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Health and Disease—Emergent States Resulting From Adaptive Social and Biological Network Interactions

Joachim P. Sturmberg^{1*}, Martin Picard², David C. Aron³, Jeanette M. Bennett⁴, Johannes Bircher⁵, Mark J. deHaven⁶, Sanne M. W. Gijzel⁷, Henry H. Heng⁸, James A. Marcum⁹, Carmel M. Martin¹⁰, Andrew Miles¹¹, Chris L. Peterson¹², Nicolas Rohleder¹³, Christine Walker¹⁴, Marcel G. M. Olde Rikkert⁷ and René J. F. Melis⁷

¹ Faculty of Health and Medicine, School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia, ² Division of Behavioral Medicine, Department of Psychiatry and Neurology, The H. Houston Merritt Center, Columbia Translational Neuroscience Initiative, Columbia Aging Center, Columbia University Medical Center, Columbia University, New York, NY, United States, ³ School of Medicine, Weatherhead School of Management, Louis Stokes Cleveland VA Medical Center, Case Western Reserve University, Cleveland, OH, United States, ⁴ Department of Psychological Science, University of North Carolina at Charlotte, Charlotte, NC, United States, ⁵ Hepatology, Department for Biomedical Research, University of Bern, Bern, Switzerland, ⁶ Health and Human Services, College of Health and Human Services, University of North Carolina at Charlotte, Charlotte, NC, United States, ⁷ Department Geriatric Medicine, Radboud University Medical Center, Nijmegen, Netherlands, ⁸ Department of Pathology, Center for Molecular Medicine and Genetics, School of Medicine, Wayne State University, Detroit, MI, United States, ⁹ Philosophy and Medical Humanities, Baylor University, Waco, TX, United States, ¹⁰ Department of Medicine, Nursing and Allied Health, Monash Health, Melbourne, VIC, Australia, ¹¹ European Society for Person Centered Healthcare, London, United Kingdom, ¹² School of Humanities and Social Sciences, La Trobe University, Bundoora, VIC, Australia, ¹³ Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany, ¹⁴ Chronic Illness Alliance, Moonee Ponds, VIC, Australia

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*Correspondence:

Joachim P. Sturmberg
jp.sturmberg@gmail.com

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Health is an adaptive state unique to each person. This subjective state must be distinguished from the objective state of disease. The experience of health and illness (or poor health) can occur both in the absence and presence of objective disease. Given that the subjective experience of health, as well as the finding of objective disease in the community, follow a Pareto distribution, the following questions arise: What are the processes that allow the emergence of four observable states—(1) subjective health in the absence of objective disease, (2) subjective health in the presence of objective disease, (3) illness in the absence of objective disease, and (4) illness in the presence of objective disease? If we consider each individual as a unique biological system, these four health states must emerge from physiological network structures and personal behaviors. The underlying physiological mechanisms primarily arise from the dynamics of external environmental and internal patho/physiological stimuli, which activate regulatory systems including the hypothalamic-pituitary-adrenal axis and autonomic nervous system. Together with other systems, they enable feedback interactions between all of the person's system domains and impact on his system's entropy. These interactions affect individual behaviors, emotional, and cognitive responses, as well as molecular, cellular, and organ system level functions. This paper explores the hypothesis that health is an emergent state that arises from hierarchical network interactions between a person's external environment and internal physiology. As a result, the concept of

health synthesizes available qualitative and quantitative evidence of interdependencies and constraints that indicate its top-down and bottom-up causative mechanisms. Thus, to provide effective care, we must use strategies that combine person-centeredness with the scientific approaches that address the molecular network physiology, which together underpin health and disease. Moreover, we propose that good health can also be promoted by strengthening resilience and self-efficacy at the personal and social level, and via cohesion at the population level. Understanding health as a state that is both individualized and that emerges from multi-scale interdependencies between microlevel physiological mechanisms of health and disease and macrolevel societal domains may provide the basis for a new public discourse for health service and health system redesign.

Keywords: health, top-down and bottom-up causation, disease networks, complex adaptive nature of health, physiology of health, psychoneuroimmunology, health system redesign, emergence

Each culture must provide a more or less successful way of dealing with its environment, both adapting to it and changing it. Moreover, each culture must define a social reality within which people have roles that make sense to them and in terms of which they can function socially. Not surprisingly, the social reality defined by a culture affects its conception of physical reality. What is real for an individual as a member of a culture is a product both of his social reality and of the way in which that shapes his experience of the physical world.

Lakoff & Johnson—Metaphors we live by (p. 147)

Social and cultural influences distinctly shape people's perception of *health*. In the Western world *health*, *healthcare*, and the *healthcare system* mostly evoke images of *non-health*, i.e., pictures of personal *suffering* and/or disablement and threat of death from *diseases* like cancer, emphysema or heart disease. Unsurprisingly then the role of the *healthcare system* is seen as that of a *repair shop*.

However, these images are neither congruent with the epidemiology of health in the community (1–3) nor do they reflect the frequency of *clinical disease* detected in primary *health care encounters* (4–6) (**Figure 1**). Discovering incongruences between perceptions (i.e., mental models) and the physical reality necessitates the search for mental models that better reflect the realities of the *real world* (8–14). In this paper we explore *health*, and by implication *disease*, as an *emergent state*. Health, as an emergent state, is the result of the interplay amongst environmental, socio-cultural and economic-political contexts and internal biological potentials, each of which is organized in complex adaptive networks. This understanding of health has implications for health care delivery and health system redesigns.

TOWARD AN EMERGENT UNDERSTANDING OF HEALTH AND DISEASE

So far no attempt has succeeded to define health in a coherent way (15, 16). Health is a *state of the whole person*, consistent with the word's Old-English etymology of *hal* meaning *whole*.

The term *illness* refers to the state of *not being whole*, and needs to be distinguished from *disease* defined by the presence of identifiable pathology or dysfunction (17). We previously explored the notion of health and disease from our respective epistemological, genomic, network physiology, personhood, and social perspectives (18–27) only to find that none of them on their own appeared sufficient to explain the observed *patterns and variations* in distribution of health and disease at both the subjective and objective level.

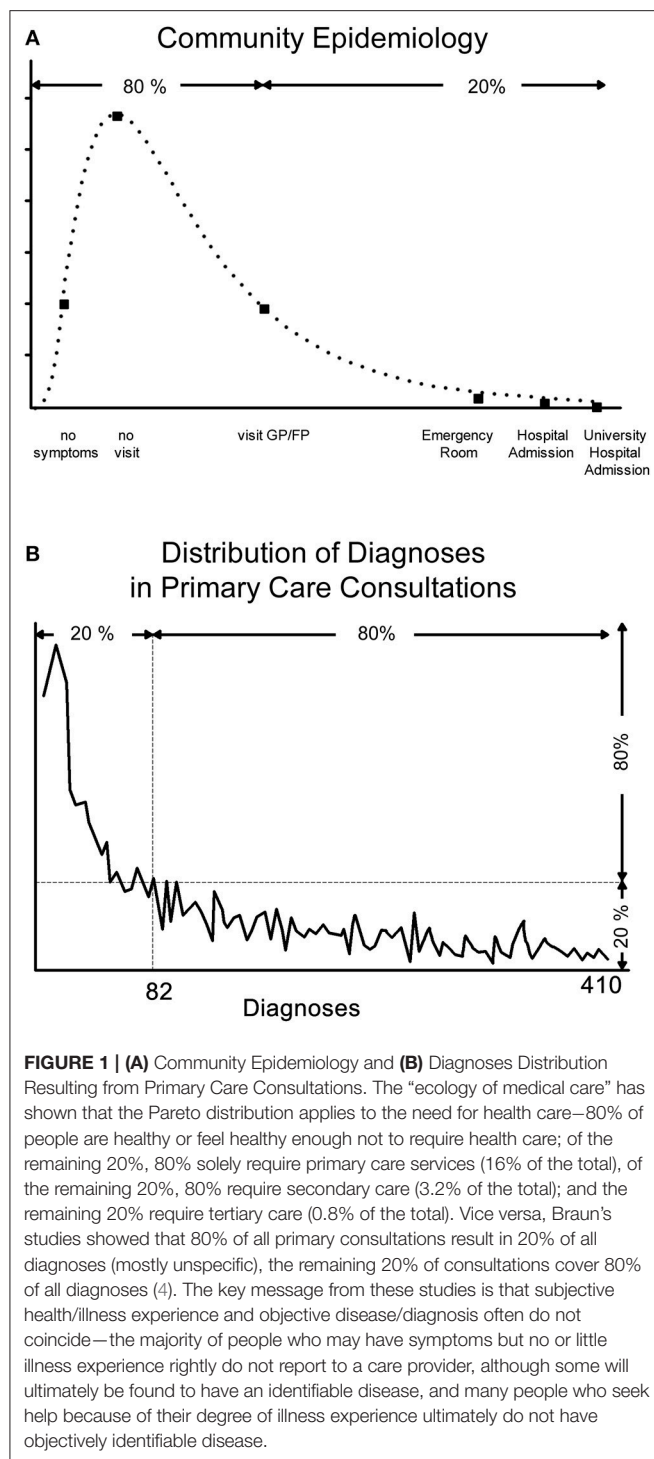
We suggest that this inability to reduce health to a single construct driven by a single bottom-up mechanism, or a combination of mechanisms, is due to the fact that health is an emergent property of a complex, dynamic, and adaptive system (28). What distinguishes living complex, dynamic and adaptive systems from non-living inert systems is the fact that the behavior of the former are not predictable based on a given set of measurable features. These systems are therefore said to behave *non-linearly* and to exhibit, as a whole, emergent properties that cannot directly be understood based on understanding their individual parts (see **Box 1** for explorations of key complexity terms).

Non-linearity and Emergence in Biological Networks

George Ellis (29) emphasized that “[t]he basis of complexity consist of modular hierarchical structures, leading to emergent levels of structure and function based on lower level network [function].” In other words, top-down actions provide contextual constraints that limit the possible bottom-up actions.

These characteristics have also been observed by West (30) who showed that organisms exhibit remarkably simple and systemic scaling laws that describe their complex structures and physiological functions across multiple physical and temporal scales. This limits the rate with which resources can be provided to sustain cellular and organ function (30, 31).

In terms of health, biology provides the common bottom-up blueprint to build anatomical structures and physiological functions, while environmental and socio-cultural top-down constraints limit the emergence of possible health states.



Health states, which can be both defined subjectively as health experiences and objectively as taxonomies of disease, thus are not static but rather *dynamic emergent whole person phenomena*.

Dynamic physiological network responses to perturbations provide adaptive *homeostatic dynamics* (32) that allow a person to transition to different *stable health states* across the life trajectory and the inevitable accumulation of diseases and frailty (33–35).

Emergence of Health (as Well as Disease)

Two features support the view that health is an emergent phenomenon. First, health is inherently related to the interconnected nature of *fractal* anatomy and physiology (30), and second, health is influenced by the layered hierarchical nature of interdependencies between the environmental and socio-cultural environments at the largest scale, personal behaviors at the intermediate scale, and molecular and physiological factors at the smallest scale. Furthermore, health and illness are also subjective states and this additional dimension needs to be distinguished from the objective taxonomic finding of disease. In particular, health can be experienced both in the presence as absence of objective disease. The latter is true exactly for the fact that a human being—as described in the previous paragraphs—is able to adapt to new situations with a *restoration* of experiencing health despite objective loss of function or accumulation of physical, emotional, social, and/or cognitive damage.

Rothman’s (7) exploration of *multiple different combinations of sufficient causes* resulting or preventing the occurrence of manifest disease supports the non-linearity that underpins the emergent nature of health. Diseases themselves, especially chronic age-related diseases with a multifactorial nature can also be best explained by this component cause model. The model can, however, also be helpful to understand (dis)congruence of illness and disease states (**Figure 2**). In many situations disease presence and illness experience coincide as diseases are obviously an important *component cause* amongst the many *multiple sufficient causes* that trigger the illness/health experience.

However, we contend that there will also be *sufficient causes* for illness experiences where objective disease is not a *component cause*, i.e., disease presence is not a necessary cause. Vice versa, there may be several *component causes* which *neutralize* the presence of objective disease in their combined impact on the illness experience, i.e., these combinations of factors result in the situation where objective disease is not accompanied by a profound illness experience and thus perhaps—depending on the definition—lack of health.

These introductory remarks expand on Engel’s biopsychosocial model of health (36, 37) and build on the implicit and explicit ideas on the *dynamic nature of health* by von Uexküll and Pauli (38), McWhinney (39), Bircher (40), Bircher and Kuruvilla (41), Sturmberg (15, 16), and Huber et al. (42). We propose that

- Health is a *system state* unique to each and every individual arising from the network dynamics of his internal physiological function, external physical and social environments and the ways of making sense of one’s experiences.
- Health is also the state that allows one to adapt to changing circumstances and demands that challenge the entropy of the system.

Embracing the theoretical framework of network relationships and dynamic interactions amongst the multitude of different factors impacting on health as a systems state, we describe—in the sense of a hypothesis—how any of four different health states

BOX 1 | Key complex adaptive system concepts.

Complex adaptive system—complex systems whose elements (or agents) learn and adapt their behaviors to changing environments through self-organization, i.e. without external control. Self-organization arises from internal feedback and underpins emergence.

Dynamic systems, by their very nature of constant activity, are never in exactly the *same state*. Over time they can emerge into a different state (like a person can be healthy, develop appendicitis and being sick, being in recuperation, before returning back to being healthy), or they may permanently change into a new and different state (like a person being involved in a car accident that makes him an amputee, a paraplegic or a person with a brain injury).

Emergence—the ability of individual components of a large system to work together to give rise to unexpected new and diverse behaviors that are not present in or predictable from its individual components.

Networks/Network Sciences—study of complex networks of any kind, agents/actors are represented as nodes, their links as edges, network sciences produce predictive models of the behavior of complex networks.

Non-linearity—the response to a stimulus is not proportional to its input which can lead to sudden massive and stochastic changes of a system's behavior. Non-linearity is one of the reasons that explain the inherent uncertainties in complex adaptive systems. A typical non-linear distribution curve in biological and social systems is the Pareto distribution, also known as the 80:20 split (see examples in **Figure 1**).

Pareto distribution—also known as the 80:20 split, describes the power-law (non-linear) distribution of observable phenomena in biological, social and other systems.

Readers interested in the historical developments of systems and complexity sciences should refer to the historical texts of Ashby, von Bertalanffy, Bak, Capra, Gell-Mann, Hollands, Jansh, Kauffman and Prigogine and Stengers.

can emerge *clinically in seemingly the same* circumstances—(1) subjective health in the absence of objective disease, (2) subjective health in the presence of objective disease, (3) illness in the absence of objective disease, and (4) illness in the presence of objective disease.

We also discuss how health experiences across the life span, socio-economic strata, and cultural norms reflect a human's adaptive capacities.

The dynamic adaptive behavior of the networks of a complex adaptive system results in variable and non-predictive outcomes—here four different health states—and thus challenge the widely held belief of strict linear causal chains resulting in particular health outcomes.

HEALTH—A WHOLE PERSON STATE

Some degree of health is a prerequisite for life, and life—like health—occurs in an open thermodynamic system at the transition between an ordered stable and a chaotic disordered state (43–45) (**Figure 3**). The maintenance of health therefore necessarily entails constant energy flux through the system (46). Health as the state of *wholeness* in the narrow discontinuous window between these two thermodynamic states requires the ability:

- To have the required resources to meet and cope with the demands of life
- To respond to stressors arising in one's environment
- To maintain one's internal homeokinetic balance
- To adapt to losses in resources, stressors, and homeostatic instability
- To manage the gap between one's biological potential and life's demands.

These requirements entail that the *state of health* can only be achieved through continual dynamic responses, often non-linear, to all forms of challenges—biological, social, emotional, and/or cognitive—to the *person as a whole* (15, 16, 33).

HEALTH, ILLNESS, AND DISEASE—THE DYNAMICS OF WHOLE PERSON ADAPTATION

Personal health/illness experiences and personal diseases cannot be separated from each other—they are a *single whole person phenomenon*. This is most evident looking at the impact of age and disability, neither precludes the *experience of health*. For example, two thirds of the eldest people (85+ years) (47) as well as people with disabilities (48) still rate their health as good or better despite having an increasing number of *disease labels*.

While particular socio-cultural and environmental contexts constrain a person's system, recursive bottom-up physiological actions aim to control the cellular and organ functions that allow the person's system to emerge toward the experiential states of health and non-health (illness as the subjective experience, disease as the objective reason).

The Physiological System's Component

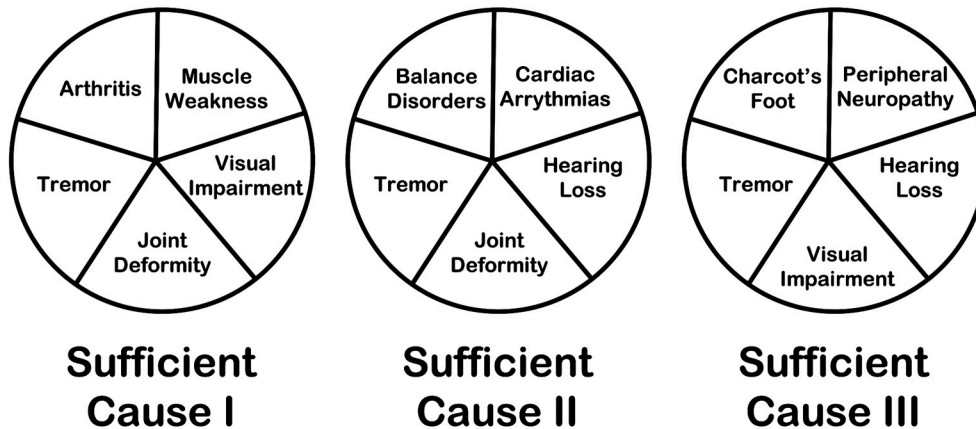
Mounting evidence indicates the prevailing linear reductive notion that diseases are caused by a single identifiable *cause* is no longer sustainable (12, 49). Rather, diseases emerge as a consequence of interactions among multiple physiological networks—in particular those that regulate gene networks (27, 50), activities of the autonomic nervous system (51) and the hypothalamic-pituitary-adrenal axis (HPA) (52, 53), as well as the bioenergetics within mitochondria in concert with other metabolic pathways (54, 55). These physiological networks are sensitive to changes in psychosocial and environmental parameters and thus may—through positive and/or negative feedback—either enhance health or contribute to the emergence of disease (see below).

The Role of the Genome

While genes as individual units provide the necessary information to produce the biological building blocks of

Rothman's Model of MULTIPLE SUFFICIENT CAUSES of Disease

A Falls in the Elderly



B Emergence of Health and Illness States

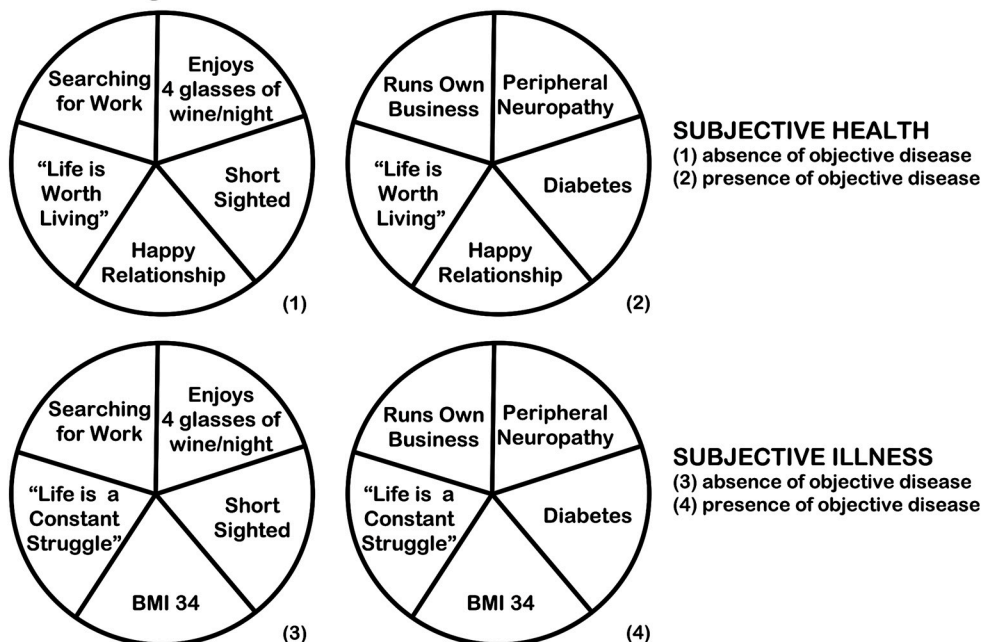


FIGURE 2 | Rothman's model of the "multiple different combinations of sufficient causes" of disease [adapted from Rothman (7)]. **(A)** Rothman's model of the "multiple different combinations of sufficient causes" illustrated in relations to "falls in the elderly." As Rothman explained: "A specific effect [a fall in the elderly] may result from a variety of different sufficient causes [three causes are illustrated]. The different constellations of component causes [Tremor, Joint Deformity, Visual Impairment, Muscle Weakness, Arthritis, Hearing Loss, Cardiac Arrhythmias, Balance Disorders, Peripheral Neuropathy, Charcot's Foot] which produce the effect may or may not have common elements. If there exists a COMPONENT CAUSE which is a member of every SUFFICIENT CAUSE, such a component is termed a NECESSARY CAUSE [in this case: only "Tremor" is a necessary cause]. [The figure suggests many synergistic relationships. For example, "[Arthritis]" and "[Muscle Weakness]" are completely synergistic with each other and each is partially synergistic with "[Tremor]," "[Joint Deformity]," and "[Visual Impairment]. Partial synergy exists between "[Joint Deformity]" and "[Visual Impairment]" — their effect is dependent on their joint presence in one sufficient cause, but each also has independent effects in another sufficient cause ["Joint Deformity" in Sufficient Cause II, "Visual Impairment" in Sufficient Cause III]."**(B)** Rothman's model can be applied to the EMERGENCE OF HEALTH and ILLNESS STATES in the presence and absence of disease. In the example "Life is Worth Living" and "Happy Relationship" are two components necessary for the emergence of the two "HEALTH STATES" (1) and (2), and "Life is a Constant Struggle" and "BMI 34" are two components necessary for the emergence of the two "ILLNESS STATES" (3) and (4).

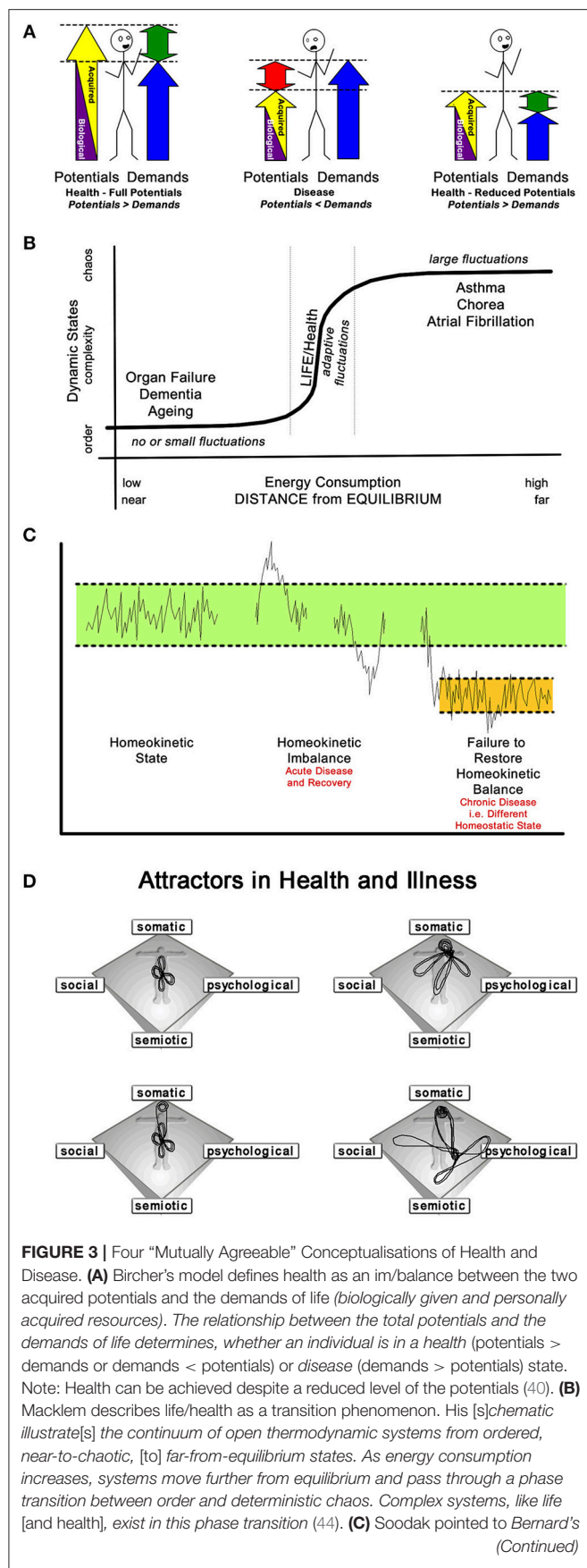


FIGURE 3 | Four “Mutually Agreeable” Conceptualisations of Health and Disease. **(A)** Bircher’s model defines health as an im/balance between the two acquired potentials and the demands of life (biologically given and personally acquired resources). The relationship between the total potentials and the demands of life determines, whether an individual is in a health (potentials > demands or demands < potentials) or disease (demands > potentials) state. Note: Health can be achieved despite a reduced level of the potentials (40). **(B)** Macklem describes life/health as a transition phenomenon. His [s]chematic illustrate[s] the continuum of open thermodynamic systems from ordered, near-to-chaotic, [to] far-from-equilibrium states. As energy consumption increases, systems move further from equilibrium and pass through a phase transition between order and deterministic chaos. Complex systems, like life [and health], exist in this phase transition (44). **(C)** Soodak pointed to Bernard’s (Continued)

FIGURE 3 | principle of the constancy of the internal environment (that is, homeostatic regulation, which may be both cyclic and adaptive) as the condition of free and independent life, is the first approximation to a theory of the organism. He suggested the new physical doctrine of homeokinesis as a second proximation to such a theory of complex autonomic systems. Recognizing the natural hierarchy of organizational levels allows a dynamic regulation scheme that allows the homeostatic persistence [to be] maintained by the action of chains of thermodynamic engine processes, [i.e., physiological interactions across all scales of human existence] (32). **(D)** Health, as an attractor, maintains a dynamic equilibrium over time. Thus, health cannot be “one” particular state, but rather a relative point in a phase space, i.e., health is a chaotic attractor. Three attractor patterns emerge; a health attractor around the center of the somato-psycho-socio-semiotic phase space, with illness, dis-ease, and [acute self-limiting] disease occur on “more distant orbits” of the attractor; a chronic disease attractor—here—centered toward the somatic corner of the phase space (but can be any other corner); and a “psychosomatic attractor” whose dynamics swap between two phase space areas, the physical and the psycho-semiotic (16).

cells and the organism, it is the genome, i.e., the gene network interactions, that encodes the system as a whole (27).

Recent evidence indicates that common and complex disease is rarely caused by specific gene mutations but rather by genome instability that manifest at the level of DNA methylation and changes in gene expression (27). The external environmental as well as internal physiological perturbations produced by stochastic or random genomic changes (27), rather than punctuated common genetic DNA mutations, are responsible for most diseases and their intra-person genome heterogeneity (27, 56, 57). Moreover, different cells may contain unique acquired genetic features in DNA sequence, DNA methylation, and protein expression (58, 59). These multiple cellular variants are essential for cellular adaptation during dynamic environmental change, but as a trade-off, they also contribute to disease (60).

Indeed, the links between the genome networks and the phenotypic disease networks, have been defined as the *diseasome* (50). The diseasome shows important genome-linked diseases and clarifies how and why certain diseases occur in clusters within the same person (50, 61).

The Role of the Autonomic Nervous System and Hypothalamic-Pituitary-Adrenal Axis Network

Selye (62) initially recognized that *irritating substances* initiate an immune response mediated by HPA-axis activation. He later recognized that external factors can also trigger the same immune response and influence health. He called these factors *stressors*, regardless of them being experienced in a positive or negative way. In addition, Porges demonstrated the integration of the multiple pathways of the vagal system in relation to stressors on organ function (polyvagal theory), visceral regulation, and emotional responsiveness (63, 64).

Stressors influence cellular function by modulating gene expression. The release of primary neuropeptides, neurohormones, and neurotransmitters leads to the production of hormones and cytokines (53), which influence the proteomic and metabolic network pathways. When dysregulated or

perturbed beyond the adaptive capacity of the system, stressors may ultimately result in the emergence of diseases (65).

At the experiential level, the brain incorporates the perception and appraisal of the current environmental experience (66). If an individual perceives greater coping ability (e.g., more resources or skills) than the situation demands, the body will likely mount an appropriate physiological response, meaning activation with quick recovery. However, if an individual decides their ability to cope whether conscious or subconscious is smaller than the demands of the situation, the interpretation leads to a loss of control—the importance of which has been highlighted by Antonovsky (67, 68)—or threat to self. This perceived threat may cause excessive activation of the stress systems and exaggerated parasympathetic withdrawal.

In a well-regulated body, sympathetic activation leads to elevated epinephrine/norepinephrine, promoting immune activity, in particular proinflammatory cytokine production (69–71). Following the stressor, unused bioavailable cortisol shuts of the neuroendocrine pathway as well as inhibits immune activity, in concert with increased parasympathetic activity (i.e., acetylcholine) as both can inhibit pro-inflammatory gene expression. Thus, during recovery, a well-regulated body critically restores the balance between the neuroendocrine and immune systems.

However, when a chronic stressor is perceived (72), this physiological recovery may not occur. Chronically elevated cortisol can lead to immune cells that become insensitive to cortisol (73). Hence, chronic stress can lead to the removal/reduction of both anti-inflammatory pathways, fuelling proinflammatory cytokine production that stimulates the stress systems—potentially creating a never-ending negative feedback cycle and multi-system dysregulation.

The Role of the Metabolic Networks

The mitochondrion regulates energy production as well as intracellular signaling and may be especially sensitive to the effects of elevated cortisol due to chronic stress (74). Mitochondria's morphology and function are altered by neuroendocrine mediators and metabolic changes associated with the stress response. If persistent, mitochondrial damage may lead to mitochondrial allostatic load (MAL) (55). MAL can trigger signaling cascades known to reduce energy production and overall capacity within the cell and influencing cellular gene expression as well as initiate extracellular damage by promoting pathogenic inflammation and altering the circulating metabolome (75). These changes yield broad ranging effects on cell-specific parameters (intracellularly) and whole organism function (systemically). Thus, mitochondria, by providing energy to animate and regulate these different regulatory networks, and via their role in cell and whole-body signaling (46) play a key role in the development of pathological changes across organ systems (54).

Mitochondrial dysfunction can cause organ-specific, as well as multi-systemic defects throughout the organism by increasing oxidative stress (54, 76). Symptoms of mitochondrial disorders often manifest simultaneously in the neuromuscular system causing exercise intolerance and myopathy, in the brain with stroke-like episodes and structural cortical and

sub-cortical anomalies, gut dysmotility and constipation, hearing and vision loss, and insulin resistance, among others (77, 78). Likewise, psychological stress and other psychosocial experiences may influence mitochondrial function via multiple neuroendocrine and metabolic mechanisms (74, 79), which influence neuroendocrine, metabolic, and transcriptional responses to acute stress (80). Therefore, metabolic activities within mitochondria may regulate cellular and organismal responses to environmental perturbations and thus contribute to generate individualized states of health or illness.

Responses to Stressors Is the Key to Understanding Health, Illness, and Disease

The amount of *stressors* has been defined as the quantity and severity of stressful events or stressors that contribute to an overall *allostatic load*. While short-term stressors promote adaptation in a constantly changing environment, persistent, and/or high levels of stressors contribute to enduring physiological dysregulation via neuroendocrine, autonomic, immune, and metabolic mediators (81). These perturbations result in epigenetic changes at the cellular level (82) and result in the accumulation of CNS or organ damage and ultimately leading to the emergence of phenotypic disease and increased premature mortality (26, 83).

Network Inter-organ Interactions—The Next Larger Spatial Scale

At the organ level, network interactions between different organs determine the phenotypes of health and disease (31). Indeed, the HPA axis is credited a central neuroendocrine role, as it has been shown to have key interface functions between the biological and psychosocial domains.

Moreover, the HPA axis is also designed to balance pro- and anti-inflammatory activities, and is the principle mediator and regulator between internal and external system perturbations (84, 85). In addition, there is cross-talk between the immune system and the brain; peripheral cytokines can stimulate the HPA axis (86), and induce illness behavior (87, 88) via indirect [e.g., the vagus nerve (63)] or direct (e.g., crossing leaky portions of the blood brain barrier) pathways (89, 90).

Considering the role of the HPA axis in inter-organ interactions within a network science framework, its *edges* and *nodes* have different values and directions. Because of these HPA-edges, CNS activation and cortisol—the principle output of the HPA axis—have the potential to influence almost every cell in the body, making them an integral feature in linking multiple physiological systems. While dysfunction in one organ system can stimulate the CNS and HPA axis and thus trigger dysfunctions in other organ systems, CNS and HPA axis dysfunctions themselves can affect peripheral bodily systems, with the consequence of “creating disease.”

Therefore, the HPA axis may play a special role in limiting or increasing the vulnerability of different organs, similar to those

describing the cascading failures in an electricity network (91). However, other organs may also play a similar pivotal role in the human organ network. The vascular tree is a space-filling and volume preserving structure; its fractal nature allows even blood flow across the network and connects organ systems (30). Its vascular edges supply organs with oxygen, nutrients and water, clear metabolic breakdown products, and signal consequences of distress in one part of the system across the entire network (e.g., by hormone transport) (31).

This network understanding of inter-organ interactions has resulted in empirical studies to support the complex adaptive network models that link human biology and psychosocial environment in health and disease (12).

The Environmental Impacts on Health and Disease—The Macro Scale

For the external—physical as well as socio-cultural and political—environment to affect health and disease over the life course (92), it has to cause perturbations of the internal physiology (29). The health effects of the external environment result from dysregulated neuroendocrine and CNS network functions as described, and if persistent have epigenetic consequences through gene regulatory effects as described by the emerging field of *social genomics* (53, 93, 94).

These fields of study provide the physiological rational to understand the overwhelming epidemiological evidence of *the macrolevel constraining* influences of socio-economic status on health (92). Poor education, housing, work conditions or underemployment, low income, social segregation, and racial discrimination, frequently coupled with personal lifestyle risk factors such as tobacco use, poor nutrition and lack of physical activity, dysregulate immunoregulation resulting in increased proinflammatory activity leading to disease formation and poor health (95–99).

HEALTH STATES EMERGE FROM INTEGRATED NETWORK INTERACTIONS

Each of the four health states—(1) subjective health in the absence of objective disease, (2) subjective health in the presence of objective disease, (3) illness in the absence of objective disease, and (4) illness in the presence of objective disease—emerges from integrated network interactions *between* and *across* the multiple scales of structure and function over time (a non-deterministic outcome). As all of these networks are interconnected within a complex adaptive system, they influence each other. This integrated network understanding explains the observations that even minor differences in environments, perceptions or biological function can lead to adaptations of health and/or illness experiences, and that they often overlap with the objective findings of disease/s (Figure 4). At a clinical level the degree of a person's *whole of system adaption* in light of these network dynamics is *clinically* measurable subjectively as *self-rated health* (35, 100–103) and objectively e.g., as *heart rate variability (HRV)* (104, 105).

CONSEQUENCES FOR HEALTH CARE¹ DELIVERY AND HEALTH CARE SERVICE DESIGN

The hierarchical modular nature of complex adaptive systems entails that every higher level provides the context, and thus constraint, for the behavior of its lower level components. Health is the *observable state* of top-down and bottom-up network interactions of a person's system components—from the small to the large-scale subsystems, from molecules to man, and beyond man to the socio-cultural and political context of his life. It is these relationships and interactions that make health a *whole person state*. Health, like the occurrence of disease, are emergent within the person but involve different system pathways and dynamics—it is the task of the health professional to untangle the pathways and dynamics for this *particular* patient.

If we want to achieve the best possible health for our patients and our communities we need to have the person and his health/illness experiences—regardless of the concomitant absence or presence of disease—at the center of the healthcare system (Figure 4) (106–110). Importantly, we must appreciate the importance of the constraining environmental and socio-cultural and political level contexts on the adaptive physiological mechanisms underpinning cellular and organ functions. Changing the context in which a system operates often shows greater effects than altering the way the fundamentals operate within the system. These insights have important implications for managing people/patients in the clinical encounter, as well as for all policies and their impact on health and the healthcare system at large (110).

Focusing Simultaneously on the Patient's Health Experience and His Disease

An understanding of the emergent dynamics with the “person as a system,” being constraint by his environment that limits the emergent possibilities of his biological function, demand an initial focus on the person's evaluation of their health [Antonovsky's salutogenic model (111)]. Pragmatically, asking: “*What are your goals for your care, and how can I help you?*” has been shown to open up this most important conversation (112), and to reveal the underlying dynamics resulting in his current health/illness state.

Managing diseases, mostly regarded as the essence of medical care, ought to be guided by the patient's goals and aspirations—not all of a person's diseases need every available biomedical intervention, and some interventions required to achieve a person's goals and aspirations will be out of the scope of the *traditional medical model* of patient care.

The context of care matters, as the epidemiology of health, illness, and disease have shown, most patients presenting to health professionals do not have acute life-threatening diseases. Those diseases are the ones that invariably benefit, in the short term, from the *traditional disease care model* interventions. The majority of people seeking health care, including those

¹Health care refers to the “delivery of care”, *healthcare* - as in healthcare system - means the “organizational institution.”

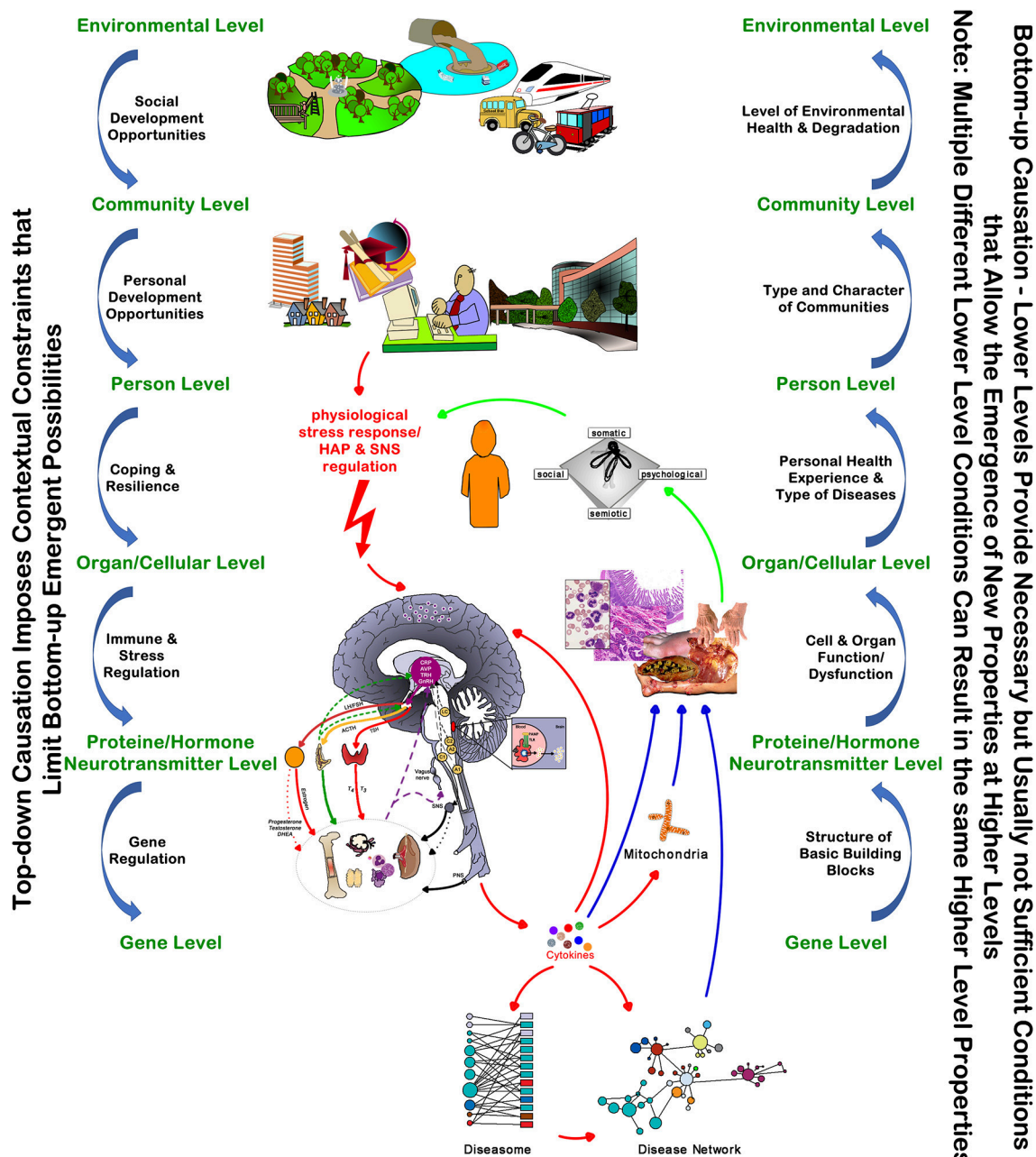


FIGURE 4 | The Top-Down and Bottom-Up Interdependencies of Health and Disease. The model highlights the key “networked” relationships between the external factors and internal mechanisms of the person’s health and illness experiences. ⚡ exaggerating effect.

having recovered from a life-threatening disease, require care that explores the network relationships resulting in the illness experience, and a *tweaking* of the *most influential* network nodes that constitute the person’s *system as a whole*.

In other words, optimal health outcomes—at the subjective and objective levels—are most likely to be achieved if the health state of the person is understood as an emergent property of their entire system, and if biomedical and psychosocial interventions go hand in hand. George Engel first outlined a system’s focused

approach to patient care (36, 37); however, three major obstacles impede this approach.

- First, the health system design, in educational, organizational as well as cultural terms, persists as an assembly of dependent units focused in a reductionist way on delivering care for acute problems or single diseases, unable to deal with complexities arising from the chronic sequelae of multiple co-occurring conditions.

- Secondly, medical practices are largely not designed to provide a *network for care*, and
- Thirdly most health systems fail to address the inequalities produced by both social inequalities (including political ideology and government policy) as well as those induced by the health financing system.

The Need for Health System Redesign

Understanding health/illness and disease as emergent network interaction presenting in one of four health states—(1) subjective health in the absence of objective disease, (2) subjective health in the presence of objective disease, (3) illness in the absence of objective disease, and (4) illness in the presence of objective disease—is a prerequisite for healthcare system improvement. These appreciations shift the redesign focus on three main issues.

- At the macro level, it must focus on the interconnected nature of the social, cultural, and economic-political factors influencing health and disease as the socio-cultural will become biological over the life course (92). In addition, the socioeconomic context has epigenetic effects that have an impact on the health of the next generations and is most detrimental for the most vulnerable portion of the population (113–116).
- At the meso level, it needs to create community partnerships to address disease promoting environmental factors.
- And, at the micro level, we must overcome the single organ focus and embrace the interconnected physiological networks of health and disease (110).

We need organizational redesign of health care services and healthcare systems to link health care professional interventions with personalized social support services and culturally sensitive community-oriented improvements of the physical social and economic infrastructure in local communities. This approach recognizes that health is a social outcome resulting from systematically combining clinical science, collective responsibility, and informed social action (117).

It also must address community priorities in partnership with community members, building on existing community assets while acknowledging the role of cultural factors, and providing evidence that can be used to mobilize and advocate for policies directed at reducing disease risk (118).

At the research level *health system redesign* needs to be supported by a shift in research priorities and funding (119, 120)—from pathogenesis to salutogenesis (120), from improving disease care to improving health care, health maintenance, health promotion and self-care (119), and from biomedical disease eradication to behavioral and social sciences approaches to disease prevention (99, 119).

How Might It Be Achieved—Suggestions to Start a Broad-Based Discourse

In practical terms, we require a shift toward a dynamic system appreciation of health at the individual and population level (110). To aid this conversion, a critical step will be to begin seeing individuals and their health behaviors as the

product of their negotiations and adaptations needed to survive in their life circumstances rather than laziness or lack of concern about their health/illness identity, i.e., exploring the pathways and dynamics leading to this person's health/illness state. This transition will require a modification in training of health and other service providers toward care delivery that integrates macrolevel (mainly environmental, socio-cultural, and political) to microlevel (mainly biological) elements in a person-centered way.

Empirical research at the nexus of hospital, community, primary, and social care indicates many challenges related to roles, responsibilities, and resources across public and private sectors. Ultimately, this is political—as Barbara Starfield stated: *primary healthcare is a “health equity-producing” social policy* (121).

CONCLUSIONS

A complex systems approach understands health and illness as the subjective and disease as the objective emergent states of the top-down and bottom-up interactions between the constraining environmental, socio-cultural and economic-political contexts and the recursive physiological and psychological interactions of cellular and organ function networks.

- The environmental, socio-cultural, and economic-political structures in which a person lives creates the contextual constraints for his internal physiology to realize itself.
- It is the degree of system stress and the inability of the organism to cope adequately, rather than the specific nature (environmental, socio-cultural, economic, political, metabolic) of the stress (122) that drives the overall system toward entropy and causes long-term cellular damage resulting in disease (27).
- The adaptive capacity of the organism and of the person is determined by interconnected energy-dependent biological, physiological, and social network processes that could be targeted to promote health.
- The physiological stress response loop relationship between CNS and HPA axis affects physical disease as much as emotional/cognitive functioning (26) and thus the nature of the socio-cultural and economic-political environment.
- Health and disease causality can be understood best in an adaptive system dynamics framework and in terms of *the life of the human organism* (as a biological object) and *the type of life a human organism is living* (as a person) (117).
- The etiology of both disease states and illness experiences can be best explained and visualized with the component (necessary and sufficient) cause model as developed by Rothman (7).
- The state of the physiological network integration between the physical, socio-cultural, economic, political, emotional, and cognitive domains (123–125) as well as the therapeutic effectiveness (126) can be assessed subjectively elucidating the state of self-rated health, and objectively by monitoring heart rate variability (HRV).

The outlined dynamics between the environmental/socio-cultural/economic-political/emotional-cognitive and biological domains explain the emergence of four observable patterns of health states—(1) subjective health in the absence of objective disease, (2) subjective health in the presence of objective disease, (3) illness in the absence of objective disease, and (4) illness in the presence of objective disease.

Healthcare providers must recognize that people live in socio-cultural, political, and economic systems that shape behaviors and influence access to the resources they need to maintain good health (97). Clinical management needs to be coordinated—ideally in a face-to-face manner—amongst all relevant providers (24) and to take into account the persons capacity to handle treatment regimens and self-management strategies (20, 127). The focus of treatment should be amelioration of and improved coping with stressors as a major driver for poor subjective health and objective disease (128).

In conclusion, this paper attempted a synthesis of facts and theories about health and disease that result in the four observable health states. It led to the insight that the effective care of patients' illnesses requires a strategy that combines person-centeredness with the scientific approach of managing the molecular network physiology, which together underlie the emergence of subjective health experiences and objective disease formation. This approach results in strengthening resilience and self-efficacy (129), builds social capital and cohesion (97, 110), and offers some pragmatic suggestions to start a necessary broad based discourse to shape the future directions of medical and social care.

Finally, we suggest that ideas explored in this paper should be tested pragmatically in routine clinical practice to capture the

individualized state of a person's health and to better understand and treat his illness.

- At the most basic level the routine integration of asking the patient to “self-rate” their health—no different to routinely checking their vital signs—not only would provide important information about the current state of health/illness experience, but also guide health professionals in managing the *most appropriate (biological, social, emotional, or cognitive) domain* underlying the patient's illness.
- HRV monitors are becoming readily available and may provide a simple objective measure to *quantify the overall physiological state* of a person's system function, however, its validity in non-critical clinical practice will require further study.
- Ongoing research aims to provide clinicians with other objective measures of the functional state of regulatory systems, including mitochondrial bioenergetics, HPA axis function, inflammatory load, and autonomic regulation.
- It is, however, important to highlight that *very similar adaptive states* can be achieved by very different combinations of objective measures. This awareness should drive future research endeavors into understanding the nature of health, illness, and disease as the basis for best possible health care delivery and health system design.

AUTHOR CONTRIBUTIONS

JS developed the ideas for this paper, and RM provided substantial inputs into its refinement. JS and RM are the guarantors for this paper. JS wrote the first draft, and all other authors contributed to the synthesis and revisions of the paper. All authors approve the final version of the article.

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