Methodological Approaches for Whole Person Research Workshop
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National Center for Complementary and Integrative Health, National Institutes of Health

Executive Summary

As a relatively new concept, research on whole person health is different from reduction-based research, which mostly focuses on a single intervention's impact on one or, at most, a few physiological systems as separate processes. Understanding how multiple physiological systems interconnect and interact is one of the key challenges for the success of research on whole person health. Gaining this understanding will require tapping into and adapting existing research strategies as well as developing new methods and designs for whole person research. The National Center for Complementary and Integrative Health's (NCCIH's) strategic plan defines whole person research as including three components: (1) exploring the fundamental science of interconnected systems; (2) investigating multicomponent interventions or therapeutic systems; and (3) examining the impact of these interventions on multisystem or multiorgan outcomes. This workshop considered examples of these three areas of research and methodologies to move the field forward. In addition to NCCIH, nine NIH Institutes, Centers, and Offices contributed to this effort.[*]

Studying Interconnected Systems: Observational Studies

Research in various individual domains (e.g., biological, behavioral, social, environmental) can be expanded into research on the interconnectedness of multiple body systems (e.g., immune, digestive, neural). The level of complexity in such studies might call for the application of network science, which can be conducted in observational studies, relying on the concepts of analysis and synthesis to understand patterns, relationships, connectedness, and changes over time. Data-driven models might include machine learning, and mechanistic models might include, for example, differential equations. These models trade off on each other depending how much data and domain knowledge are available. The choice of methods depends on what is being modelled. Methods and modelling should be based on the type of intervention being tested, the types of questions being asked, the kinds of variables being measured, and the number of observations available. Examples of approaches to studying interconnected systems include:

- The "Almost Matching Exactly" method performs data-driven causal analyses from complex interconnected systems. It aims to match a current situation with almost identical situations from the past, in order to use these past situations to predict the future.
- Machine learning methods, both supervised and unsupervised, can be used to study and model various dynamic interconnected networks within and between cells and other biological components. These methods can be used to model interactions across multiple systems from large multiscale datasets.
- A person-oriented approach typically seeks to identify prototypical individual profiles across a set of variables, characterizing the process under study with the potential to capture highly interactive nonlinear relationships among predictive factors and outcomes.

[*] The workshop was led by NCCIH. Workshop collaborators included the National Institute on Aging, National Institute on Minority Health and Health Disparities, National Institute of Nursing Research, National Institute of Dental and Craniofacial Research, Fogarty International Center, Office of Research on Women's Health, Office of Behavioral and Social Sciences Research, Office of Disease Prevention, and the Office of Nutrition.

- Deep learning offers the potential for integrating data from the level of the molecular profile to the predicted response to a potential therapy.
- The DunedinPACE measure assesses an individual's personal pace of biological aging. It is implementable in whole blood and has strong test-retest reliability. The tool has been used to predict mortality in the Framingham Heart Study, capture Black-White disparities in mortality, and capture accelerated aging in Texas adolescents who had early life adversity.

Studying the Impact of Single Component Interventions or Manipulation on Interconnected Multiple Systems

A methodological challenge is how to study the impact of single component interventions or manipulations on interconnected multiple systems. For example, we know that stress reduction techniques such as mindfulness can help with sleep, glucose metabolism, weight loss, and chronic musculoskeletal pain, but we know very little about how these effects may be interrelated because that understanding requires including these various outcomes in the same study. Presenters described the challenges of finding matching controls for these studies; overcoming selection effect; assessing the accuracy of animal models for complex human studies where genetic heterogeneity is inherent; addressing the need for intervention analysis and the usefulness of combining experimental and observational data; identifying methods for measuring and assessing multisystem outcomes; identifying surrogate outcomes; and standardizing data collection across multiple sites to increase cohort sizes. Several approaches were described:

- Observational studies of stress resulting from emotional, physical, or sexual abuse reveal how it affects mental health outcomes and immune dysfunction, with cumulative abuse exposure yielding an additive effect.
- Total-body positron emission tomography (PET) can be a transformative tool for quantitative whole-person research. PET data can be used to simultaneously examine the effects of chemotherapy on the brain, liver, kidneys, and entire body systems. PET data also have been used in studies on the effects of meditation on metabolism and on the systemic effects of COVID-19, inflammatory arthritis, and acute myocardial infarction.
- The Molecular Transducers of Physical Activity Consortium conducts preclinical and clinical studies to discover and assemble a comprehensive map of molecular changes that occur in response to exercise.
- Manipulating microbiomes can generate reproducible changes in behavior, and microbiota abnormalities have been linked to several health conditions, such as anxiety, Alzheimer's disease, and multiple sclerosis.
- A health equity perspective posits that upstream determinants influence health outcomes and should be the focus of interventions. Upstream conditions also influence the health-related choices that people make for themselves and their families. The Adolescent Brain Cognitive Development Study examines 22 contextual environmental variables across several domains.

Investigating the Impact of Multicomponent Interventions or Therapeutic Systems on a Single Outcome

New or adapted strategies are needed to investigate the impact of multicomponent interventions or therapeutic systems on a single outcome. Complex problems, such as chronic pain, may require multicomponent treatment. However, we often do not know which components are necessary for an effective outcome. Discussions focused on determining when animal models are appropriate, using quasi-experimental designs with one arm as a means of proof of concept, addressing the need for formative studies, expanding interventions to other populations that have unique characteristics, scaling up from preclinical to clinical studies, stating the scientific question clearly, finding reliable and valid measures, and recognizing the need to sometimes estimate effect sizes rather than narrowly focusing on p values. Examples include:

- Two studies used a multicomponent intervention that models whole system naturopathic medicine to ascertain the relative impact of neuropathic therapies.
- A progressive translational science model was used to determine if adding a mindfulness component to diet and physical activity can achieve sustained remission of metabolic syndrome.
- To achieve greater public health impact, interventions should be developed in consideration of affordability, scalability, and efficiency, along with effectiveness from the outset and interventions should be optimized to achieve ease of implementation. Research using these strategies has been applied to optimization of a smoking cessation intervention with the goal to arrive at an efficient smoking cessation intervention made up of all active components.
- Community Wise is a multilevel behavioral group intervention created in partnership with service providers, residents of marginalized communities, and individuals with histories of substance use disorders and incarceration to reduce health inequities related to alcohol and substance misuse. The intervention was developed based on what is known to be effective, rather than by conducting a pilot study and then conducting an efficacy trial.
- Two analytic strategies for understanding the mechanisms underlying multicomponent pain interventions are mediation and cross-lagged panel design analyses.
- Many studies of botanical natural products are carried out with poorly characterized study material, such that the results are irreproducible and difficult to interpret. Mass spectrometry metabolomics approaches have been used to capture and compare the chemical diversity of the complex botanical natural products.

Examining the Impact of Complex Multicomponent Interventions on Multisystem or Multiorgan Outcomes

Examining the impact of complex multicomponent interventions on multisystem or multiorgan outcomes requires innovative study designs and analytical tools. Discussions focused on translating temporal and spatial scales from animal models to humans, harmonizing data on integrative medicine across multiple sites, using designs that examine the effect on multiple outcomes, noting the challenges of composite outcomes, using computational tools to extract and curate data, determining the need for appropriate modelling, recognizing the importance of context, and acknowledging the logistics and cost of complex study designs. Examples of approaches include:

- The composition of the microbiome has been studied to determine if specific medications will be safe or effective for an individual. Personalized nutrition plans can be developed based on

predictions for how an individual's microbiome will influence that person's metabolic response to specific foods.

- N-of-1 clinical trials can examine the utility of an intervention for an individual, rather than a trial that focuses on population effects. This type of study can employ many statistical strategies, such as randomization, blinding, multiple crossovers, and multivariate analyses, to achieve greater scientific rigor. Results from these trials can be aggregated for meta-analyses to determine common factors among participants who responded to an intervention.
- An organizing framework was described for selecting an experimental design. Importantly, scientific questions should motivate an experiment's design; the design should not dictate the study's objectives. Two approaches were discussed: sequential, multiple assignment, randomized trials (SMART), and micro-randomized trials (MRT).
- Complex systems science is a set of tools developed from a variety of quantitative and qualitative perspectives. It can be used to design intervention studies that are multifaceted and have multiple outcomes. It has been used for a multifaceted multi-outcome whole-of-community intervention to prevent childhood obesity.
- Large longitudinal health datasets, when combined with an area deprivation index map (socioeconomic status at the neighborhood level based on income, education, employment, and housing quality), can be valuable when examining social determinants of health.
- Different tools within systems science can be used to model complex systems. The reconstructability analysis methodology called discrete multivariate modeling can be used for fuzzy systems, set theoretic models, information models, neutral systems, directed systems and time-dependent systems. A dual diagnosis may be needed in a study to apply the results to both Western medicine and an allopathic field, such as traditional Chinese medicine.
- Identifying structural determinants of health is key to advancing health equity research. Operationalizing social and structural determinants requires weighting factors such as level of influence, time, multidimensionality, and interconnectedness. To fulfill the promise of a whole person research agenda, research needs to be translatable to the real-world context of populations that have a disproportionate impact of health burdens.

Future Needs and Themes

Speakers were asked to comment on methodologies from other fields and the gaps and challenges of the current methodologies. The following suggestions emerged:

- Innovative trial design is needed. Most designs make assumptions of linearity and unidirectionality (e.g., progression of pathogenesis from health to disease); researchers need to design studies that address nonlinearity, including bidirectional processes such pathogenesis/salutogenesis, nonlinear grouping, grouping that can have partial membership, simple behaviors that have complex outcomes, and agent-based modeling.
- The field needs to create infrastructures that permit bridging across different disciplines. Cross-disciplinary methodological innovation needs to be encouraged early in researchers' careers.
- A paradigm shift away from traditional scientific perspectives of individual-level outcomes and randomized controlled trials is needed. NCCIH can take a leadership role. A highly specific request for applications might force reviewers to accept nontraditional methodologies.
- Research efforts have tended to separate the biological from the social and behavioral, but the problems people care about almost always transcend those areas and involve mechanisms that cross or bring together levels of scale. Crossing this divide requires dedicated funding.

- More feasibility studies are needed to inform future studies.
- Methodologists could advance research by releasing information about their methods in a way that others can use them without assistance.
- Cross-national studies can increase understanding of differences within populations. Researchers need to find ways to leverage global research to understand outcomes and the evolutions of those outcomes.
- Flexibility in methods and designs is needed and proposed funding mechanisms should be flexible as well.

Recurring themes raised during the 2 days included:

- Focusing on a single disease, condition, or body part will not solve the major health problems in the United States.
- Although correlation does not equal causation, correlations can provide clues to complex relationships within a system that might be affecting many types of outcomes.
- An intervention developed without using a systems approach may be a temporary solution, be unsustainable, ignore follow-up effects, have unintended consequences, and waste time, effort, and resources.
- Data need to be curated, organized, and analyzed in a useful way. Failing to understand the complexity of data can lead to bias and inaccurate conclusions.
- Standard research methods may not be useful in all situations. Studies that have multiple components and outcomes may require more complex methodologies. Some studies require a top-down approach that examines patterns and associations, but others may need a bottom-up approach that examines the mechanisms that make up the system. Computer modeling can be used to help understand and address complex systems.

In conclusion, research on complex systems, that is, whole person research, requires specialized methods and approaches. No single method or approach will apply to multiple systems or resolve all the issues within one system. However, different methods and approaches can be used together to help uncover different parts of the system. To better leverage different types of methods, a hybrid connectors, glue, and mortar approach is needed. This approach involves breaking down the separation of research fields and finding people, organizations, and even funding mechanisms that can serve as connectors across disciplines. These connectors work together as the glue to holistically address research questions.

Researchers investigating whole person health can coexist because there is a role for everyone. To advance the whole person research field, people and organizations need to understand that systems are complex, and they need to work collaboratively to learn about those systems and develop advantageous and equitable interventions.