Published in final edited form as:
Stat Med. 2012 September 28; 31(22): . doi:10.1002/sim.5496.

Exposome: Time for Transformative Research

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Introduction

Life expectancy is an overall measure of population health, and has reflected a positive trajectory for several decades in the United States when estimated either at birth or 65 years of age [1]. Despite such improvements, life expectancy varies by socio-demographic characteristics and the availability of adequate medical care. Concerns about the continual sustainability for improving life expectancy have grown in light of the obesity epidemic currently occurring in the United States and in other countries across the globe [2, 3]. For example in 2010, all 50 States comprising the United States reported an obesity prevalence of 20% or more, with 12 states reporting a prevalence of 30% or more [2]. Overall, approximately 33% of adults and 17% of children in the United States are currently estimated to be obese [4].

Other notable changes in population health include the marked reduction in fertility rates over time [5], which has partially but not entirely been attributed to changes in cultural norms and behaviors regarding childbearing practices. In fact, an evolving body of evidence is suggestive of temporal declines in human fecundity, which is defined as the biologic capacity of men and women for reproduction irrespective of pregnancy intentions [6]. The body of evidence supporting a decline in male fecundity over the past few decades includes diminished semen quality and increasing rates of genital-urinary malformations and testicular cancer, all of which are hypothesized to originate *in utero* or the so-called TDS or testicular dysgenesis syndrome [7]. This conceptual framework has recently been extended to women. Specifically, the ovarian dysgenesis syndrome (ODS) posits that female fecundity is established at conception or *in utero* with early impairments arising during prepubertal or reproductive years as manifested by alterations in the onset or progression of puberty or gynecologic and gravid disorders, respectively [8]. Assuming that human fecundity may be positively associated with survival as recently reported for semen quality [9], its decline may be at a ‘critical tipping point’ for human health as recently suggested [10] underscoring the importance of new research pardigms such as the exposome for assessing the early origins of fecundity and its implications for health across the lifespan.

How might researchers further impact the health and well being of populations across the globe? Certainly, new research paradigms are needed for transforming how we think about health and disease and design research, acordingly. Novel paradigm changes are already underway (e.g., genome and epigenome), though noticeably absent is a paradigm that

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captures the multitude of environmental exposures that impact human health and disease. This data gap prompted the development of the exposome paradigm, which compliments the (epi)genome while providing a multitude of opportunities for intervention if exposures can be eliminated or minimized. The exposome paradigm focuses on the simultaneous measurement of a multitude of biomarkers including those that originate from external and internal sources. External environmental exposures may include chemicals or physical agents such as radiation among many other types of exposures, while internal environmental exposures arise from bodily functions and processes that govern homeostasis. Internal exposures may include chemicals or biomarkers generated via inflammation or stress along with various other pathways. Of note is the absence of biomarkers for some external environmental exposures (e.g., noise or vibration) resulting in missing data or the need for proxy biomarkers. These issues are further discussed below along with the unique aspects of the exposome such as the longitudinal and high dimensional nature of biomarkers across the lifespan.

This paper provides a brief overview of the exposome paradigm along with the resources needed for getting started, research hurdles and challenges to overcome and opportunities for discovery. The overview is organized as responses to five questions: 1) What is the exposome? 2) Why is the timing right for exposome research? 3) What resources are needed for moving forward? 4) What research hurdles and challenges need to be overcome? and 5) What impact might the exposome have for transforming population health? We use human fecundity to illustrate how the exposome might be implemented, though the issues pertain to most (non-Mendelian) health outcomes.

1. What is the exposome?

The exposome is defined as the totality of environmental exposures from conception onward as first published by Wild in 2005 [11]. Implicit in this definition are two important conceptual domains that have implications for measurement and analysis: 1) humans interface with a *mixture* of exposures and 2) exposures occur across the *lifespan* including during critical or sensitive windows of development, or time intervals of heightened susceptibility. Included in the mixture of environmental exposures are the thousands of man-made and naturally occurring chemicals (e.g., heavy metals, persistent organic pollutants) that need to be considered along with physical agents (e.g., noise, vibration, temperature), macro level factors (e.g., population density, sanitation), and a spectrum of lifestyle factors (e.g., diet, physical activity, sleep). To reiterate, not all environmental exposures currently have available biomarkers for measurement. As such, the exposome is intended to help ground and compliment genomic research by providing the environmental context for the rigid genome established at birth, when attempting to delineate the etiology of disease or its absence.

Soon after the introduction of the exposome, some authors suggested the need to categorize exposures as either being external (e.g., environmental chemicals in food, water or air) or internal (e.g., chemicals of inflammation as generated by reactive nitrogen species) to the body [12–15]. With regard to the latter, the biochemistry of homeostatic mechanisms continually changes, necessitating the need for measuring even smaller and rapidly changes biomarkers. At the National Academies of Sciences' workshop entitled "Emerging Technologies for Measuring Individual Exposomes" that was held on December 8–9, 2011 and as recently summarized [16], authors called for the integration of both the external and internal environment as one in keeping with the nature of human exposure and biologic response. As originally intended, the intent of the exposome is to compliment (not compete) with genomic research, given our recognition of the importance of gene*environment interactions for select diseases, and the importance of environmental (non-genetic)

exposures on epigenetic expression including human fecundity [17, 18]. As such, the exposome is inclusive of biomarkers that may arise from various biologic, biochemical or chemical processes [19] that are indicative of exposure, susceptibility or disease. Implementation of exposome research will require the development and refinement of analytic methods capable of handling the diverse array of biomakers and also other exposures for which there is no known or measurable biomarker. Such analytic approaches include environmental wide association studies (EWAS), which build upon genomic wide association studies (GWAS) developed during the past decade as discussed below.

2) Why is the timing right for exposome research?

The timing for exposome research is right for a number of reasons. First, genetic risks for most chronic diseases are markedly less than for environmental exposures. For example, it is estimated that approximately 70%–90% of chronic diseases are attributed to environmental factors, while results from twin studies suggesting modest (≈10%) genetic contributions for cancer or degenerative diseases [20–22]. In addition, the increasing secular patterns for many diseases such as asthma, autism and fecundity related impairments argue for environmental in lieu of genetic influences on disease susceptibility and occurrence. To this end, a more comprehensive understanding of environmental exposures, including in the context of genetic factors, is likely to lead to discovery and transform our understanding of human health across the lifespan.

A second timing issue supporting implementation of the exposome paradigm is the Developmental Origins of Health and Disease (DOHaD) hypothesis, which posits that exposures during critical and sensitive windows may induce epigenetic changes to prepare the embryo or fetus for expected extrauterine life [23]. The biologic basis for looking at early environmental exposures reflects, in part, the considerable epigenetic reprogramming that occurs during gametogenesis and embryogenesis. The embryo/fetus by definition is continually developing and not biologically mature, as measured by its inability to repair DNA damage or detoxify enzymes, its lack of a blood/brain barrier and biologically immature organs among other sensitivities. As such, the epigenome responds to environmental signals especially during critical and sensitive windows of human development and, thereby, has the ability to influence gene function and phenotypic expression. Data in support of this hypothesis have rapidly grown with numerous trans-disciplinary publications supporting associations between prenatal or early life course environmental exposures and later onset adult health and disease such as body size, reproductive site cancers, and heart disease [24–26]. This collective body of evidence has facilitated the life course approach to understanding chronic diseases [27].

Lastly, there is trans-disciplinary interest in measuring, characterizing and understanding the multitude of biomakers that characterize human health and disease, and to use this information in such a way as to treat, ameliorate, reverse, or prevent disease processes. The novel discovery of even smaller biomarkers coupled with increasing technology for their measurement poses exciting analytic challenges and well suited for discovery. The exposome is positioned to build upon the wealth of knowledge that has followed the genomic revolution including the development of laboratory and analytic methods coupled with the availability of cohort studies, many of which are still actively following study participants across the lifespan. The availability of longitudinal data in the context of time-varying biospecimen collection positions research teams to develop and implement exposome proof-of-concept research initiatives.

Human reproduction and development is uniquely positioned for exposome research, particularly given its many critical and sensitive windows that are comparatively short

relative to chronic disease as recently summarized, viz., spermatogenesis ≈72 days; menstruation ≈29 days; ovulation (≈1 day); fertilization (3–4 hours); fertile window (≈5 days); implantation window (≈6 days); and pregnancy (≈266 days) [28]. With increasing evidence that human fecundity arises peri-conceptionally or *in utero* coupled with its implications for later onset disease [7,8], these early windows of human development offer promise for implementing the exposome paradigm of research. This approach, however, should not discourage cross-sectional or observational attempts for considering the exposome as was recently done. Specifically, Patel and colleagues [29] utilized a two-stage environment wide association study (EWAS) analytic approach to assess 266 candidate chemicals and type 2 diabetes using four NHANES surveys. Strong associations were observed for type 2 diabetes and heptachlor epoxide, γ-tocophperol, βcarotenes and polychlorinated biphenyls, with effect sizes comparable to the strongest loci reported in GWAS studies. More recent work with these survey data revealed important associations for environmental factors and serum lipid levels that were later validated [30]. As with GWAS research, EWAS methods appear feasible and have utility for generating hypotheses for more targeted and purposeful study. EWAS may help get the right research questions assembled for empirical investigation.

3. What resources are needed for moving forward?

Moving forward requires greater trans-disciplinary awareness of the exposome paradigm, a willingness for novel thinking and exploration including recognition of the need to measure both the external and internal environments [31], and identifying suitable resources for both proof-of-concept or other types of observational research. With regard to human reproduction and development, one suitable starting point is to leverage the many existing cohort studies with longitudinally measured environmental exposures and banked biospecimens as recently summarized. For example, there are at least 37 European prospective cohort pregnancy representing >350,000 mother-infant pairs with environmental data and biospecimens [32] along with a number of U.S. cohort studies. Of note are two prospective pregnancy studies with preconception recruitment of both partners of the couple for whom environmental exposures have been captured at the daily level and with timed biospecimen collection during sensitive windows of human reproduction and development [33, 34]. Leveraging existing cohorts will help with discovery and permit validation with the eventual goal of defining normal variation, biologic susceptibilities and, eventually, health and disease.

Assuming the availability of sufficient databases, statistical and laboratory resources are needed and both domains can build upon existing technologies that have been developed to support genomic research. On the laboratory side, this includes high-throughput assays suitable for hypothesis generation and exploration, and other technologies suitable for untargeted or unbiased methods needed for characterizing exposures in relation to proteins, metabolism and, possibly, reactive electrophiles or adductomics [35]. Trans-disciplinary laboratory teams will require varying resources such as mass spectrometry, gene and protein chips, microfluid technologies, or a host of commercially available technologies such as fertility monitors and acccelometers. An ultimate goal is the creation of environmental chips that would capture human exposures across the lifespan. Until such time, the development of exposure chips for more sensitive windows may be instrumental in obtaining novel signals for reproduction and development.

The exposome presents big data issues for researchers, and the totality of environmental exposures even for specific critical or sensitive windows will dwarf the amount of genomic data at the individual level. Big data issues include the collection, processing, storage, and analysis of exposure data. It may be worth keeping in mind that big data issues are not

unique to researchers, as they also impact governments and businesses across the globe. In fact, advertising campaigns are already launched with the goal of getting the public to use "cloud" storage for personal data including music and photos. An interesting challenge will be to determine how cloud computing might help researchers access exposome data from study participants across the globe.

Novel statistical methods are need for exposome research including further development and refinement of EWAS techniques capable of handling the totality of exposures, phenotypes and diseases in the context of interrelated disease states across the lifespan. For example, fecundity impairments such as polycystic ovarian syndrome are associated with gravid diseases such as gestational diabetes or preeclampsia, which in turn are associated with later adult onset diseases such as type 2 diabetes or metabolic syndrome as recently summarized [8]. In light of the exposome's data driven approach, analytic plans will need to accomodate the complex and high dimensional nature of environmental mixtures that reflect large to small biomolecules or biomarkers (e.g., proteins to metabolome), while recognizing their interrelatedness and continually changing nature to aid in model specification and statistical analysis. Refinement of analytic techniques will ultimately need to include multiple testing, false discovery thresholds, joint modeling of health outcomes across the lifespan, missingness of data on multiple time scales due to the varied nature of exposures, and the need for replication to validate initial associations. The focus of EWAS studies is in identifying critical windows of exposure, requiring time-varying effects of the exposures to be estimated. EWAS approaches necessitate statistical methods that go beyond the currently available bioinformatics methods, which were developed to address issues of high dimension from genetics data (fixed across time). Despite these important and challenging considerations, proof-of-concept EWAS research has been successfully attempted [29, 30] with more research underway. This platform of research offers promise for understanding health and disease, and also for developing therapies for repairing epigenomic changes occurring in early life [36].

The first step in developing an analytic strategy for handling the exposome has already been undertaken, in that authors borrowed heavily from GWAS techniques in their extension to research focusing on environmental exposures and Type 2 diabetes [29]. Briefly, this work utilized regression techniques in assessing the association between environmental exposures and diabetes, while adjusting for risk factors and controlling for false discovery rate. A remaining limitation of this work reflects the cross-sectional design of the NHANES data used for analysis. Machine learning techniques are another possible analytic strategy in that they require little to no information about exposures and outcomes (37). This analytic approach utilizes an algorithm that is grounded in causal inference and multiple-testing methodologies for traditional non-parametric inference.

These methods are semi-parametric in contrast to the previously utilized methods [29], and provide a gain in local efficiency. However, this approach could prove to be computationally intensive if applied to exposome research. Applied to critical or sensitive windows of human reproduction and development, the machine learning approach will require the integration of longitudinally measured exposures or biomarkers in the context of dimension reduction and multiple testing considerations. This could be achieved either by a two-staged analytic approach or, potentially, a joint modeling approach comprising high dimensional exposures and health outcomes.

4. What research hurdles and challenges need to be overcome?

Without question, the exposome paradigm poses many exciting challenges for researchers that are beyond the scope of this paper. Like many emerging areas, terminology can be

confusing with related terms arising such as *biomes* or *omes* in the context of current terms such as the genome or epigenome. As such, it is important for the exposome to be inclusive of all exposures irrespective of source, timing or duration. Delineating the critical and sensitive windows for human reproduction and development or any disease outcome for that matter is an important first step in attempting to measure and analyze the exposome. The manner in which critical and sensitive windows can be put together across the lifespan is an important area of discussion, and one that may benefit from the work already done on human growth and development either while *in utero* [38] or across the lifespan [39]. In fact, the former resource is specifically tailored for endocrine disrupting chemicals and human development.

Another challenge is the many important steps in utilizing existing resources or cohorts ranging from the harmonization of data if more than one cohort is used, developing plans for EWAS analysis, and other considerations such as data access and sharing, research ethics, and reporting back to participants. Many of these considerations are discussed in a recent supplement of *Paediatric and Perinatal Epidemiology* as related to pregnancy cohorts [40]. While there may be fewer considerations for data driven or untargeted exposome initiatives, eventual targeted approaches will need to consider how best to model mixtures in the context of their likely inherent inter-relatedness, other relevant time-varying exposures and intra- and inter-individual susceptibility and toxicokinetics. Peters and colleagues [41] recently noted other important exposure-related considerations: 1) not all exogenous exposures have a biomarker (e.g., noise, electromagnetic frequency); 2) not all exogenous biomarkers have a good biomarker of internal dose; and 3) functional genomic changes likely are a function of susceptibility and internal dose. Analytic approaches are best served if they consider these limitations to the fullest extent possible.

From the laboratory perspective, currently there is no one chip for measuring all environmental exposures even assuming our ability to delineate all relevant exposures. It may be that chips will need to be designed to measure specific types of exposures in a comprehensive manner, and that multiple chips would be needed for fully characterize human exposure even during a particular sensitive window. Arriving at a minimum data set for exposures during critical and sensitive windows is daunting, but not impossible. For example, considerable efforts already have been undertaken to assist with gene*environmental interactions and include the PhenX Toolkit. This resource comprising 338 standardized measures relevant for assessing complex diseases, phenotypic traits and environmental exposures [42]. These past efforts coupled with more inclusive environmental assessments may be instrumental for helping to delineate and measure exposures across the lifespan.

A final last hurdle to plan for and overcome is the eventual combining of exposome, genome and epigenome data. This undertaking is likely to produce an unprecedented high dimensional longitudinal hierarchical data structure, but one most closely resembling the human*ome.* To date, the exposome is a critical missing element of this ultimate mega database. This critical data gap should be one that trans-disciplinary teams seek to overcome in the interest of discovery and beyond.

5. What impact might the exposome have for transforming population health?

While considerable progress has been made for promoting and maintaining population health as evident by the positive secular trend for life expectancy during the past century, our approach to understanding health remains fragmented or globally defined by type (e.g., basic, clinical or population), organ or disease specific (e.g., diabetes, cancer) or lifespan

(e.g., pregnancy, reproduction). While specialized research needs to continue, opportunities for larger scale research initiatives are needed with the goal of transforming how we think about, approach and conduct research on human health and disease. In fact, a new taxonomy of disease has recently been developed, and one that includes the exposome as a key aspect for building the "knowledge network" that will be instrumental for understanding exposures and the mechanisms underlying disease [43]. Thus, the exposome offers an exciting and timely platform for such thinking and novel research opportunities, and one that parallels human life. It has the potential to transform our conceptual framework for thinking about human health in its continuum, while encompassing other noteworthy paradigm shifts such as the DOHaD hypothesis and life course epidemiology. The pinnacle of the exposome's success will lie with improved life expectancy (and the removal of disparities) for all populations.

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