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Statistical approaches for investigating periods of susceptibility in children's environmental health research

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Abstract

Purpose of Review: Children's environmental health researchers are increasingly interested in identifying time intervals during which individuals are most susceptible to adverse impacts of environmental exposures. We review recent advances in methods for assessing susceptible periods.

Recent Findings: We identified three general classes of modeling approaches aimed at identifying susceptible periods in children's environmental health research: multiple informant models, distributed lag models, and Bayesian approaches. Benefits over traditional regression modeling include the ability to formally test period effect differences, to incorporate highly time-resolved exposure data, or to address correlation among exposure periods or exposure mixtures.

Summary: Several statistical approaches exist for investigating periods of susceptibility. Assessment of susceptible periods would be advanced by additional basic biological research, further development of statistical methods to assess susceptibility to complex exposure mixtures, validation studies evaluating model assumptions, replication studies in different populations, and consideration of susceptible periods from before conception to disease onset.

Keywords

critical windows; susceptibility; vulnerability; children's health; environmental epidemiology; statistical methods

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Introduction

Periods of heightened susceptibility (also known as critical windows) are developmental periods during which exposure to some agent (chemical or non-chemical) results in a greater effect on an outcome than does exposure to that same agent at other times. Examining susceptible periods can have several advantages for environmental epidemiology studies of children's health. First, investigators may compare associations of exposures measured at different time intervals with the aim of elucidating biological mechanisms based on known underlying developmental processes. Second, the ability to optimize timing of exposure measurements for the most susceptible period(s) can reduce exposure misclassification and improve effect estimation. Third, knowledge of the most susceptible periods can inform targeted exposure interventions or recommendations to maximize public health impact.

The importance of investigating susceptible periods in children's health research has been emphasized for more than two decades (1, 2), and identifying periods of susceptibility was a specific goal of the National Institute of Environmental Health Sciences (NIEHS) 2012–2017 Strategic Plan (3). Despite increased emphasis on this topic, identifying susceptible periods remains a key challenge in the field of children's environmental health research (4).

Reduced cost of biomarker assays, novel biomarker measurements, and advances in exposure modeling have resulted in a greater number of studies with repeated measures of a multitude of exposures. These advances necessitate methods capable of modeling high-dimensional repeated exposure data to maximize its utility for inference. While familiar statistical approaches for estimating effects of repeated exposure measures can be applied to the study of susceptible periods, recent methodological work has focused on developing approaches to overcome the limitations of standard methods and new challenges. Exposures measured at multiple time intervals may be highly correlated due to common sources, necessitating control for confounding among periods. When simultaneously considering susceptible periods and multiple exposures, the problem of correlation is magnified by both within and between measure correlation. Methods for assessing exposure mixtures have been rapidly developing, though most approaches consider mixtures measured at a single time interval (recently reviewed in (5) and (6)).

This review discusses novel statistical approaches for identifying susceptible periods, with emphasis on methods developed for the setting of highly time-resolved or correlated exposure data. After providing an overview and rationale for assessing susceptible periods, we describe key articles published in the past five years and make recommendations for additional research and methodological development.

Biological Rationale

The idea of periods of heightened susceptibility has a long history in epidemiology and clinical medicine, with origins in the study of teratogens. Teratogenic agents can cause adverse effects when exposure occurs during well-defined time intervals such as gestation when major organ systems undergo rapid and synchronized development at discrete periods (7). Perturbation of sensitive biological processes during discrete periods of gestation can

increase the risk of a variety of birth defects. For example, thalidomide, a pharamaceutical agent used in the 1950–1960s to treat nausea in pregnant women, is one of the most infamous teratogens. Thalidomide caused limb defects in thousands of children born to women who used the drug (8). Notably, the presence of limb defects depended on the timing of thalidomide use, where exposure between 21 and 36 days after conception was necessary to cause these birth defects. The effect of teratogens is not limited to limb or organ malformations. For instance, primary cytomegalovirus infection during pregnancy is the one of the leading non-genetic causes of sensorineural hearing loss and is also associated with other developmental deficits (9).

Terminology around the concept of susceptible periods is variable, with authors referring to a number of related terms: *window* vs. *period* as well as *critical* vs. *susceptible* vs. *vulnerable*. We prefer *period* over *window* because the former is routinely used in the developmental biology literature to distinguish between critical and sensitive periods. *Critical periods* are well-defined time intervals during which an exposure can affect an outcome. For example, teratogens typically have effects only when exposure occurs during a very narrow period during fetal development (10), as noted above. *Sensitive periods* are less discrete; the effect of an exposure may be greatest during a given period while also having lesser or different effects at other periods (e.g., cytomegalovirus infection) (11). Next, we note the distinction between *susceptible* and *vulnerable*. *Susceptibility* refers to the induction of health effects after exposure, whereas *vulnerability* additionally considers the probability of exposure and capacity of response (e.g., coping and adaptability) (12). In environmental epidemiology, we are typically concerned with determining *susceptibility* given that we assess health effects resulting from exposure in extant populations for which exposure and response have already occurred. When considering public health implications of such research, the resulting interventions, policies, and recommendations typically deal with *vulnerability* as they consider susceptibility in conjunction with likelihood of exposure and response capacity of the target population.

Statistical Approaches

Periods of susceptibility are often operationalized based on developmental stages of interest, such as trimesters during pregnancy or stages of child development. Exposure during each period is typically assigned *a priori* based on a single measurement during the period or by creating period-averaged exposure variables. A common statistical approach is to estimate associations of exposure during each period with the outcome to determine which effect estimate has the greatest magnitude. Such period-specific effects are estimated in either separate regression models for each period or in a simultaneously-adjusted model to account for correlation in exposure over time. Raz et al. provides an illustrative example in the context of particulate matter (PM) exposures in relation to autism spectrum disorders (13). The authors examined five unique developmental periods by operationalizing period-averaged $PM_{2.5}$ during the 9 months prior to conception, each trimester of pregnancy, and 9 months after birth. The magnitude of association was strongest during the third trimester, which the authors' describe as evidence supporting a prenatal origins of autism spectrum disorders (13), a finding that has been replicated (14).

Limitations of the above approach include the inability to formally test for differences among periods, difficulty in addressing missing data or unequally timed exposure measures, multiple comparisons, multi-collinearity, and loss of information or measurement error due to period-averaging (15–17). Many of these limitations can be addressed by examining exposure periods continuously rather than as discrete periods (16) and applying approaches to account for repeated exposure measures over time. We refer the reader to previous reviews discussing linear and generalized additive mixed effects models for examining susceptible periods, which compare and contrast model assumptions and utility in various settings (15, 16). Notably, Chen et al. compares nine approaches for examining repeated exposure data in relation to a time-fixed outcome including the traditional approaches above and several mixed model and clustering- based methods (15). The authors also compare results of the nine approaches using an application to repeated phthalate biomarkers during pregnancy and preterm birth (15). The authors conclude that the two mixed effects models evaluated performed best for identifying susceptible periods.

We focus the remainder of our discussion on novel methods for identifying susceptible periods with applications to children's environmental health published in the past five years. We identified three general classes of approaches: multiple informant models, distributed lag models, and Bayesian approaches. Key features of these statistical methods for identifying periods of susceptibility are summarized in Table 1.

Multiple Informant Models

Multiple informant models, originally developed to evaluate data from different sources that relate to the same underlying construct (18, 19), can be adapted to the setting of multiple exposure measures from the same individual (16). This model jointly estimates exposure-outcome associations for each period, defined *a priori*, and produces a statistical test of whether the period-specific estimates differ from one another. Models can be fit using generalized estimating equations or maximum likelihood (see (16) for details and code). This method can be applied in settings with a single exposure with sparse measures over time; however, it is not well-suited to high-dimensional or highly correlated data. Moreover, the method does not jointly adjust the exposure-outcome association at one period for the exposure-outcome associations in other periods.

In the Health Outcomes and Measures of the Environment (HOME) Study, we have applied multiple informant methods to identify susceptible periods to several classes of environmental chemicals in studies of child neurobehavior and thyroid hormone levels (20–29). Notably, we found that urinary triclosan concentrations at the time of delivery, but not during pregnancy or childhood, were inversely associated with child intelligence quotient at age 8 years (29). In addition, we found that urinary bisphenol A concentrations during pregnancy but not childhood were associated with more parent-reported behavioral problems in girls from ages 2 to 8 years (30).

Distributed Lag Models

Extensions of distributed lag models (DLMs) can be used to examine susceptible periods when exposures are measured with fine temporal resolution, such as weeks (31, 32).

Generally, DLMs describe exposure-lag-response relationships of a time-varying exposure with a time-fixed outcome, and distributed lag *non-linear* models apply a smoothing function or penalty to flexibly model the time-varying exposure effects (33). Because DLMs use a data-driven approach for estimating period effects rather than averaging over pre-defined periods (e.g. trimesters of pregnancy), they can identify narrow or protracted periods of susceptibility (17).

In a simulation study, DLMs provided unbiased estimates and correctly identified susceptible periods while models using pre-specified, period-averaged exposure (with or without simultaneous adjustment) resulted in biased estimates (17). Susceptible periods for perinatal and pediatric health outcomes have been investigated using DLMs in studies of air pollutants (34–37), temperature (38–41), and tooth manganese levels (42). For example, Chiu et al. estimated associations of $PM_{2.5}$ with child neurodevelopment using 1) pre-specified trimester- or pregnancy-averaged $PM_{2.5}$ exposure modeled using multivariable linear regression models, and 2) weekly-averaged $PM_{2.5}$ exposure modeled with DLMs (34). DLMs identified susceptible periods that were not evident using period-averaged models.

Others have extended the DLM framework to assess susceptible periods for exposure mixtures by developing lagged weighted quantile sum (WQS) regression and a tree-based DLM (43). The lagged WQS approach, based on penalized regression, models longitudinal exposure mixture trajectories over time and can accommodate missing or unequally-timed exposure data (43). A limitation of lagged WQS is the requirement that effects of all exposures at all periods are constrained to be in the same direction (i.e., positive or negative), which may not be reasonable in some settings. The tree-based method applies a non-parametric random forest algorithm to model summed mixture effects of exposures that must be measured at identical, discrete time intervals for all subjects (43). In simulations, both of these novel approaches performed better than generalized additive models using thin-plate splines in settings with more than 3 chemicals and 5 periods. The authors demonstrate the two DLM-based methods using a study of neurobehavior in relation to longitudinal metal exposures measured in deciduous teeth, where both approaches found similar periods of susceptibility in relation to the metal mixture and identified manganese as the largest contributor to the mixture effect (43).

Bayesian Approaches

Bayesian extensions of DLMs have been developed to investigate susceptible periods in complicated data structures. Bayesian DLMs can incorporate prior information on the shape of period-specific effects over time (44) and have been applied to identify susceptible periods without the need to specify time intervals *a priori* (45). Bayesian distributed lag interaction models were developed to formally investigate and test susceptible periods in the context of effect measure modification, where the timing of susceptible periods may depend on a modifier (32). This method has been applied to examine whether child's sex or maternal stress modify the timing of susceptibility in studies of early life pollutant exposures and perinatal or pediatric health outcomes (46–49).

Lagged Bayesian kernel machine regression (LKMR) combines the DLM framework with Bayesian Kernel Machine Regression (BKMR) to identify periods of susceptibility to

exposure mixtures (50). LKMR allows the effect of a mixture on an outcome to differ over time, allowing for non-linear and non-additive effects as well as interactions among exposures and within exposures over time. When applying LKMR to examine tooth metal mixtures in relation to child neurodevelopment, Liu et al. identified a time-varying association of manganese with visual spatial ability that was modified by zinc level (50). While LKMR is fit in a DLM framework, it is best-suited to exposure data with low temporal resolution such as biomarker data (50).

Warren and colleagues developed a flexible Bayesian spatial-temporal hierarchical probit regression model that applies a data-driven approach to determining susceptible periods for multiple pollutants, allowing that susceptible periods may differ spatially and by pollutant (51, 52). By incorporating spatial flexibility, this model accommodates the fact that air pollution constituents vary regionally and may lead to different biological effects. Warren and colleagues have applied this method to examine susceptible periods for associations of weekly-averaged air pollution exposures with preterm birth, cardiac defects, and low birthweight (51–53). Joint modeling of multiple outcomes and multiple exposures is also possible in this framework, such as the assessment of susceptible periods for multiple species of $PM_{2.5}$ in relation to the development of multiple classes of cardiac defects (52, 54). This model was adapted to examine time-varying exposure effects on time-to-event outcomes, and notably applied to assess associations of $PM_{2.5}$ with preterm birth that allowed associations to depend both on timing of exposure and timing of preterm birth treated as a time-to-event outcome (55).

Considerations for Future Research

Ideally, evaluation of susceptible periods is informed by developmental biology or toxicology studies that provide insight into the importance of exposure timing on disease etiology. In the absence of prior data for specific environmental exposures, investigating susceptible periods is often warranted based on the general concept of developmental plasticity or by analogy to effects of other exposures on the outcome of interest. Continued basic biological and toxicological research to understand developmental processes and susceptible periods will strengthen future epidemiologic work. Likewise, findings of unique susceptible periods in epidemiologic studies can inform experimental work exploring mechanisms underlying heightened susceptibility. Of particular importance for both experimental and observational research is assessment of susceptible periods outside of gestation, including preconception and adolescence (4).

Examination of susceptible periods requires repeated exposure measurements collected at times corresponding to the underlying susceptible period(s). For studies using biomarker assessments of exposure, longitudinal biospecimens are logistically difficult to collect and repeated assays are expensive to perform. While within-subject pooling can reduce exposure measurement error by providing a better estimate of long-term exposure, it precludes analysis of susceptible periods within the timeframe of the pooled samples and may even increase measurement error if specimens collected during a susceptible period are pooled with those from irrelevant periods (56). A balance in terms of cost might be achieved by collecting repeated samples but initially analyzing biomarkers in within-subject pooled

samples; if an association is observed, archived samples can be subsequently analyzed to identify susceptible periods. While we are not aware of an application, an alternative approach warranting further study is to analyze repeated samples in a subset of participants and apply measurement error correction methods (57–59) to estimate period-specific associations.

As exposures are measured in a greater number of susceptible periods, we expect a shift in assessing independent effects of single exposures during single periods towards the examination of joint effects of several exposures in multiple susceptible periods. Such work will build on toxicological studies identifying multiple susceptible periods for the same health effect (60) and an expanding literature assessing effects of exposure mixtures (61, 62). Epidemiologists will need statistical tools capable of leveraging high-dimensional longitudinal data to answer such questions. To our knowledge, LKMR is the only statistical approach that has been applied to identify susceptible periods that allows for interaction between multiple exposures and among exposures over time (50). Additional work evaluating potential bias arising from correlation among repeated exposure measures is also needed as few studies have investigated the influence of exposure measurement error (63), correlated exposure measurement error (64, 65), or amplification bias (66) in the setting of multiple or repeated exposures.

Finally, it will be critical to determine if periods of heightened susceptibility are observed across populations. Given the potential for spurious results when examining numerous exposures in multiple time intervals, there is a compelling need for replication in separate study populations. However, lack of replication may also be due to differences in factors that modify susceptibility to environmental exposures at different developmental periods. In the United States, the NIH Environmental Influences on Child Health Outcomes (ECHO) Consortium is one resource that could be useful and well-powered for replication studies given that it includes several cohorts that have repeatedly assessed multiple exposures at similar developmental stages.

Conclusions

Statistical approaches to investigate susceptible periods have been developed for a range of complex data settings. Whereas traditional approaches require *a priori* specification of exposure periods, distributed lag models and Bayesian approaches allow for data-driven determination of periods of heightened susceptibility that may provide more nuanced insight into underlying mechanisms. We find Bayesian methods to be highly customizable, with the ability to assess susceptible periods while addressing correlated exposure data, high-dimensional data, effect measure modification, and other common statistical challenges. As approaches continue to be developed and validated, availability of software packages will be critical to facilitate their uptake by children's environmental health researchers interested in examining periods of susceptibility.

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Table 1.

Key features of selected statistical approaches to identify periods of susceptibility in children's environmental health research

Approach	Adjusts for confounding by exposure in other periods	Formally tests period effect heterogeneity	Accommodates highly time-resolved exposure data	Stabilizes highly correlated exposure periods	Key references
Single-period regression models					N/A
Multiple-period regression models	X				N/A
Generalized linear mixed models	X	X			(15)
Multiple informant models		X			(16)
Distributed lag models	X	X	X		(17, 31)
Bayesian extensions of distributed lag models	X	X	X	X	(32, 50)
Bayesian spatial-temporal hierarchical probit model	X	X	X	X	(51)