MODELING CUMULATIVE ENVIRONMENTAL STRESSORS USING A CONSILIENCE APPROACH SUPPORTS A TOTAL LOAD MODEL OF CHRONIC CHILDHOOD HEALTH CONDITIONS

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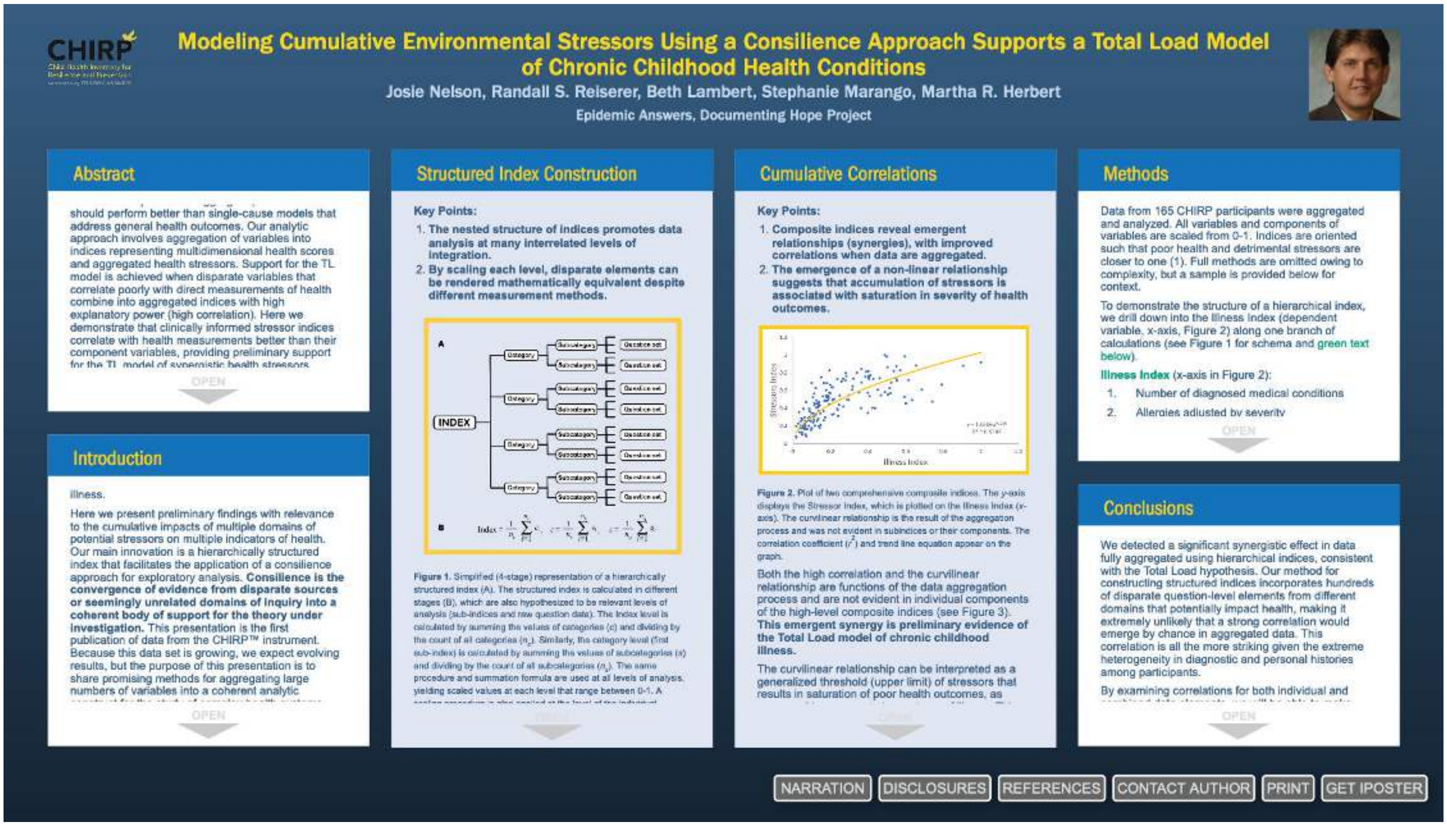
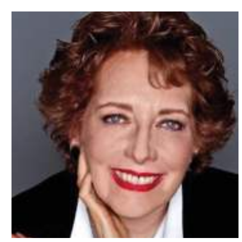








ABSTRACT

Over the past three decades, public health concerns have increased concerning the effects of environmental toxins on chronic health conditions. Many of the 86,000 plus synthetic chemicals listed by the EPA are ubiquitous in the environment. To date, studies have been limited on the cumulative effects of these chemicals, their potential interactions, and their aggregate influence on chronic health conditions. We hypothesized that the escalation of chronic health conditions relates to both the pervasiveness environmental chemicals and the synergies (interactions) among toxins and other stressors. We refer to the accumulation of these stressors as Total Load (TL), and we hypothesize that cumulative exposures result in cumulative health impact. To address the TL hypothesis in children (a particularly vulnerable population), we developed a comprehensive survey, the Child Health Inventory for Resilience and Prevention (http://documentinghope.com/chirp-study/) (CHIRP™) and began gathering data in 2018. The TL Hypothesis predicts that many synergies will exist among variables that represent health stressors. Thus, models that treat cumulative impact as

an aggregate predictor variable should perform better than single-cause models that address general health outcomes. Our analytic approach involves aggregation of variables into indices representing multidimensional health scores and aggregated health stressors. Support for the TL model is achieved when disparate variables that correlate poorly with direct measurements of health combine into aggregated indices with high explanatory power (high correlation). Here we demonstrate that clinically informed stressor indices correlate with health measurements better than their component variables, providing preliminary support for the TL model of synergistic health stressors.

INTRODUCTION

The Documenting Hope Project (https://documentinghope.com/) (DHP) is a research program pursuing the causes of chronic diseases in children. The overarching hypothesis guiding this investigation holds that a vast number of environmental factors contribute to the epidemic of deteriorating health in children—some more than others. These many factors include **exposures to toxins and biological stressors in food, water, soil, household products, clothing, industrial emissions, conventionally farmed crops,** and many other sources.

The DHP Child Health Inventory for Resilience and Prevention (https://documentinghope.com/chirp-study/) (CHIRP™) Survey is a comprehensive, HIPAA compliant, online instrument, custom-built in collaboration with LivingMatrix

(https://livingmatrix.com/), that parents/guardians complete for children between ages 1-15 years. **This survey captures data from many different domains of life function, including family history, health diagnoses, genetic variants, medical symptoms, healthcare history, diet and nutrition, behavior, lifestyle, environmental exposures, and more**—and covers important potential exposure histories from pre-conception to present-day.

The study of cumulative health impacts from multiple environmental stressors is an emerging field, so new analytic tools and methods are needed to assess the synergies among and between a multiplicity of potentially relevant quantifiable domains. Most clinical research seeks to test a particular pharmaceutical, medical, or nutritional therapeutic agent, and researchers often narrow their focus to a single disease. **Our analysis goal is to understand the big picture of chronic childhood disease (i.e., many different conditions all modulated by cumulative stressors) while capturing enough detail to analyze and understand underlying causal patterns** (e.g., key differences in environmental, behavioral, and genetic influencers).

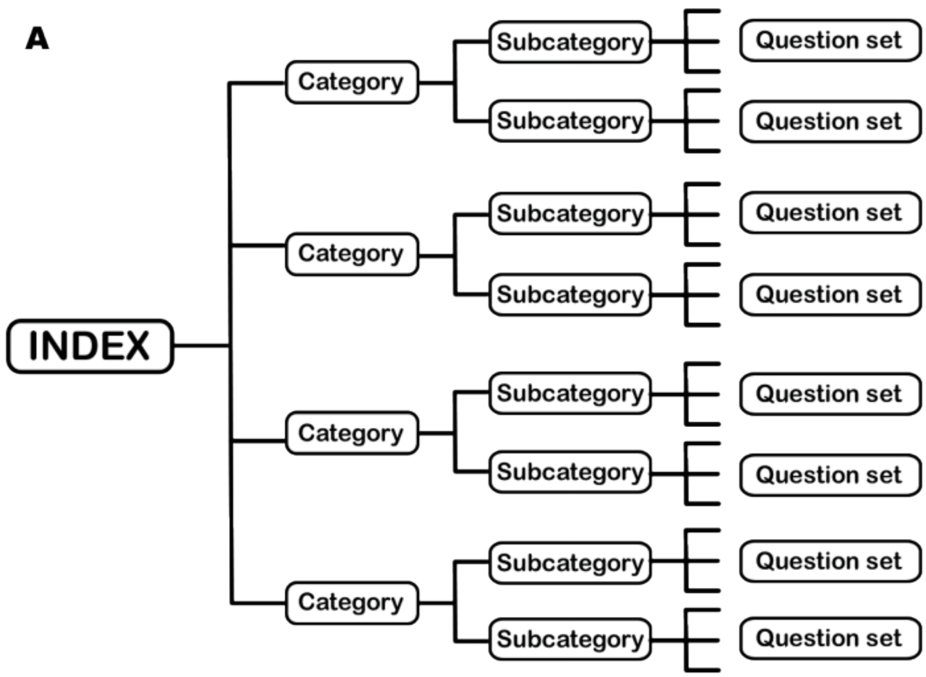
The study of cumulative impacts on health from multiple potential channels of causation is a formidable research challenge, as evidenced by the void of research in this area. The lack of interest is largely due to an absence of robust methods for aggregating many different potential contributors to illness.

Here we present preliminary findings with relevance to the cumulative impacts of multiple domains of potential stressors on multiple indicators of health. Our main innovation is a hierarchically structured index that facilitates the application of a consilience approach for exploratory analysis. **Consilience is the convergence of evidence from disparate sources or seemingly unrelated domains of inquiry into a coherent body of support for the theory under investigation.** This presentation is the first publication of data from the CHIRP™ instrument. Because this data set is growing, we expect evolving results, but the purpose of this presentation is to share promising methods for aggregating large numbers of variables into a coherent analytic construct for the study of complex health systems.

STRUCTURED INDEX CONSTRUCTION

Key Points:

1. The nested structure of indices promotes data analysis at many interrelated levels of integration.
2. By scaling each level, disparate elements can be rendered mathematically equivalent despite different measurement methods.



B

$$\text{Index} = \frac{1}{n_c}\sum_{i=1}^{n_c} c_i, \quad c = \frac{1}{n_s}\sum_{i=1}^{n_s} s_i, \quad s = \frac{1}{n_q}\sum_{i=1}^{n_q} q_i$$

Figure 1. Simplified (4-stage) representation of a hierarchically structured index (A). The structured index is calculated in different stages (B), which are also hypothesized to be relevant levels of analysis (sub-indices and raw question data). The Index level is calculated by summing the values of categories (c) and dividing by the count of all categories (n). Similarly, the category level (first sub-index) is calculated by summing the values of subcategories (s) and dividing by the count of all subcategories (n). The same procedure and summation formula are used at all levels of analysis, yielding scaled values at each level that range between 0-1. A scaling procedure is also applied at the level of the individual question (q).

The purpose of a structured index is to capture meaningful variation in the relationships among many variables that relate to each other through a theoretical framework.

A well-constructed index should:

1. Permit comparison of aggregate data with other measurements of covarying phenomena,
2. Allow for tests of its assumptions, and
3. Permit validation of its predictive elements.

Accordingly, a multitude of potential causal factors must be represented in the index as:

1. A single factor for the broadest analysis,
2. A small set of factors (latent variables) composed of aggregate data from soundly derived domains related to health, which, when analyzed, produce amplified signals, and
3. Subsets of the latter factors that form natural subcategories appropriate for analysis, each comprised of related metrics or aggregate data.

To realistically represent the underlying health-systems biology, different levels of aggregation should form a hierarchical set of nested categories and subcategories (Figure1A) that form natural groups. Any number of nested levels may be incorporated, but each subcategory must be justified as reasonably equivalent (with respect to expected signal) to other subcategories within its level of integration.

The index is structured into a hierarchical set of categories and subcategories, each level roughly representing an equivalent tier of analysis, and each nested tier more inclusive than the level below it. The base level of analysis is the single variable, but aggregate variables properly scaled provide for generalized analysis at different levels. A hierarchically structured index represents a testing framework—a hypothesis of relationships—that can be statistically interrogated for internal consistency, as well as for correlations among elements, associations, interactions, and non-independence.

CUMULATIVE CORRELATIONS

Key Points:

1. Composite indices reveal emergent relationships (synergies), with improved correlations when data are aggregated.
2. The emergence of a non-linear relationship suggests that accumulation of stressors is associated with saturation in severity of health outcomes.

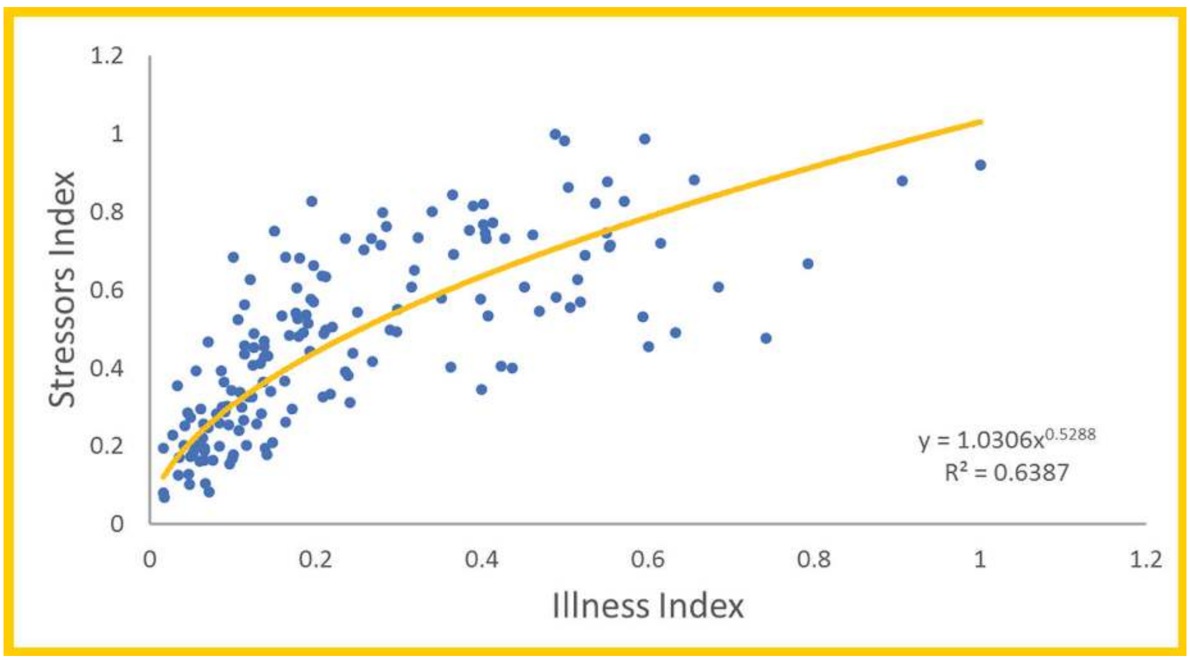


Figure 2. Plot of two comprehensive composite indices. The y-axis displays the Stressor Index, which is plotted on the Illness Index (x-axis). The curvilinear relationship is the result of the aggregation process and was not evident in subindices or their components. The correlation coefficient (r2) and trend line equation appear on the graph.

Both the high correlation and the curvilinear relationship are functions of the data aggregation process and are not evident in individual components of the high-level composite indices (see Figure 3). This emergent synergy is preliminary evidence of the Total Load model of chronic childhood illness.

The curvilinear relationship can be interpreted as a generalized threshold (upper limit) of stressors that results in saturation of poor health outcomes, as measured by aggregated symptoms of illness. This strong curvilinear relationship was not present in any of the subindices, nor was there a strong correlation associated with the individual subindices (see e.g., Figure 3).

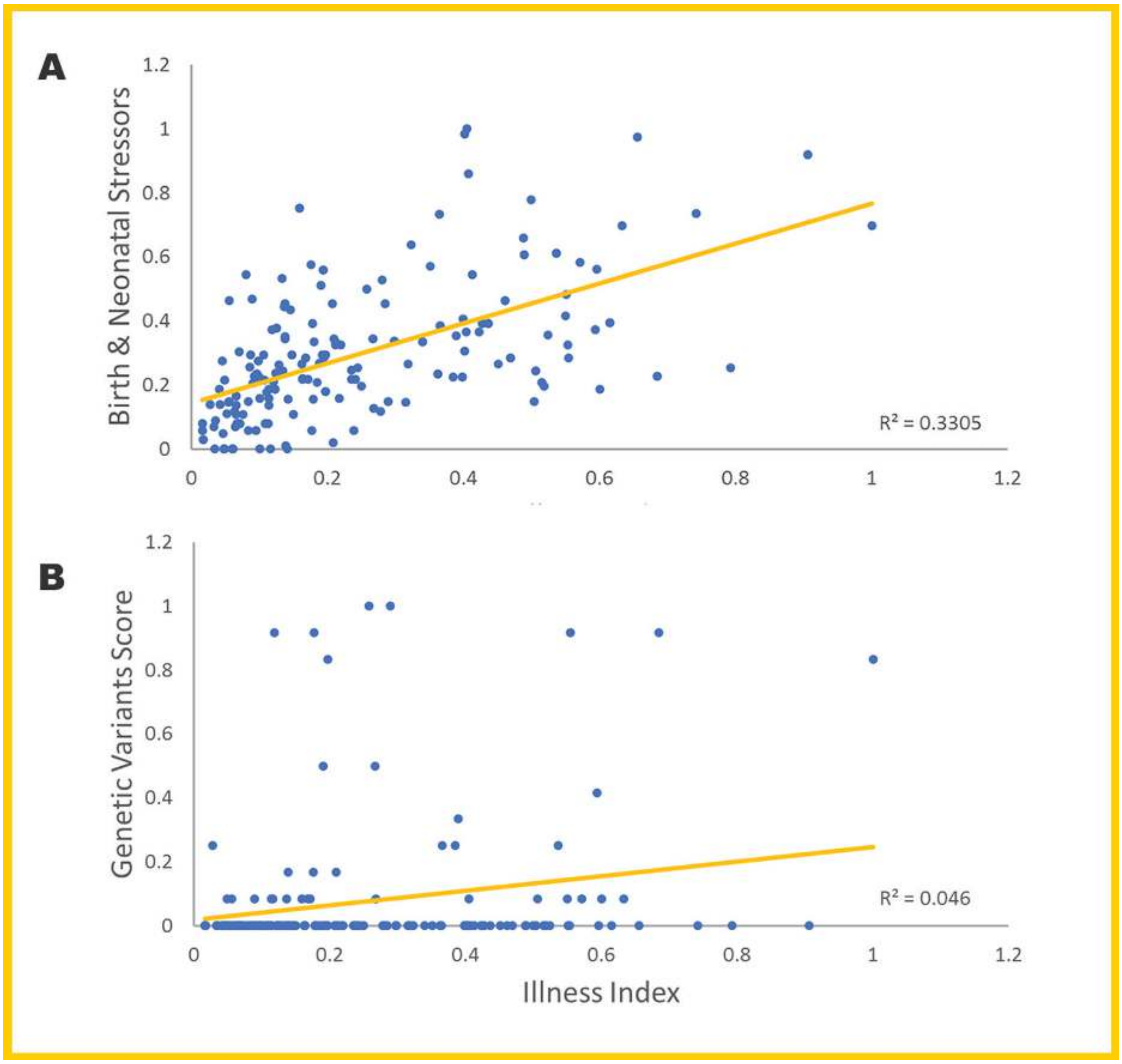


Figure 3. Plots of relationships between two of the 11 major components of the stressor Index and the full composite Illness Index. The plots displayed depict both the highest (A) and lowest (B) correlation coefficients (displayed on graphs). The average r2 value for all 11 subindices was 0.158, SD = 0.096.

The subindices used to construct the two main indices in Figure 2 are sketched out in Methods and a sample calculation pathway is displayed for context.

Note: Correlation coefficients in this presentation (r values) provide a measure of the proportion of variance in the dependent variable (x-axis) that is predictable from the independent variable (y-axis). An r value of 0.63, for example, means that the x variable explains 63% of the variation in the y variable, whereas an r2 value of 0.04 means that the x variable explains 4% of the y variable.

METHODS

Data from 165 CHIRP participants were aggregated and analyzed. All variables and components of variables are scaled from 0-1. Indices are oriented such that poor health and detrimental stressors are closer to one (1). Full methods are omitted owing to complexity, but a sample is provided below for context.

To demonstrate the structure of a hierarchical index, we drill down into the Illness Index (dependent variable, x-axis, Figure 2) along one branch of calculations (see Figure 1 for schema and green text below).

Illness Index (x-axis in Figure 2):

1. Number of diagnosed medical conditions
2. Allergies adjusted by severity
3. Bodyweight diagnoses
4. Physical Composite Subindex
   A. Developmental milestones composite
   B. Motor delays composite
      i. Milestones score

Survey question: At approximately what age did this child achieve the following milestones. Please indicate if this child skipped or has not yet achieved this milestone.

Question choices: roll over from front to back, roll over from back to front, sit up unassisted, bear weight on feet (when being held), crawl on belly ("commando" crawl), crawl on all fours, pull up to standing, cruise (e.g., walk holding on to furniture), walk unassisted, run.

      ii. Motor delays score
      iii. Orthopedic devices score
      iv. Current coordination score
   C. Coordination history composite
   D. Musculoskeletal composite
5. Behavioral problems composite subindex
6. Infections composite subindex
7. Nose and throat symptoms subindex
8. Cardiac symptoms subindex
9. Pulmonary symptoms subindex
10. Gastrointestinal symptoms subindex
11. Stooling symptoms subindex

The choices for milestone questions were scored as binary (yes/no) conditionals based on typical developmental timelines. For example, "roll over from front to back" was scored 1 if the reported age was > 1 year. Binary answers were summed for each participant and divided by the number of question choices to derive the score for the question. A similar process was used to aggregate higher-level components across levels of integration.

Examples of aggregated indices and subindices are plotted in Figures 2 and 3. **Components of the Stressors Composite Index used in y-axis in Figure 2**:

1. Composite immune exposures
2. Birth and neonatal stressors
3. Prenatal stressors
4. Prenatal exposures
5. Child's screen time

Note that many such calculations go into the construction of a fully aggregated index. The CHIRP™ Survey includes many types of questions that were coded as binary (nominal), ordinal (e.g., Likert), or scale variables. The hierarchical organization effectively allows nominal and ordinal data to be transformed into scale variables.

The CHIRP™ Survey was recoded from the LivingMatrix output in MS Access. Graphs and regression fitting were constructed in MS Excel. Statistical verification (not shown), such as correlation matrices and classification analyses, was performed in the R statistical software platform.

6. Chemical exposures composite
7. School environmental exposures

8. Genetic variants score
9. Lifetime cumulative medications use
10. Composite antibiotics score
11. Injectable medications use

CONCLUSIONS

We detected a significant synergistic effect in data fully aggregated using hierarchical indices, consistent with the Total Load hypothesis. Our method for constructing structured indices incorporates hundreds of disparate question-level elements from different domains that potentially impact health, making it extremely unlikely that a strong correlation would emerge by chance in aggregated data. This correlation is all the more striking given the extreme heterogeneity in diagnostic and personal histories among participants.

By examining correlations for both individual and combined data elements, we will be able to make informed decisions about how to refine composite indices. By using a hierarchical framework that stratifies causal relationships into "fair comparisons," we hope to elucidate the deep relationships between childhood chronic health conditions and the multiple stressors that cause them.

Because our analysis is in an early stage, we have only recently begun to apply a statistical framework to the construction and analysis of indices. Factor analyses and machine learning approaches have shown promise and we anticipate applying many other analytic techniques as CHIRP™ data continue to be coded into analyzable formats.

These early results indicate that the CHIRP™ Survey has the potential to be a powerful practice-based research tool for clinicians. The Documenting Hope Project is actively enrolling participants in CHIRP™, including communities and medical practices interested in evaluating environmental exposures and health outcomes in a comparative framework that includes control communities and the broader U.S. population. Interested clinicians and communities are encouraged to inquire about participation (https://documentinghope.com/comparison-report/).

A sample community/physician recruitment page (https://cr142.infusionsoft.com/app/form/samplephysician) can be viewed online.

DISCLOSURES

The authors declare no conflicts of interest.

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