Applications of Systems Science in Biomedical Research Regarding Obesity and Noncommunicable Chronic Diseases: Opportunities, Promise, and Challenges[1–4]

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ABSTRACT

Interest in the application of systems science (SS) in biomedical research, particularly regarding obesity and noncommunicable chronic disease (NCD) research, has been growing rapidly over the past decade. SS is a broad term referring to a family of research approaches that include modeling. As an emerging approach being adopted in public health, SS focuses on the complex dynamic interaction between agents (e.g., people) and subsystems defined at different levels. SS provides a conceptual framework for interdisciplinary and transdisciplinary approaches that address complex problems. SS has unique advantages for studying obesity and NCD problems in comparison to the traditional analytic approaches. The application of SS in biomedical research dates back to the 1960s with the development of computing capacity and simulation software. In recent decades, SS has been applied to addressing the growing global obesity epidemic. There is growing appreciation and support for using SS in the public health field, with many promising opportunities. There are also many challenges and uncertainties, including methodologic, funding, and institutional barriers. Integrated efforts by stakeholders that address these challenges are critical for the successful application of SS in the future. *Adv Nutr* 2015;6:88–95.

Keywords: systems science, obesity, noncommunicable chronic diseases, models, child, simulation, intervention, policy

Introduction

The interest in the application of systems science (SS)[7] in biomedical research, particularly with regard to obesity and noncommunicable chronic disease (NCD) research, has grown rapidly over the past decade, especially due to the rapidly growing global obesity epidemic (1). The recent US Institute of Medicine report, "Bridging the Evidence Gap in Obesity Prevention," calls for a "systems perspective" to informed decision making (2). Obesity and NCDs are a serious growing threat to global health. They share many common biological, behavioral, and social risk factors that are complex and interact with each other, thus affecting the conditions. Effective and sustainable management and prevention of such diseases need to involve many sectors of society. SS will help us to better understand the dynamic complexities of obesogenic systems with which public health issues are involved and offers useful insights for fighting the growing global epidemic of obesity and NCDs.

This article provides an overview of the applications of SS in biomedical research, with a focus on obesity and NCDs, and discusses the promise, opportunities, and challenges. Some projects are described as examples. This article will guide interested researchers in understanding some of the key basic concepts and some new developments in the field.

Opportunities and Promise—SS and Biomedical Research

"Systems science" is a broad term referring to a family of modeling approaches that aim to elucidate the behavior of complex systems and to inform efforts that address one or

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[7] Abbreviations used: EPODE, Ensemble Prévenons L'Obésité Des Enfants; NCD, noncommunicable chronic disease; SA, systems approach; SS, systems science.

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more problems manifested in a system or system of systems. An SS approach appreciates the structure, complexity, nonlinearity, context, dynamic nature, and emergent phenomena associated with the problems under study. It views issues, phenomena, causes, and effects in a holistic manner rather than through a purely reductionist lens. SS promotes gaining insights into the whole by understanding the looped linkages and dynamic interactions between the elements that comprise the whole "system." SS methodologies enable investigators to examine the dynamic interrelations of system components, which may span multiple scales of analysis (e.g., from cells to society) while simultaneously studying the behavior of the system as a whole over time (3–5). SS provides useful insights for studying and addressing complex problems and challenges affecting public health, such as obesity and NCDs.

SS provides a conceptual framework for interdisciplinary and transdisciplinary approaches. In using these approaches, "team members not only combine or juxtapose concepts and methods drawn from their own different fields, but also work more intensively to integrate their divergent perspectives, even while remaining anchored in their own respective fields.... Team members representing different fields work together over extended periods to develop shared conceptual and methodological frameworks that not only integrate but also transcend their respective disciplinary perspectives" (6).

It has been demonstrated that developing and implementing sustainable policies are critical to the success of public health efforts, such as reducing infectious diseases, tobacco use, and obesity prevention and control. Key policy shifts or other interventions will affect each stakeholder involved (e.g., food producers, distributors, and consumers) differently, and each stakeholder has a different sphere of potential influence as an agent of change. Without taking into account the complex relations and interests of these stakeholders, policies cannot leverage potential synergies and face the risk that well-intentioned interventions in one area may be counteracted by responses elsewhere in the system, i.e., policy resistance or counterintuitive system behavior. SS provides a useful conceptual framework to help consider and study such complex issues, including the dynamics and interactions between the various factors.

Figure 1 provides an example of the complexity of obesity in a systems dynamic framework. It depicts the complicated mechanisms implicated in the obesity epidemic, such as the roles of food prices, social networks, genetics, neurobiology, environment, and social norms toward eating, physical activity, and obesity. The population dynamics (7) were also incorporated in the framework.

Promise of SS for Biomedical Research Including Obesity and NCD Research

As an emerging approach adopted in public health, SS focuses on the dynamic interactions between agents and subsystems defined at 3 different levels: micro, meso, and macro (**Figure 2**). At the micro level, the major research focuses on exploring

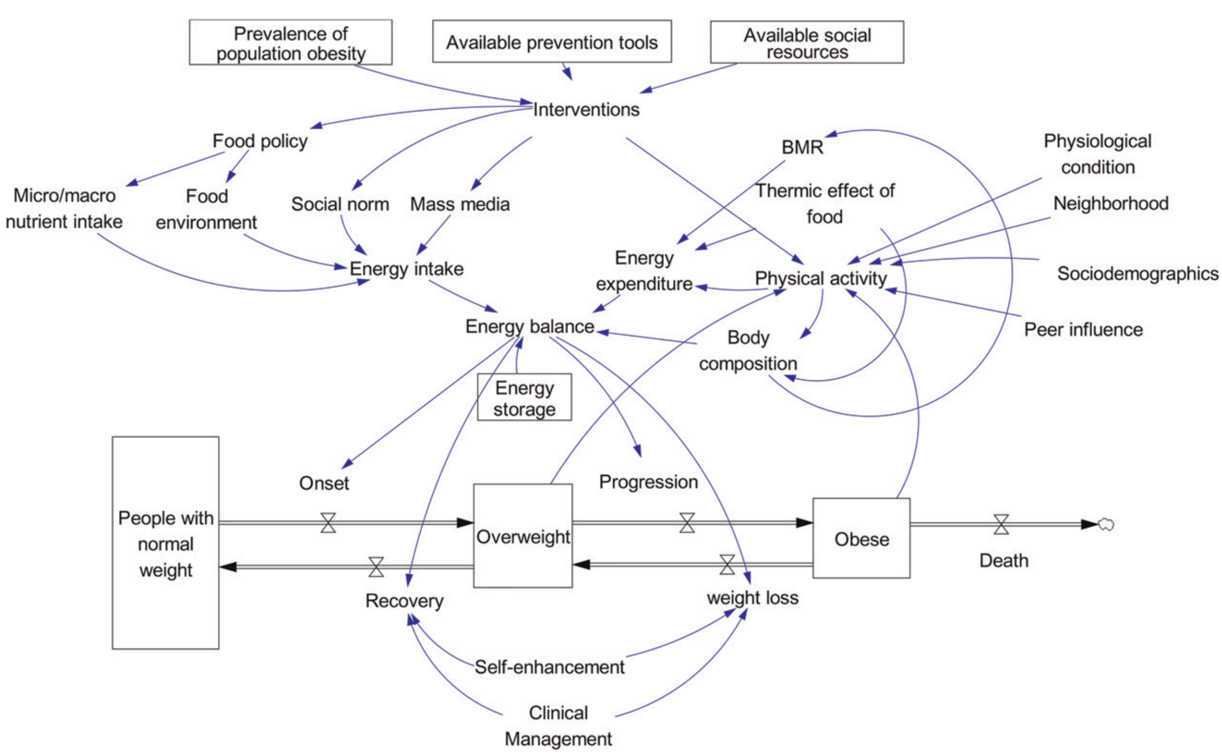

FIGURE 1 Complex obesity etiology and population dynamics: an example of the complexity of obesity in a systems dynamic framework. The rectangles represent the stocks or states of the variables; the arrows indicate potential casual relations; the pipes represent the flows in and out of the stocks; the valves represent the flow rates; and the cloud represents the destination of the flow. The diagram borrowed some concepts from reference 7.

the emergent properties of cells, tissues, and organisms (8–12). With a better understanding of the system structure complexity and dynamics at this level, researchers and practitioners are able to observe and illustrate the emergent behaviors at the meso level such as individual health and the impacts of genetic heritage on disease. At the macro level, with in-depth understanding of people's behavior and their interactions with their epigenetic environments, policy makers can begin to understand why some interventions fail while others succeed in reversing vicious cycles (13–16). Having understood the system structure at the macro level, policy makers and decision makers can better understand the dynamic impact of their proposed interventions and implementations on individuals (17–20).

There has been rapidly growing interest in SS methodologies among the behavioral and social science research communities in the past decade. A 2010 Institute of Medicine report (21) stated that the pathways between the social, economic, and environmental causes of poor health are complex and interconnected. The report recommends that the US Department of Health and Human Services coordinate the development, evaluation, and advancement in the use of predictive and systems-based simulation models to understand the health consequences of underlying determinants of health and to use modeling to assess intended and unintended outcomes associated with policy, funding, investment, and resource options.

Over the past decade, the CDC and the NIH supported the application of SS in NCDs and obesity-related research. The NIH is the world's largest supporter of biomedical, behavioral, and social science research and training. Several institutes and centers at the NIH support SS-related research through specific program announcements [PAR-13-374, Modeling Social Behavior, and PAR-11-314, Systems Science and Health in the Behavioral and Social Sciences (R01)], requests for applications, and investigator-initiated mechanisms. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the Office of Behavioral and Social Sciences Research have played key roles in promoting the applications of SS methods in obesity research since the late 2000s (see below).

SS approaches have also received growing support in the international health community. The International Council for Science recently released a Scientific Plan on Health and Wellbeing in the Changing Urban Environment: A Systems Approach. It argues that the behavior of a complex system cannot be understood or reliably improved by studying the behavior of its parts in isolation and suggests much better results would be obtained if the system is viewed as a dynamic, interactive whole (22).

Strengths of SS Approaches for Obesity and NCD Research

Systems approaches (SAs) offer unique advantages for studying complex problems such as obesity and NCDs in comparison to traditional analytic approaches. **Table 1** summarizes the main strengths of applying SAs in obesity and noncommunicable chronic disease (NCD) research. Individuals' energy balance–related behaviors occur not in isolation but as a function of the interactions between individual-level factors and their broader context. This requires researchers to simultaneously consider, examine, and address the whole wide range of biological and socioenvironmental drivers of the target outcomes (i.e., drivers ranging from genes to policy) in order to fully understand the underlying mechanisms and causes and to develop effective and sustainable interventions (23–25) (**Figure 3**). The complex causal loops and feedback relations between exposure and outcomes, including desired and unexpected outcomes, and interpersonal influences/interactions that

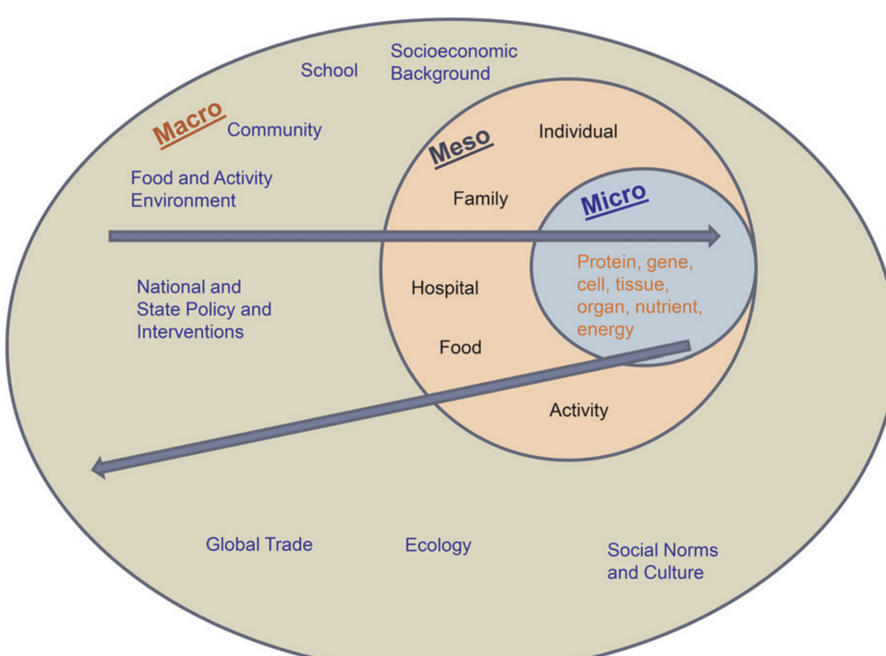

FIGURE 2 Systems science research at different scales.

TABLE 1 Strengths of applying SAs in obesity and NCD research[1]

1. SA as a novel nonreductionist approach (Figure 3)
• SA, as the opposite of reductionist methodology, holds a nonreductionist view of science, which enables researchers and policy makers to observe both the leaves of a tree (analytical approach) and the whole forest (systems thinking) as well. Therefore, systems analysis provides the mechanisms that help us understand emergent phenomena, in which the emergence is more than the sum of subsystems that produce it.
2. SA as a powerful structure and dynamic complexity study tool kit
• SA enables observers to explore behaviors at a higher level of hierarchy through studying structures anchored at lower levels in the hierarchy. This helps unfold the black box, which is intentionally ignored in traditional regression analysis, because systems behavior is determined by systems structure. Emergence of behavior can also be observed with changes in the system structure due to interventions implemented.
• SA helps explore dynamic complexity instead of combinatorial complexities, which is desirable because complexities come from the interactions of agents, subsystems, a family of systems of complex health, or biological systems.
3. SA as an innovative solution to tackle complex obesity problems
• SA integrates related factors in a system and focus on the whole obesogenic environment affecting the childhood obesity epidemic. Most previous studies in the field have only focused on some selected factors in the epidemic, chosen for analysis on the basis of theories and evidence.
• SA allows for nonlinear and circular causality: e.g., obesity causes reduced PA, which causes further weight gain. However, traditional regression-based analyses only allow for linear causality, e.g., reduced PA causes weight gain.
• SA allows for feedback loops: e.g., children's overweight status may promote changes in parenting styles, then affect child eating and PA behaviors, which, in turn, may result in child weight loss.
4. SA as a convenient and cost-effective policy simulation platform
• SA allows simultaneous changes in a variety of factors and examines the effects of those systematic changes.
• SA and simulation enable researchers and policy makers to observe the simultaneous changes in multiple variables that manifest in important health issues; some of them would have been assumed to be constant in traditional research.
• SA renders a dynamic scenario analysis possible and makes it easier for policy makers to test their assumption and policy proposals, given the often very limited data available before implementations can be made.

[1] NCD, noncommunicable chronic disease; PA, physical activity; SA, systems approach.

are relevant to childhood obesity cannot be demonstrated by using conventional statistical models. A number of related challenges demonstrate that traditional analytic approaches are inadequate to address the obesity problem, whereas SAs offer new insights and unique opportunities.

History and Growth of Applications of SS in Biomedical Research

Systems biology. General systems theory was founded by Ludwig Von Bertalanffy as an interdisciplinary practice applied to open systems such as growing organisms. This system fills the void that classical laws of thermodynamics cannot elucidate because they only work for closed systems (26). Along with his contribution to theoretical biology, Von Bertalanffy pioneered the development of modern systems bioscience (26). Kamada (27) put forth a theory and practice of systems biomedicine in 1992. Thereafter, Zieglgänsberger and Toile (28) proposed the concept of systems biology. In 1994, Zeng developed the concepts of systems bioengineering and systems genetics (29–31).

Growing applications. The application of SS in biomedical research dates back to the 1960s with the development of computing capacity and the necessary simulation software. Research was initiated and bolstered by using SS tools in modeling systems from the micro, cellular level through the macro, socioeconomic level and the impacts of these various systems on population health and health disparities. There have been an increasing number of studies on health-related issues using SS models since the 1960s. However, often the studies found it hard to get a hearing through publication in top journals in the biomedical field. Fortunately, as **Figure 4** shows, the number of publications regarding systems biology has being increasing rapidly since 2003, in fact, at a rate much faster than that for the total publications included in the PubMed database (32). The SS tools widely used include system dynamics modeling (with a focus on populations, but not on individuals), agent-based modeling (individual-based modeling or rule-based simulation), social network analysis, discrete event simulation, Markov chain, and soft systems (holistic and conceptual system analysis) (6).

We recently searched publications published until 2013 on modeling health-related issues by using SS models and identified a total of 2677 articles. Preliminary analysis indicated an increase in the number of published articles in recent years and that the studies used different SS methods. More than 61% of the studies used network analysis methods that first started in the early 1960s, ~5% used system dynamics models, approximately one-sixth used discrete event simulation, and approximately one-sixth used agent-based models (**Figure 5**).

Different SS methods have been used in the public health field to help establish policy and intervention agendas. With the objective of observing heterogeneous behavior change, agent-based models were extensively used to explore interactions between individuals and their impacts on the interacting agents. Research in this regard has included but has not been limited to topics such as substance abuse and influenza epidemics (33–35). Aggregate behaviors of population-level interventions were produced and examined by using a system dynamics model to evaluate the dynamics of the population being affected. SS is also useful in evaluating the outcomes of interventions under the condition of constrained resources (36–38). To pinpoint the right targets for the sake of implementing more efficient and cost-effective interventions, social network analysis has been used to identify leading cause factors and major players in complex networks. Related research in this area has covered epidemic contact investigations, substance abuse, hospital networks, etc. (17, 39–42). With regard

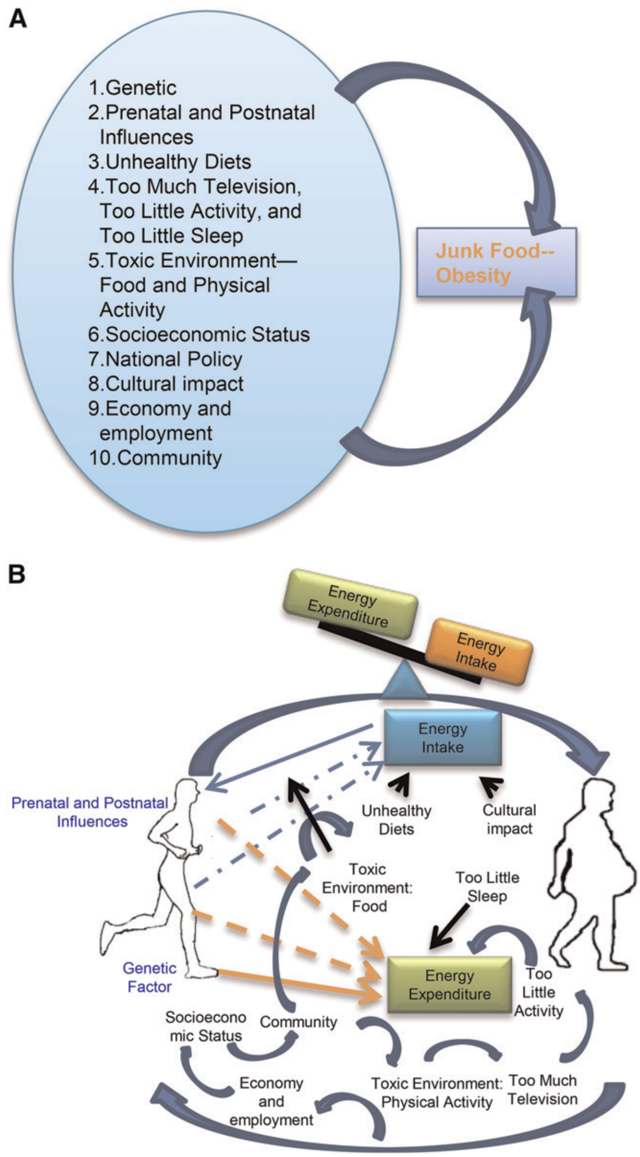

FIGURE 3 Reductionist (A) versus Non-Reductionist (B) Research Paradigm: the key drivers (risk factors) and prevention of obesity.

to the application of SS in cancer research, discrete event simulation was used to evaluate the performance of treatment for cancers (43, 44). Markov modeling was used to study the treatment of breast cancer (45).

Other noticeable applications of SS in public health research include the following: a systems dynamic model for diabetes prevention (36), the National Cancer Institute–funded project for tobacco control, the Initiative on the Study and Implementation of Systems system dynamic models for tobacco control (46), and the NIH- funded Models of Infectious Disease Agent Study (MIDAS) project (24).

Recent Large Projects Related to Childhood Obesity Interventions Using SS Methods

Over the past decade, SS has been applied to studying the growing childhood obesity epidemic. This effort started in Europe and the United States. To our knowledge, its application in other countries has been limited thus far.

The United Kingdom Foresight Project Tackling Obesities—Future Choices Project. The project was sponsored by the United Kingdom Department of Health, involved >300 experts from a wide range of disciplines, and was overseen by a large stakeholder group. The project gathered scientific evidence across a wide range of disciplines to form a strategic view of obesity. The project had the following objectives: *1*) use the scientific evidence base from across a wide range of disciplines to identify the broad range of factors that influence obesity, *2*) create a shared understanding of the relations between the main factors influencing levels of obesity and their relative importance, *3*) build on this evidence to identify effective interventions, and *4*) analyze how future levels of obesity might change and the most effective future responses.

The US National Collaborative on Childhood Obesity Research Envision Project. This project aims to use SS and statistical models to address obesity research questions. Primarily funded by the NIH with additional funding from the Robert Wood Johnson Foundation, it has funded several teams to develop statistical, computational, and SS models to help predict the impact of policies and interventions on childhood obesity. The National Collaborative on Childhood Obesity Research (NCCOR) Envision Project is a collaboration between the CDC, the NIH, the Robert Wood Johnson Foundation, and the USDA to accelerate progress on reversing the epidemic of childhood obesity in the United States. As part of the NCCOR's effort to build capacity for multilevel, integrated research, members examine the effects of individual, sociocultural, economic, environmental, and policy forces on children's diet, physical activity, energy balance, and body weight. Launched initially with a group of researchers from the United States, Canada, the United Kingdom, and Australia, Envision has brought together >50 leading modelers worldwide, including those from our research team.

The NIH–funded Systems-oriented Pediatric Obesity Research and Training Global Center of Excellence. In 2011 the NIH funded the Systems-oriented Pediatric Obesity Research and Training (SPORT) center based at the Johns Hopkins University with participation from multiple United States and international institutions via a $16 million U54 Center contractual agreement award sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the NIH Office of Behavioral and Social Sciences Research. The center, led by Dr. Youfa Wang, was named as the Johns Hopkins Global Center on Childhood Obesity—Where Systems Science Meets Public Health. The U54 initiative was designed to foster innovative systems-oriented research, fight against the growing global childhood obesity and NCD epidemic, support interdisciplinary and international collaborations, develop new SS methodologies for obesity and NCD research, and help train a new generation of systems-oriented researchers, policy makers, and public

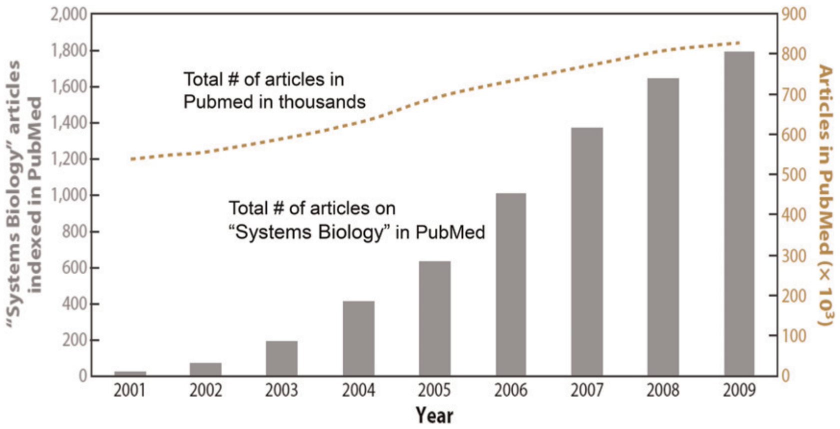

FIGURE 4 Over time increase in the number of publications using "systems biology" compared with total articles in PubMed during 2001–2009. The gray bars show the number of articles indexed in PubMed per year that were labeled with the medical subject heading (MeSH) "systems biology"; as a reference, the gold dashed line shows the number of total articles indexed in PubMed per year. Adapted from reference 32 with permission.

health professionals. The center supports 3 key research projects based in the United States and China and other pilot project programs. Additional training programs are also supported by the NIH U54 Center grant. This initiative provides researchers from multiple institutions worldwide with research, training, and funding opportunities.

The EPODE International Network. To our knowledge, the Together Let's Prevent Childhood Obesity Enfants [Ensemble Prévenons l'Obésité Des Enfants (EPODE)] International Network is the world's largest obesity prevention network for childhood obesity (47). EPODE is a not-for-profit organization created on 7 April 2011 in Brussels, Belgium. EPODE embodies a community-based approach to aligning community interests and creating a coordinated and mutually reinforcing set of strategies to tackle healthy eating, active living, access to preventive care, and health-promoting policies. EPODE has led to a 10–22% decrease in the prevalence of childhood obesity in communities in France and Belgium in recent years. In May 2014, EPODE announced the launch of an innovative project to scale up efforts to prevent childhood obesity across Europe. It aims to reach almost 4 million people across Europe, including 975,000 children and adolescents, with the goal of helping individuals and communities achieve and sustain active, healthy lifestyles.

Challenges of Using SS in Obesity and NCD-Related Research

Although the promise of SS application is great, there are many challenges as well. A serious challenge is the lack of research funding. Although the NIH has released some funding announcements over the past decade, often applications that propose using SS methods are not favorably reviewed or funded because of suspicions of the validity of the methods and the challenge for expert reviewers to fully understand the methodology and content issues. The challenge arises because building SS models depends on many decisions made by modelers and SS models need much more data than do the conventional statistical models. However, with the availability of systemic big data and the feasibility of collecting the data, SS models would tend to accurately map the virtual world with reality. It enables policy and decision makers to develop and identify more operable interventions to help improve existing systems. Combining big data with SS forms a new paradigm. Training more researchers who understand both SS and content issues will help overcome the challenge.

Another serious challenge is the validity of SS methods and results, which is a result of many factors such as the limitations of current SS methods and the lack of available data to fit the models. There is also the challenge of teaming researchers from related fields to work together effectively with SS modelers. Often, the content expert may not understand the SS concepts, methods, and assumptions needed in fitting the models or how to interpret the related results. The SS modelers may not have knowledge of the needed content background. The tunnel views of traditional methodologies

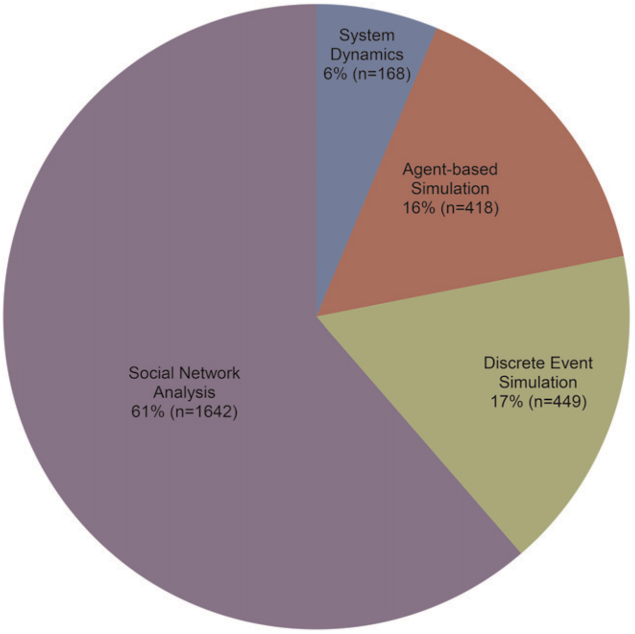

FIGURE 5 The use of dynamic simulation tools in health-related research. The chart shows statistics on articles published in peer-reviewed journals that used dynamic simulation methodology to model systems, manifested important issues, and evaluated outcomes of relevant interventions in biomedical and public health.

and experts have limited obesity- and NCD-related research using SS. The complex etiology of obesity and NCDs (e.g., compared with infectious disease and tobacco control) does make it more challenging to study with the use of SS methods. For these issues, group modeling is a potential solution. However, researchers may lack a common professional language, because they are trained in different fields (e.g., epidemiology, nutrition, public health, engineering, sociology, economics, and computer and information sciences).

The issue of publication is another challenge. Often, such articles are difficult to get published in mainstream journals in the researchers' fields. Even articles that are published in a good journal in one field may not be fully appreciated or valued in another field. This could compromise the researchers' career development, especially for young and junior researchers. For example, our research literature search indicated that for applications of system dynamics models in health-related research (although some mainstream health journals have published some such research), the acceptance rate (based on our experience and that of other researchers we consulted) is still very low. On the basis of our calculation, only ~15% of health-related studies applying system dynamics models were accepted, which is relatively low compared with those in other, non-health-related journals.

Young and junior researchers are the key players for such work because they can learn, understand, and use the new SS methods. Some senior researchers may be too busy to learn and use such methods, in addition to the fact that their previous training and research may have limited their openness to and understanding of the new SS methods. A more supportive environment is needed for the young people who conduct SS-related research in the biomedical field.

Conclusions

In conclusion, SS offers many promises for studying and addressing complex public health problems such as obesity and NCDs. There is growing appreciation and support for using SAs in related research, which results in many promising opportunities. However, there are also many challenges and uncertainties looming in the future with regard to the applications and funding support for using SS. A truly effective and insightful SA to studying and fighting the obesity epidemic requires more than just SS models using simulation or empirical data, or multilevel or multicomponent interventions. An effective SA appreciates the complexity of the problems and the importance of the synergies and interconnections across levels and among situational components and the various stakeholders. Obesity- and NCD-focused interventions based on systems thinking and design would value those synergies and interconnections that lead to structural changes underlying the behavior of the systems and individuals and will be more effective and sustainable in the long run.

Acknowledgments

All authors contributed to the study and approved the final version of the manuscript.

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