Zimmern R, Ioannidis JP; Human Genome Epidemiology Network; Network of Investigator Networks. The emergence of networks in human genome epidemiology: challenges and opportunities. *Epidemiology*. 2007;18(1):1-8.