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Transdisciplinary research strategies for understanding socially patterned disease: the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project as a case study

Estratégias transdisciplinares de pesquisa para entender uma doença social: o projeto Asthma Coalition on Community, Environment, and Social Stress (ACCESS) como estudo de caso

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Abstract ***As we have seen a global increase in asthma in the past three decades it has also become clear that it is a socially patterned disease, based on demographic and socioeconomic indicators clustered by areas of residence. This trend is not readily explained by traditional genetic paradigms or physical environmental exposures when considered alone. This has led to consideration of the interplay among physical and psychosocial environmental hazards and the molecular and genetic determinants of risk (i.e., biomedical framing) within the broader socioenvironmental context including socioeconomic position as an upstream "cause of the causes" (i.e., ecological framing). Transdisciplinary research strategies or programs that embrace this complexity through a shared conceptual framework that integrates diverse discipline-specific theories, models, measures, and analytical methods into ongoing asthma research may contribute most significantly toward furthering our understanding of socially patterned disease. This paper provides an overview of a multilevel, multimethod longitudinal study, the Asthma Coalition on Community, Environment and Social Stress (ACCESS), as a case study to exemplify both the opportunities and challenges of transdisciplinary research on urban asthma expression in the United States.***

Key words ***Asthma disparities, Transdisciplinary, Social epidemiology, Multilevel***

Resumo ***Com o aumento da asma observado em nível mundial nas últimas três décadas, também ficou claro que se trata de uma doença social, conforme evidenciado por indicadores demográficos e socioeconômicos agrupados por áreas residenciais. Esta tendência não pode ser explicada apenas por paradigmas genéticos tradicionais ou influência física do ambiente, quando considerados isoladamente. Por isso passou-se a considerar a interação entre riscos ambientais físicos e psicológicos e os determinantes de risco moleculares e genéticos (i.e. enquadramento biomédico) no âmbito de um contexto socioambiental mais amplo, incluindo a posição socioeconômica como "causa das causas" (i.e. enquadramento ecológico). Estratégias de pesquisa transdisciplinares ou programas que acolhem esta complexidade por meio de uma estrutura conceitual comum integrando teorias, modelos, medidas e métodos analíticos específicos das diversas disciplinas à pesquisa atual da asma podem representar contribuições particularmente significantes a uma melhor compreensão de uma doença social. Este artigo em forma de relato de caso pretende dar uma visão geral de um estudo longitudinal usando vários níveis e métodos - o Asthma Coalition on Community, Environment and Social Stress (ACCESS) -, para mostrar as oportunidades e desafios de um estudo transdisciplinar investigando a expressão urbana da asma nos Estados Unidos.***

Palavras-chave ***Disparidades na asma, Transdisciplinaridade, Epidemiologia social, Multinível***

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The global burden of asthma continues to rise. Recent data from the International Study of Asthma and Allergies in Childhood (ISAAC) finds an increased prevalence of asthma symptoms in Africa, Latin America and parts of Asia in particular[1]. In the United States (US), these trends disproportionately affect nonwhite children living in urban areas and children living in poverty [2]. While the preponderance of epidemiologic evidence suggests that asthma morbidity is inversely related to socioeconomic status (SES), the association is not universal but rather varies significantly across countries, cities, neighborhoods, and sub-populations [3]. Regardless of SES, ethnic minorities seem to be disproportionately burdened [4-10].

The observed geographic and sociodemographic variation in asthma expression remains a paradox largely unexplained by accepted genetic or physical environmental risk factors and has led to reconsideration of the interplay among physical environmental hazards and social conditions [11], a position supported in recent consensus statements by both the National Academy of Science [12] and the National Institutes of Environmental Health Sciences in the US[12, 13]. The needed framework to explain asthma disparities is still more complex as other scholarship points to the notion that connections between health and economic well-being embedded within the larger social context of people's lives are the result of influences operating at several levels, including the individual, the family, the communities, and the countries in which these individuals live[14, 15].

It has become clear that no single scientific discipline can address the myriad factors that influence asthma disparities. Rather, research strategies that embrace this complexity through a shared conceptual framework and incorporate the methodological expertise, analytic resources, and conceptual imagination of multiple disciplines promise to make significant contributions to understanding socially patterned disease[13]. The bridging of these different disciplinary perspectives challenges scientists to consider both molecular and genetic "causes" (i.e., biomedical framing) within the broader socioenvironmental context including social position as the upstream "cause of the causes" (i.e., ecological framing)[16], thus embracing the real world complexity of asthma epidemiology[3].

There is a growing body of literature addressing the unique features of such transdisciplinary research. While "interdisciplinary" research focuses on answering a question of mutual concern to those from various disciplines and "multidisciplinary" research involves research on questions of both mutual and separate interest to participating investigators, transdisciplinary research "implies the conception of research questions that transcend specialized knowledge bases because they are intended to examine questions that are, by definition, beyond the purview of the individual disciplines[17]." Transdisciplinary research is challenging. Barriers include the difficulty researchers have understanding and valuing one another's language, concepts, and methods; the lack of data resources to support TD research; and the organization of academic institutions and reward systems along disciplinary lines[18]. There are many scientific methods, paradigms and cultures differentiating scientific disciplines [19, 20] which certainly can complicate the building of these bridges. At the same time there is potentially significant "value-added" in cultivating collaborative research teams that are willing to cross-fertilize across disciplines. Concepts (e.g., objectivity, causation) that orient scientific work evolve over time [21], a process that can be accelerated when borders between disciplines blur[22].

We illustrate the challenges, opportunities, and potential "added value" to developing a transdisciplinary approach to researching underlying causes of health disparities by using an ongoing longitudinal study of asthma as a case study underscoring relevant conceptual and methodological issues that may be more broadly applicable. This study also illustrates how the transdisciplinary scientific goals must be balanced with the practical constraints related to budget and participant burden concerns in epidemiologic research.

Asthma Coalition on Community, Environment, and Social Stress (ACCESS): a case study

Relevant historical background

One obstacle became apparent from the early stages of developing a proposal for this research program – how to engage scientists to step outside their more narrow disciplines to contribute substantively to high-risk research that went outside of a paradigm that more likely ensures academic advancement (i.e., research driven by an individual investigator with recognized expertise in a clearly defined discipline either related to disease outcome, exposure assessment, or particular methodology). This tension is fortunately being eased by validation of the need for trans-

disciplinary science through high profile position statements[12, 13, 16] and sponsored meetings [e.g., the National Science Foundation sponsored conference on "Trading Zones, Interactional Expertise, and Interdisciplinary Collaboration" that highlighted the importance of "interactional expertise" in moving science forward (Conference on trading Zones, Interactional Expertise and Interdisciplinary Collaboration. Arizona State University, May 21-25, 2006)], validation from funding agencies in recognizing multiple principle investigators (PIs) as equally contributing to the advancement of the work, and calls for a publication culture that is more conducive to publishing transdisciplinary scientific results[23].

Validation through initiatives within the National Institutes of Health (NIH) establishing funding opportunities related to reducing health disparities was an important influence in our case. The purpose of the solicitation was to foster multidisciplinary research to elucidate the mechanisms operating between the interaction of the social and physical environments that contribute to health disparities (cite http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-00-004.html) and required the collaboration between social/behavioral scientists and biomedical scientists. The bridging of these different disciplinary perspectives challenged our team to consider an array of risk factors from the molecular and genetic scale to the household scale to the community and societal scale. This mechanism of support was critical as it enforced from the early design stage the need for having a diverse community of investigators which in turn shaped the kinds of questions that were asked and the methods used to address them. Moreover, having the call for such an approach integrated into the RFA validated the need to establish such research collaboratives in our more traditional academic setting.

The project next took advantage of an NIH initiative to develop Centers for Reducing Asthma Disparities (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-02-006.html) which expanded the aims to include additional exposures (including traffic-related air pollution) and to explore gene-environment interactions that may help account for asthma disparities. These initial funding streams provided support for establishing a transdisciplinary team of researchers to conduct integrative work bridging asthma epidemiology, immunoepidemiology, psychology, stress, child development, genetics, sociology, environmental science, geographic information systems, qualitative research methods and advanced statistical methods (e.g., multi-level methods, latent variable analysis, structural equation modeling).

Study population

The ACCESS study is a prospective cohort of prenatally enrolled mother-child pairs designed to study the interactive effects of early life stress and other physical environmental factors on urban childhood asthma risk in the US. Recruitment occurred between August 2002 and January 2007, enrolling pregnant women receiving prenatal care at Brigham & Women's Hospital, Boston Medical Center, three urban community health centers and women attending Women, Infants and Children (WIC) programs associated with the health centers in the Boston metropolitan area and surrounding suburbs. WIC is a federally-funded program that provides monthly vouchers for food and child care as well as health care referrals and nutritional education, and which includes women from 3 months gestation to 5 years postnatally. The project was designed to take advantage of the structure of the affiliated WIC programs given particular difficulties with recruitment and retention of study participants in this largely lower-income, ethnically diverse population, many of whom have moved frequently and/or do not have telephones at different stages as the study has progressed.

Women who did not speak either English or Spanish and who were less than 18 years of age at the time were excluded. All women receiving prenatal care were approached by trained research assistants on selected clinic days that changed weekly depending on patient flow. Participants in the ACCESS cohort include 997 pregnant women constituting 81.4% of those approached who also met eligibility criteria. Those eligible women who were approached but did not want to participate in the longitudinal study answered a brief screener questionnaire including information on race/ethnicity, annual household income, perceived stress levels and violence exposure; there were no significant differences in these covariates between those who agreed to participate and those who declined. Written informed consent was obtained in the subject's primary language (English or Spanish) and the study was approved by the human studies committees at the Brigham & Women's Hospital and the Boston Medical Center.

Overall conceptual framework

This is a multi-level, multi-method longitudinal cohort which aims to examine the role of psychosocial stressors in a systems biology framework considering multiple biologic pathways through which stress can contribute to asthma causation. The conceptual framework provided in Figure 1 summarizes the domains of outcomes and etiologic factors being studied in ACCESS and the interrelationships among these domains. We not only study the independent effect of stress on asthma/wheeze phenotypes but also consider stress as a modifier of physical environmental factors and genetic predisposition on asthma risk. We hypothesize that multi-level life stresses prevalent in disadvantaged populations can influence immune system development and airway inflammation in early life, thus making the populations more susceptible to other environmental factors and genetic risk factors explaining, in part, observed asthma disparities associated with social

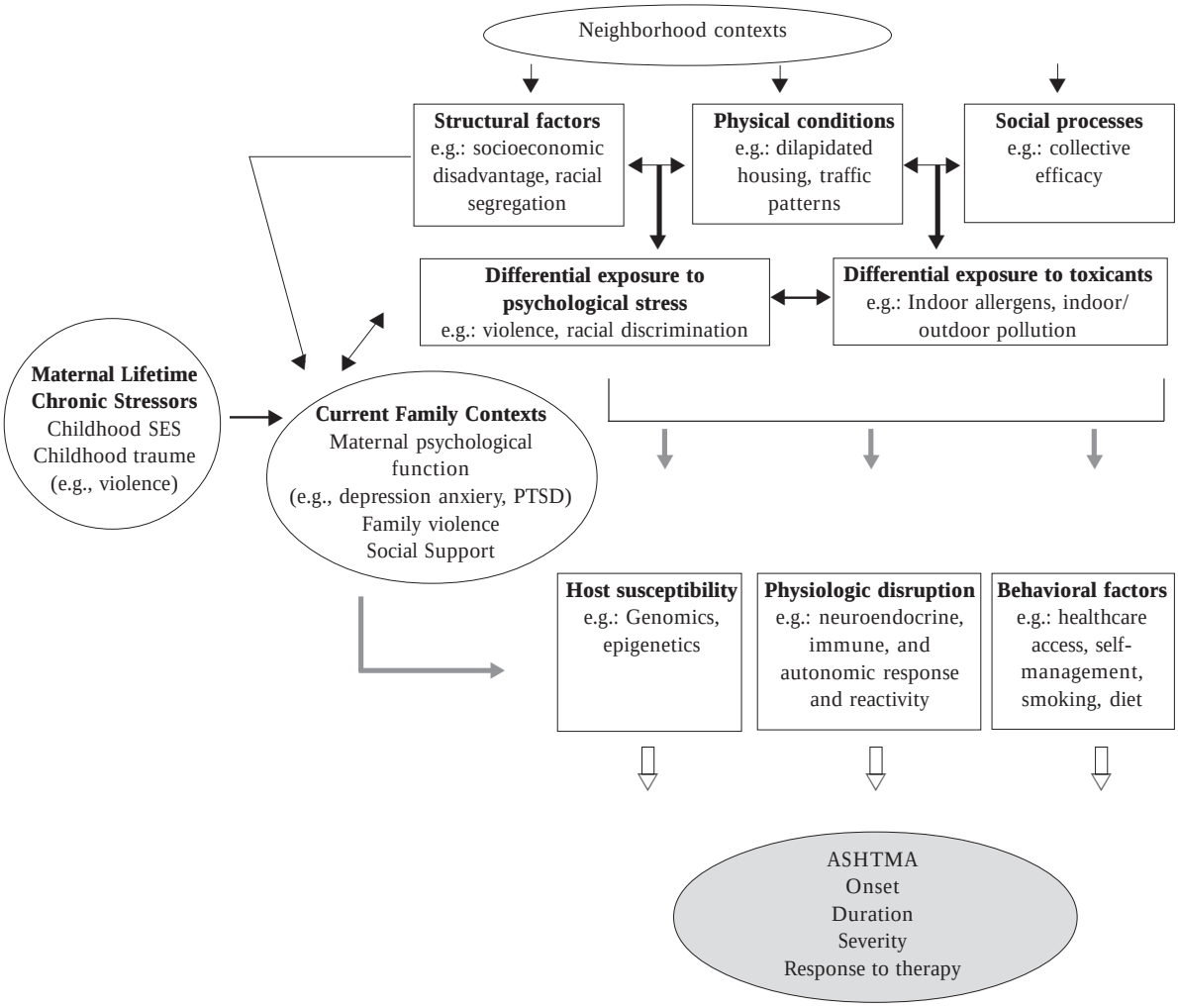

Figure 1. Conceptual framework.

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status. For example, to determine the role of stress as a modifier of the physical environment, we concurrently assess indoor allergens, tobacco smoke, and indoor/outdoor air pollution (e.g., fine particulate matter ($PM_{2.5}$), elemental carbon (EC), and nitrogen dioxide (NO_2), all associated in part with traffic), other factors thought to influence immune system development and airway inflammation in early life which may also differentially burden subjects based on SES and race/ethnicity (see Table 1 for a summary of baseline measures in ACCESS).

The design is also theoretically grounded in life course epidemiology which conceptualizes determinants of disease occurrence in terms of biological and social exposures experienced during different stages of life[24]. Adverse childhood exposures during critical periods may have both latent effects[25] and cumulative effects that negatively impact health outcomes and trajectory[26]. Critical periods of exposure for children related to childhood asthma include prenatal and early childhood developmental stages as recently reviewed in detail[27]. However, this project goes even fur-

Table 1. Overview of Baseline Measures in ACCESS.

Construct	Measure	Source
Individual-level Sociodemographics		Maternal Respondent
Race/ethnicity		
Self-identified race/ethnicity		
Country of origin/time in US		
Ethnic Identity	Multi-group Ethnic identity	
Socioeconomic Status (SES)	measure (MEIM)[60]	
Education level, household income		
SES Strain		
Maternal childhood SES	Parental home ownership [61]	
Subjective social status	10-rung ladder [62, 63]	
Individual-level Psychosocial Factors		Maternal Respondent
Maternal Stressors		
Negative Life Events	CRISYS [64]	
Global stress appraisal	PSS [65]	
Pregnancy related stress	Pregnancy Anxiety Scale [66]	
Gender role conflicts		
Childhood trauma/abuse	CTQ [67]	
Intimate Partner Violence (adolescence/ adulthood)	Revised CTS [68]	
Community Violence	ETV [69, 70]	
Housing Stress (derived using mixed methods, i.e., quantitative and qualitative)		
Stress Buffers	Brief COPE [71]	
Coping	Berkman-Syme Social Network	
Social supports/networks	Index [72]	
	Interpersonal Support	
	Evaluation List (LISEL-12) [73]	
Maternal Psychological Functioning		
Depression	EPDS [74, 75]	
Generalized Anxiety	STAI [76]	
Posttraumatic Stress Symptoms	PCL-C [77]	

it continues

Table 1. continuation.

Construct	Measure	Source
Community-level Psychosocial Constructs		Census data/geographical information systems (GIS)/ geocoding
Concentrated disadvantage		
Percent households below poverty line; percent receiving public assistance; percent unemployed; percent female-headed families with children		
Demographic concentration		
Percent white/Black/Hispanic/Asian; percent foreign-born (by race/ethnicity and length of stay in US		
Residential stability		
Percent residents five years and older who resided in the same hose five years earlier; percent owned home		
Informal social control		Maternal Respondent
Constructed from respondent assessment of likelihood that their neighbors could be counted on to intervene in 5 situations (e.g., children skipping school, fighting, generating graffiti)		
Social cohesion and trust		Maternal Respondent
Constructed from a cluster of 5 conceptually related items measuring respondent's agreement with statements such as "people around here are willing to help their neighbors"		
Perceived Violence		Maternal Respondent
Constructed from cluster of 5 conceptually related items measuring respondent's knowledge of events in the neighborhood including "fight in which a weapon was used", "gang fight", etc.		
Environmental Exposure Assessment		
Indoor Allergens Quantified in House Dust		In-home Dust collection
Der p, Der f; Bla g I, Bla g II; Cat; Dog; Mouse antigen		
Prenatal tobacco smoke/Postnatal Second Hand Smoke		Maternal Questionnaire; salivary cotinine validation
Indoor/Outdoor Air Pollution		Derived utilizing publicly available data (e.g., central site monitors, GIS, property assessment data), questionnaire responses from cohort participants, and selective direct sampling of indoor/outdoor pollutants[33, 34]
Primary Outcomes		
Physician diagnosed asthma, eczema, allergy (and intermediate phenotypes)		
Secondary Outcomes		
Maternal prenatal total IgE		
Maternal RAST (prenatal)		
Cord Blood Total IgE		
Child pBMNCs (proliferative response; cytokine expression)		
Maternal prenatal diurnal salivary cortisol response		
Prenatal CRH in maternal blood		
Child diurnal cortisol response		

ther to consider mothers experiences, both during pregnancy and more remotely. Adverse childhood exposures in the mother during critical periods may have both latent effects (not observed for a number of years)[25] and cumulative effects (adding up as subjects age) that negatively impact health outcomes and trajectories over the life course through biological disruption[26]. When the dysregulation of these systems persists, has its onset or is accentuated during pregnancy there may be health consequence transmitted to the next generation [28]. Even remote exposures, such as trauma (childhood abuse in the mothers) being considered here, may be relevant. Both short- and long-term traumatic stress effects transmitted ***in utero*** may augment or modify the response to the physical environment (e.g., chemicals, particles) for these children going forward.

Potential mechanisms through which stress may potentiate sensitivity to other environmental hazards (e.g., tobacco smoke, allergens, air pollution) will be explored through the epidemiologic measurement and analyses of biomarkers reflecting differentiation of the immune system and identified shared vulnerability pathways (e.g., hypothalamic-pituitary-adrenal (HPA) axis, autonomic response and reactivity)[29]. Specifically, our laboratory examines the influence of stress on T-helper cell differentiation as reflected in cytokine profiles and IgE production (TH2 phenotype) and cortisol functioning in both mothers and the index children. Blood and saliva samples have been banked for mothers and their children for future DNA analysis. In addition, mid-pregnancy blood samples are available on mothers to be analyzed for corticotrophin-releasing hormone and total and specific IgE. Cord blood is stored on children which is analyzed for total IgE. At approximately 2 to 3 years of age, blood is collected on the index children to be analyzed for IgE expression as well as nonspecific and specific lymphocyte proliferative response and cytokine profiles in selected subsamples.

Measurement of environment

Upstream social environment

To date, asthma research has mainly focused on individual-level risk factors with little attention to the broader social context that produces the risks. This can limit our understanding of the etiology of disease causation. The mechanisms that cause asthma (***e.g.***, cellular, gene, organ, individual, household, population sub-group, or community level) are rarely mutually exclusive. There is evidence that the risk factors associated with asthma, are unevenly distributed across communities and neighborhoods. It is likely that individuals living in poor households in disadvantaged neighborhoods are more likely to be exposed to indoor allergens than those in non-poor households in advantaged neighborhoods. Failure to view these risk factors within its context can be limiting[30]. There is evidence to suggest that there may be interaction between an individual's socioeconomic position (***e.g.***, education, income, occupation) and their exposure to environmental risk factors including, outdoor air pollution[31]. The social, political, and economic forces that result in marginalization of certain populations in disadvantaged neighborhoods and communities may also increase exposure to the known environmental risk factors to asthma[32]. There is a need to understand how the physical and psychological demands of living in a relatively deprived neighborhood may increase an individual's susceptibility (including genetic predispositions) to such exposures.

Physical environment

One of the complexities of a transdisciplinary epidemiological investigation is the need to characterize numerous exposures with sufficient precision to allow for multifactorial analyses while recognizing the inherent financial and logistical constraints. For characterization of air pollution exposures, it would not be feasible to monitor pollution levels at all participant homes throughout the duration of the study. At the same time, ambient monitors do not provide sufficient spatial coverage or information on residential indoor air pollution, which is a greater driver of personal exposures (especially for young children) and may be socioeconomically patterned.

To incorporate this exposure, measurements of multiple pollutants with hypothesized links to asthma and potential spatial heterogeneity within an urban area ($PM_{2.5}$, EC, and NO_2) were collected in multiple seasons at a subset of homes selected to represent multiple neighborhoods of interest and a gradient of traffic exposures[33, 34]. Questionnaires were administered to these households and to all participants in the cohort study, and regression models were developed to predict measured exposures as a function of questionnaire data, GIS data, and other information available for all members of the cohort.

Indoor-outdoor relationships varied across pollutants, with systematically higher levels of $PM_{2.5}$ and NO_2 indoors for cohort members as

compared with non-cohort households, driven by factors such as high occupant density and greater usage of gas stoves[33]. The measurements were ultimately incorporated into GIS-based regression models, which found that all pollutants were associated with ambient central site monitoring data and whether windows were opened or closed during sampling, with indoor $PM_{2.5}$ additionally predicted by cooking time and occupant density, indoor EC by distance to the nearest designated truck route, and indoor NO_2 by gas stove usage and traffic density within 50 meters of the home. These models demonstrated the feasibility of estimating long-term air pollution exposures across a large cohort, and also emphasized the multiple roles played by SES in the context of asthma (i.e., low-SES homes may tend to have higher air pollution exposure given smaller homes, high occupant density, and the need to use gas stoves as supplemental heating sources, in addition to the effect of SES on psychosocial stress and other risk factors).

Additional measurements of the physical environment included house dust measurements. ACCESS staff collect dust in participant homes at two time points to ascertain mother's exposure prenatally and the child's exposure during the first 2-3 months of life. Dust is analyzed for the dust mite allergens (D. Pteronyssinus [Der p 1] and D. Farinae [Der f 1]), German cockroach (Bla g 1, Bla g II), domestic cat (Fel d I) and dog and mouse antigen. In addition to collecting the dust samples, the research assistant also completes a brief standardized observational home survey at the time of home visiting.

We also assess maternal, paternal and other caregiver personal cigarette smoking through a combination of repeated measurement on standardized questionnaires and cotinine validation taking into account particular complexities with measuring smoking status during pregnancy [35]. As large numbers of prospective measurements are not feasible in many epidemiologic studies (especially one with a transdisciplinary focus), self-reported, retrospective reconstructions of the pregnancy smoking history may be the best way to capture complex patterns of smoking over time. Such "timeline follow-back" procedures have been used successfully with adolescent smokers, [36] who also exhibit complex patterns of smoking over time, as well as for measurement of other substance use [37]. Alternatively, Matt and colleagues have shown that using "fuzzy set" measures that incorporate the highest and lowest values of reported exposure to environmental tobacco smoke during pregnancy explains additional variation in infant cotinine levels over mean exposure level alone[38]. Similar analytic strategies can be applied to studies of fetal exposure to maternal smoking.

Role of qualitative research

Combining qualitative and quantitative methods, in which the separate approaches are used to inform one another to develop a more robust evaluation of specific constructs or findings, has increasing appeal in disparities research[39, 40]. Qualitative methods designed to capture social life as participants experience it, rather than in categories predetermined by the investigators as in standardized survey research, promises to further our ability to characterize the social structures of the host population contributing to stress and coping resources, for example. Qualitative methods may also extend our understanding of social and psychological constructs (i.e., stress) that may be influenced by characteristics of the particular population under study (e.g., culture/acculturation, language, etc.). Moreover, coping with community-level characteristics that may contribute to psychological stress (violence) requires flexible adaptation to local circumstances which are unlikely captured using existing standardized survey measures. Researching these complex patterns can be strengthened through the complimentary application of both qualitative and quantitative methods (an approach known as triangulation)[41]. Qualitative research has identified housing stress as a particular community concern in the ACCESS project which is being pursued further using mixed methods to develop a standardized measure to be used in future research[42].

Genetics and health disparities

It is likely that gene-by gene and gene-by-environment interactions will be important determinants of asthma occurrence to understand in this context. Genetic variants that have causal effects but also modify the host response to social and physical environments may not be unique to minority populations and are likely to be common among the general population. Differential exposure to relevant environmental exposures could explain disease disparities[43], meaning that both the environmental exposure and the genetic factor will be critical determinants in the causation pathway of the disease. Subjects who are ***exposed*** to toxins which are more prevalent in urban communities (stress, smoking, aeroaller-

gens, diesel exhaust) and carry the genetic susceptibility variants will have the ***greatest*** increased risk of disease, whereas subjects who are exposed to the toxins but do not have the genetic variant will have only a ***modest increased*** disease risk.

Genetic susceptibility due to inherited sequence cannot fully explain the mechanisms by which prenatal or early childhood stress and other environmental factors impact asthma risk. One possible mechanistic pathway only beginning to be explored in humans is via epigenetics[44]. Epigenetics is the study of heritable changes in gene expression that occur without changes in DNA sequence. DNA methylation is the best studied of the epigenetic processes that regulate gene silencing. DNA methylation of many genes changes with age, disease status, and environmental signals including chemical exposures such as diet, drugs and toxins as well as the social environment[45, 46]. Determining the range of environmental exposures which might affect the epigenome in early development and influence asthma risk is an expanding area of research.

Overview of analytic approach

The data being collected in ACCESS have a multi-level longitudinal structure and statistical analyses need to take advantage of recent advances in quantitative statistical modeling when operationalizing particular exposure variables as well as testing specific relationships in the conceptual model [[47]and cites therein]. While it is beyond the scope of this description to detail all specific hypotheses to be tested, the discussion here is limited to the types of quantitative models that we have already found useful in such a complex study design. This process exemplifies the need for researchers to extend beyond their discipline-specific analytical approaches to take full advantage of the complex data in answering specific questions, a hallmark of transdisciplinary research. One problem has been that powerful analytical tools and methods often exist in the specific scientific disciplines for which they were developed (e.g., economics, psychometrics, behavioral science) and often specialized software is needed to apply the techniques and existing general purpose statistical packages, more broadly familiar to environmental epidemiologists, often do not provide built-in routines with which to perform the desired analysis. Fortunately, there are a number of analytical techniques that have been recognized as particularly useful in analyzing the types of data available in the ACCESS project which are crossing over in the literature (i.e., being applied more often in epidemiology) and being developed in more mainstream statistical packages that make them more accessible to transdisciplinary research scientists [48]. The following discussion exemplifies how the ACCESS project has taken advantage of selected applications.

We have adapted a number of strategies that can be broadly classified as latent variable analytical approaches and we provide some relevant examples below.

Item response theory

Survey-based studies often present unique problems associated with characterizing predictors that are not directly measured. Increasingly epidemiological studies are applying latent variable statistical theory to create a predictor that is not directly measured but rather is ascertained through standardized questionnaires typically consisting of multiple items related to the exposure of interest (e.g. quality of life, work stress, treatment satisfaction). One latent variable approach used to characterize latent constructs is item response theory (IRT) and specifically Rasch models. Although applications of IRT modeling have increased considerably, its application may be more fully integrated into epidemiological research given advances in statistical theory and the incorporation of those advances into general purpose statistical software such as the Statistical Analysis System (SAS). This allows researchers to analyze measurement data by using a class of models known as generalized linear mixed effects models which include IRT models as a special case[49].

Although standardized survey measures of the psychosocial constructs including particular life stressors were selected when available (Table 1), latent variable approaches may be allow one to more precisely operationalize complex social indicators. In the ACCESS study, we were motivated to adopt this approach in characterizing violence exposure, a specific community-level stressor which had previously been linked to asthma expression[50]. Measurement of violence exposure presents a number of recognized challenges[51]. Not all discrete items are created equal, i.e. being a victim of a shooting generally does not have the same impact as hearing gunshots. Moreover, research focusing on violence exposure has generally not accounted for factors that may influence the impact of certain events (e.g. severity, frequency). Inclusion of this information is important as it may provide a more complete and accurate determination of the covariate

of interest. Trauma theory suggests still other social ecological factors that may contribute to the impact of violence exposure during development. For example, when considering early childhood risks, the family may be viewed as the most important social context influencing the health and development of children as interactions with primary caregivers may be important sources of both stress and resilience [52]. Thus, consideration of whether the perpetrator or victim of the witnessed event is a child's caregiver or someone else from the most proximate environment to the child may provide a more complete and accurate determination of the covariate of interest. Extending an application of IRT modeling in SAS using PROC NLMIXED that was previously reported[49], incorporation of this more detailed contextual information grounded in trauma theory reduces measurement error in the assessment of the child's true exposure to violence in their environment[53]. We have demonstrated applications of IRT to show associations between community violence exposure and childhood pulmonary function [54] and the interaction between community violence exposure and environmental air pollution in predicting asthma risk in another urban cohort in Boston[55].

Structural equation modeling

Another latent variable statistical approach being adapted more often in transdisciplinary epidemiological research is structural equation modeling (SEM). Studies examining complex pathways linking social position to health can be more rigorously assessed if they are modeled simultaneously (e.g., social position operating through determinants of environmental toxicant exposure, psychological factors, and behavioral factors)[56]. Moreover, neglect of temporal ordering of covariates that may be related to or correlated with one another (e.g., level of education and one's current income or one's occupation) in multiple regression type analysis has been shown to systematically underestimate their influence on health [48, 57]. Thus, one can also use SEM to ask questions from a lifecourse perspective[24]. Structural equation modeling also allows one to simultaneously estimate a set of interrelated regression models and then to assess the relative magnitude or effect size for each pathway. SEM has the added advantage of allowing latent constructs to be modeled, enabling a comprehensive assessment of all variables in the model. Estimates may be made more precisely, taking into account the covariance structure of all of the variables. Downward bias that results from putting variables on the casual pathway into the regression may be avoided. The system of equations may be compactly written in terms of a path diagram that illustrates the multiple relationships and the relative size of the effect in each pathway. Finally, unmeasured (latent) variables may be included when there is sufficient ancillary information. While this produces noisy estimates of the latent variable, recognizing its existence usually increases the precision of the estimates of the associations among the measured variables. For example, in ACCESS, we are exploring SEM to model the construct of stress as a latent variable that is not directly observed by modeling self-report of stressors [e.g., negative life events, family and community violence, physiologic disruption, and behavioral responses (e.g., being more likely to smoke cigarettes)].

Positive matrix factorization

Air pollution exposure assessment provides an interesting example of the ways in which common statistical methods may be applied to diverse exposures in transdisciplinary research. While the air pollution measurements listed above characterize a subset of pollutants, these may not be the precise causative agents for urban asthma, and some pollutants may be considered to represent a latent source effect (as in traffic or diesel-related traffic). We explored the application of SEM and other latent variable approaches before settling on positive matrix factorization (PMF) as the optimal strategy to use particle composition data (determined using x-ray fluorescence and inductively-coupled plasma mass spectrometry) to determine latent source contributions. As with psychosocial stress, this will allow us to characterize an unobserved exposure and should help to increase the precision within the multivariate epidemiological models.

Multilevel approaches

Because we will be measuring some constructs (e.g., stressors such as violence) at the community level as well as the individual level, it will be important to account for the resulting multilevel structure of the data. From one perspective, this simply means that we will need to account for possible correlations in outcomes measured on individuals living in the same or nearby neighborhoods. We have recently published an extensive review on the approaches being considered to which the reader is referred for further detail[47].

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Analytical approach for stress-genetics interaction

We will assess a series of candidate genes thought to influence immune development and airway inflammation in early life, including corticosteroid regulatory genes, adrenergic system regulatory genes, biotransformation genes, cytokine pathway genes. Genetic data will be analyzed along with the exposure and outcome data to assess the main effects of these genes, as well as to assess their role in modifying the role of the social and physical environment in the development of childhood asthma and related conditions.

Summary

The overview provided here of the conceptual design of the Asthma Coalition on Community, Environment, and Social Stress project is meant to exemplify one transdisciplinary approach to investigating social disparities in asthma. The ACCESS study has been conceptualized and designed based on the understanding that the potential explanatory factors for asthma disparities go beyond the classical physical factors to include complex interactions with social factors operating at the individual and community levels, likely modified by genetics. Investigations examining socioeconomic inequalities in health and mortality have largely been carried out in the US and Europe. There is a need for research in other parts of the world to more fully explicate pathways linking social structure and health disparities. Using this project as a case study highlights the challenges and opportunities raised in transdisciplinary research.

Research emerging from other NIH-funded transdisciplinary research further highlights the new ideas, integrative models, institutional changes, and innovative policies emerging from TD research[58, 59].

Collaboration

RJ Wright, principal investigator for the ACCESS project, JI Levy and RO Wright contributed to the overall theoretical conception, elaboration and final text with specific contributions to the final text on community violence exposure assessment (SF Suglia), transdisciplinary research framework (K Fortun, A Shields), and multi-level methods (SV Subramanian).

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