Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

Journal of Evaluation in Clinical Practice ISSN1365-2753

DISCUSSION PAPER

'Multimorbidity' as the manifestation of network disturbances

Joachim P. Sturmberg MD PhD,[1] Jeanette M. Bennett PhD,[2] Carmel M. Martin MD PhD[3] and Martin Picard PhD[4]

[1]Associate Professor of General Practice, Department of General Practice, Newcastle – Australia, The University of Newcastle, Wamberal, NSW, Australia
[2]Assistant Professor of Psychology, Department of Psychology, The University of North Carolina at Charlotte, Charlotte, NC, USA
[3]Associate Professor of General Practice, Department of Medicine, Nursing and Allied Health, Monash Health, Clayton – Australia
[4]Assistant Professor of Behavioral Medicine, Division of Behavioral Medicine, Department of Psychiatry, Department of Neurology and CTNI, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA

Keywords
complex adaptive systems, mitochondria, multimorbidity, nonlinear dynamics, philosophy of medicine, philosophy of health, psychoneuroimmunology

Correspondence
Joachim P. Sturmberg
Department of General Practice
Newcastle – Australia
The University of Newcastle
PO Box 3010, Wamberal, NSW 2250, Australia
E-mail: jp.sturmberg@gmail.com

Accepted for publication: 17 May 2016

doi:10.1111/jep.12587

Abstract

We argue that 'multimorbidity' is the manifestation of interconnected physiological network processes *within an individual in his or her socio-cultural environment*. Networks include genomic, metabolomic, proteomic, neuroendocrine, immune and mitochondrial bioenergetic elements, as well as social, environmental and health care networks. Stress systems and other physiological mechanisms create feedback loops that integrate and regulate internal networks within the individual. Minor (e.g. daily hassles) and major (e.g. trauma) stressful life experiences perturb internal and social networks resulting in physiological instability with changes ranging from improved resilience to unhealthy adaptation and 'clinical disease'. Understanding 'multimorbidity' as a *complex adaptive systems response* to biobehavioural and socio-environmental networks is essential. Thus, designing integrative care delivery approaches that more adequately address the underlying disease processes as the manifestation of a state of physiological dysregulation is essential. This framework can shape care delivery approaches to meet the individual's care needs in the context of his or her underlying *illness experience*. It recognizes 'multimorbidity' and its symptoms as the end product of complex physiological processes, namely, stress activation and mitochondrial energetics, and suggests new opportunities for treatment and prevention. The future of 'multimorbidity' management might become much more discerning by combining the balancing of physiological dysregulation with targeted personalized biotechnology interventions such as small molecule therapeutics targeting specific cellular components of the stress response, with community-embedded interventions that involve addressing psycho-socio-cultural impediments that would aim to strengthen personal/social resilience and enhance social capital.

> Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.
>
> Sir William Osler, 1903

Introduction

Diseases are essentially defined [1] and organized [2] based on patterns of patient reported symptoms, clinical signs and pathology/radiology findings. As distinct entities, each disease is recommended to be managed according to an agreed best-evidence-based guideline (glossary). The term 'multimorbidity' (glossary) has arisen as a numeric conceptualisation to capture the presence of several diagnosable diseases within the same individual [3]. Unsurprisingly – and internally consistent – patients are managed for each individual disease according to its disease-specific guideline, often involving an array of clinicians and/or clinical teams each focused on one specific disease. This method has shown many limitations resulting more recently in a call to move towards integrated approaches (glossary) to 'multimorbidity' care that better meets the needs of individual patients. However, current integration approaches have shown only limited impact on improving patients' health and health experiences.

We suggest that the conception of 'multimorbidity = sum of individual diseases' overlooks that 'multimorbidity' arises uniquely in the 'one body' of a particular patient. This holistic view suggests that common linked physiological/pathophysiological pathways underlie the development of 'disease(s)' in a non-organ-specific manner. Multiple diseases within the one person are, thus, not necessarily caused by independent events and/or mechanisms. They are better appreciated as the result of the body's interconnected, that is, *systemic*, response to all types of challenges and its overall function. This knowledge necessitates thinking about *complex adaptive systems* with important implications for designing and optimizing clinical approaches to manage patients with 'multimorbidity'.

This paper proposes an alternative unifying multi-level complex adaptive systems framework for thinking about 'multimorbidity'. Firstly, we describe interconnected physiological, cellular and molecular pathways, the state of balance that promotes healthy functioning, and their disturbances in disease/'multimorbidity'. We then propose that effective 'multimorbidity-based' health care must focus on counterbalancing the 'sources of such disturbances', rather than only tinkering with visible disease processes (such as drug treatment for hypertension) and/or only palliating symptoms. This approach in turn has implications for health care delivery; integrated care is more than just health professional care. Personalized medicine (glossary), besides addressing disease-specific mechanisms, needs to pay much more attention to each person's needs, that is, addressing the particular context in which disease is occurring. We start with a case study to illustrate these notions.

Case study: a fairly typical person with 'multimorbidity'

Jim is a 76-year-old man, recently widowed, living by himself in a small dilapidated public housing flat at the edge of the city. He is surrounded by mostly younger families with boisterous adolescent children, some of whom are heavily into drugs and alcohol. His son and daughter, both of whom are tertiary educated, live at the other side of town and visit him semi-regularly. Most of his friends are deceased; he meets with a couple of previous work mates in the local pub on a Friday night.

Jim had been a heavy smoker during his work life as a foreman in an aluminium smelter. He only recently stopped smoking after suffering a mild stroke, which has left him, in his own words, with 'some clumsiness' in his non-dominant left arm. His smoking resulted in moderate severe chronic obstructive pulmonary disease, and he has medically controlled angina and diabetes. He had cataract surgery at aged 63 years and 3 years ago hip replacement surgery following a fall-related fracture of his femur. Since that time he requires a four-wheel walker for mobility. He is on 11 different medications and has to take 23 tablets spread across the day.

Following his stroke, he had a comprehensive assessment by the hospital discharge team. They felt he should be able to manage at home with minimal support; an occupational therapist assessed his home and organized handrails and shower aids, and a new bed that allowed for more space manoeuvring with his walker.

Jim's story embodies the typical multi-dimensional nature and context in which 'multimorbidity' often occurs.

Jim's situation illustrates all the hallmarks of a complex adaptive system consisting of the internal (biological) and external (environmental) agents of his particular environment. This system has a history (Jim's biography) and influences the emergence of his illness trajectory. Emergence results from the interactions and feedback between all agents from the cellular and organ levels to those that define his home and social environment [1].

Jim's story provides the backdrop to describe in more detail the interconnected physiological systems of 'multimorbidity', to allude to the multiple modes of physiological activation and to consider the implications for person-centred needs-based care.

The physiology of 'multimorbidity'

Emerging evidence indicates that disease is a consequence of interactions between multiple physiological networks – in particular, those that regulate gene networks [4] including the activities of the autonomic nervous system [5], the hypothalamic-pituitary-adrenal axis (HPA) [6,7] and the bioenergetics within the mitochondrion [8,9]. It is in this context that Goh *et al*. [4] framed the notion of the *diseasome*, linking the underlying *human disease networks* with their *gene networks,* that is, combining the *disease phenome* with the underlying *disease genome*. These maps show important genome-linked diseases and clarify how and why certain diseases occur in clusters within the same person [4,10]. This emerging knowledge challenges the cellular/organ-based pathological basis of current disease taxonomies and treatment strategies [2,11,12] (Fig. 1).

Mounting evidence indicates that many system diseases are produced by stochastic or random genomic changes [13]. Inherited genetic heterogeneity contributes to diseases more strongly than individual genes, which explains the low penetrance of specific gene mutations within populations, and emphasizes the 'gene x environment' interactions or *epigenetic* changes that occur over time and across generations [13]. Phenotypic disease, the individual uniqueness of a disease's characteristics and progression, results from intricate feedback interactions between the complex genomic, proteomic, metabolomic, neuroendocrine, immune and bioenergetics networks. Furthermore, networks are modulated by the complex dynamic environmental contexts of the patient (Fig. 2) [1,10].

Physiological network interactions in 'multimorbidity'

Physiological pathways aim to maintain the body's homeokinetic stability (glossary) [14–17]; persistently, exceeding homeokinetic boundaries result in physiological instability and 'clinical disease' [17]. Physiological pathways form intricate networks that control the complex intercellular and intracellular activities are associated with cell and organ functions. Excessive perturbation of these networks ultimately leads to disease [10] because of changes in the balance of proinflammatory and anti-inflammatory cytokine activity, dysregulation of stress systems and elevated stress hormone levels such as cortisol and epinephrine and in gene transcription activity and the control of mitochondrial function.

The role of cytokines

Health, in the sense of 'absence of disease' as well as 'the experience of health', is principally associated with a balance of proinflammatory and anti-inflammatory activities that vary across the day [18,19]. Figure 3 summarizes the effects of increasing levels of proinflammatory cytokines caused by disease on the person's experience of illness. There is crosstalk between the immune system and the brain. For example, peripheral cytokines can stimulate the HPA axis [20] and induce sickness behaviour [21,22] via indirect (e.g. the vagus nerve) or direct (e.g. crossing leaky portions of the blood brain barrier) pathways [23,24], whereas cortisol, the end product of the HPA axis, has potent anti-inflammatory effects on immune cells and reduces cytokine production during healthy regulation. Furthermore, cortisol has the potential to influence almost every cell in the body – making it an integral factor in linking multiple physiological systems.

© 2016 John Wiley & Sons, Ltd.

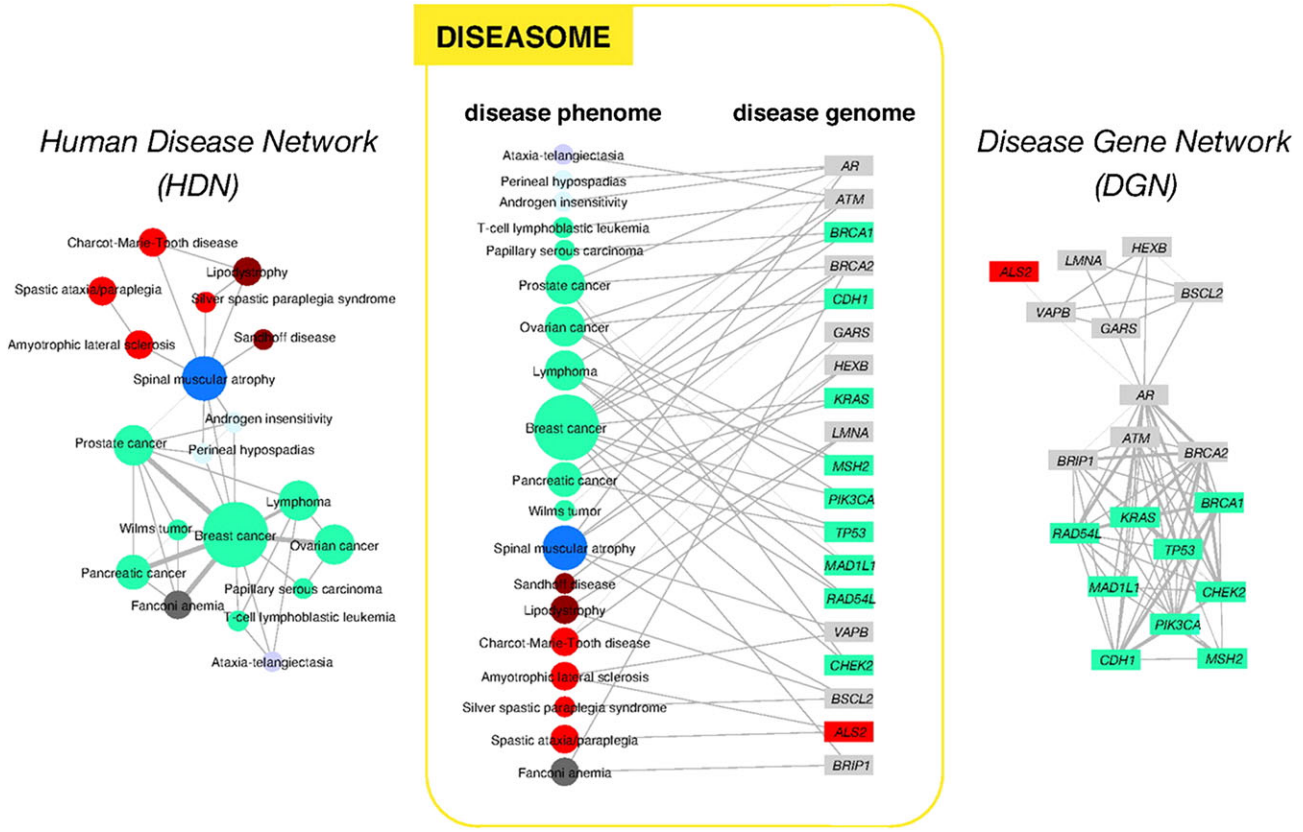

Figure 1 The diseasome – the link between the phenotypic appearance of selected diseases and their underlying genomic blueprint. These networks show that many phenotypic diseases like cardiovascular disease and diabetes share the same genome [ref], which has important implications for understanding the co-occurrence of many 'common diseases' within the one person. (reproduced with permission: Goh K-I, Cusick ME, Valle D, Childs B, Vidal M, Barabási A-L. The human disease network. Proceedings of the National Academy of Sciences. 2007;104(21):8685–8690).

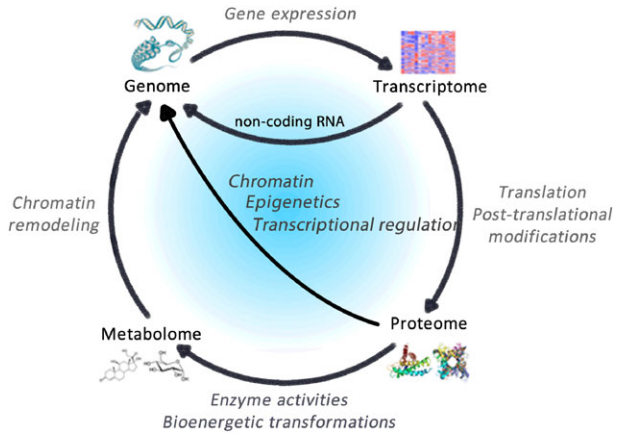

Figure 2 Regulatory cycle linking the omics of life. The genome comprises the totality of genes within an organism, which constitute the blueprint for the transcriptome, whose translation leads to proteins that accomplish enzymatic functions including bioenergetics transformations that consume and produce metabolites constituting the metabolome. In turn, gene transcripts, proteins and metabolites all impact the expression of genetic elements via dynamic processes subject to regulation.

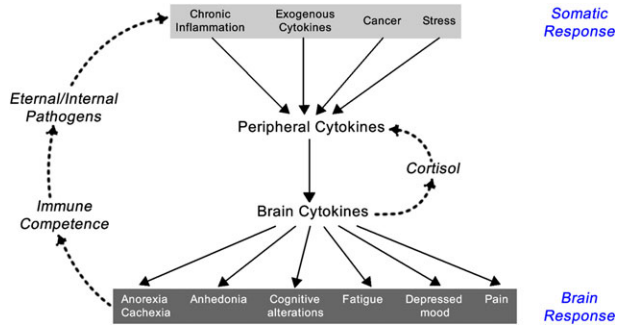

Figure 3 The link between somatic and brain responses to illness. Disease results in the increase of circulating proinflammatory cytokines, which activate brain cytokines that produce the various features of the 'illness experience'. Cortisol dampens the inflammatory response (negative feedback loop); however, chronic inflammation results in cortisol resistance and ongoing inflammation (positive feedback loop). (adapted from Dantzer R. Innate immunity at the forefront of psychoneuroimmunology. Brain Behav Immun 2004;18:1–16).

© 2016 John Wiley & Sons, Ltd.

Neuroendocrine mechanisms

Based on past experiences and current appraisal, the brain controls how the body responds to environmental stressors [25]. If one perceives to have the resources or skills to handle a situation, the body does not mount an excessive physiological response. However, the conscious or subconscious experience/interpretation as a *loss of control* or *threat of self* results in activation of the stress systems and withdrawal of the calming nervous system's influence.

When facing a threatening situation, the sympathetic or activating nervous system activates; thus, high levels of epinephrine/norepinephrine permeate throughout the body and promote immune activity (i.e. proinflammatory cytokine production). During recovery, cortisol and acetylcholine inhibit immune activity, therefore, restoring balance among the neuroendocrine and immune systems. Figure 4 summarizes the crosstalk between the neuroendocrine and immune networks with focus on peripheral cytokine levels. When facing a chronic threat, recovery of the calming nervous system may not occur, and immune cells become resistant to the constant presence of cortisol, leading to the removal/reduction of both anti-inflammatory pathways. Hence, proinflammatory cytokine production escalates and continues to fuel the stress systems – creating a vicous negative feedback cycle and multi-system perturbation.

Stress reactivity not only serves as a tool of cellular and systemic adaptation; but as a trade-off, it also contributes to disease

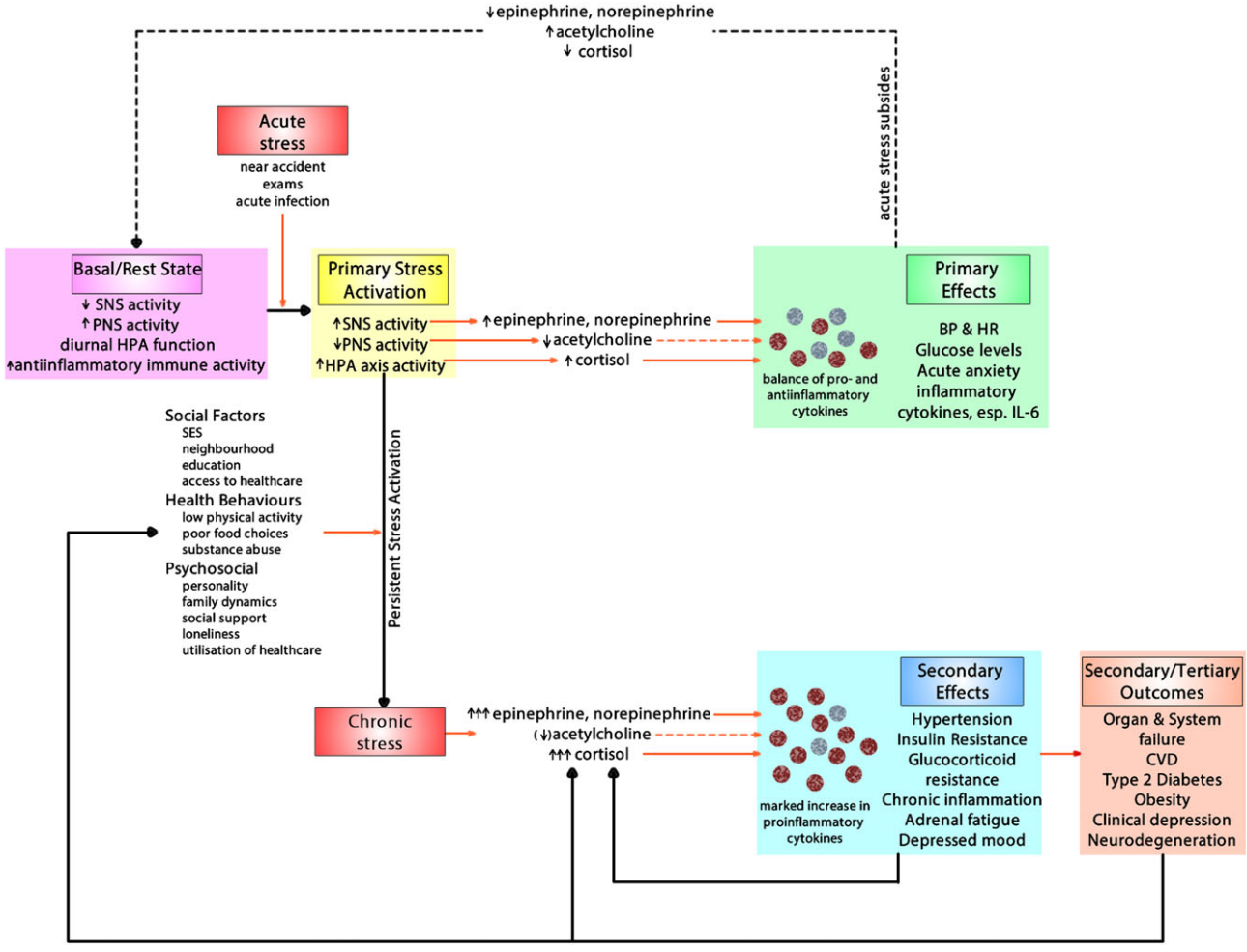

Figure 4 Schematic review of communication between the stress systems and immune cells during acute and chronic situations. During acute stress, sympathetic nervous system (NS) activation directly releases norepinephrine into the periphery and stimulates the adrenals to secrete epinephrine into circulation. Although the sympathetic activation is immediate, it cannot be maintained long-term. Thus, the brain simultaneously activates the hypothalamic–pituitary–adrenal (HPA) axis leading to the production of cortisol. This acute stress response shifts immunity towards the antibacterial immunity via adrenergic receptors on immune cells; yet, following resolution of the stressor, excess cortisol and re-activation of the parasympathetic NS force immune cells to acquiesce because of alpha 7 nicotinic acetylcholinergic (α7 nACh) and glucocorticoid (GC) receptor activation. However, chronic stress forces the body into a modified basal state where immune cells develop GC resistance and experience little activation of α7 nACh receptor because of sympathetic NS dominance. Both factors lead to elevated systemic inflammation thriving off the self-feeding vicious feedback cycle (e.g. cytokines can activate the HPA axis) that can be further compounded by psychosocial factors, health behaviours and dysregulation of multiple organ systems, progressing to 'multimorbidity'. Dashed lines indicate inhibitory or anti-inflammatory effects, and solid lines indicate activating or proinflammatory effects.

© 2016 John Wiley & Sons, Ltd.

manifestation [13]. Acute activation of the stress systems can result in behaviour changes that lessen the perceived threat; however, today, individuals may not be able to reduce the threat, leading to chronic activation of both stress systems [6]. These neuroendocrine mediators and their end-products have pervasive, wide-ranging effects at the system and cellular levels, being responsible for the inflammatory changes in diseases like asthma and allergic rhinitis [26], obesity [27,28], insulin resistance [29] and diabetes [30], coronary artery disease [31,32] and osteoarthritis [33–35].

Cellular mechanisms of 'multimorbidity'

Particularly sensitive to the effects of chronic stress is the mitochondrion, which regulates cellular energy production and cell function through intracellular signalling [36]. Mitochondria are present in cells throughout the body, and thus, mitochondrial dysfunction may simultaneously cause organ-specific defects throughout the organism (Fig. 5) [9,37]. Mitochondria 'sense' neuroendocrine mediators and associated metabolic perturbations, which affect their morphology and function resulting in mitochondrial damage (mitochondrial allostatic load, MAL) [8]. MAL can initiate pathogenic signalling cascades known to triggering systemic inflammation, altering the circulating metabolome, reducing energy production capacity and influencing cellular gene expression [38], imparting broad effects on cell-specific parameters and whole organism function. Thus, the mitochondrion, by providing energy to animate and regulate these different regulatory networks, plays a key role in the development of pathological changes across organ systems [9].

At the cellular level, gene expression can be modified via primary neuroendocrine mediators, neurotransmitters, hormones and cytokines [7]. The chronic presence of these primary stress mediators can promote MAL, which in turn dysregulates multiple physiological systems.

At the whole person level, psychosocial and behavioural factors activate nonlinear homeokinetic network mediators including catecholamines, glucocorticoids, oxidative stress, pro-inflammatory and anti-inflammatory cytokines, blood glucose, insulin and others [39]. Systemic physiological recalibrations affecting all organ systems under chronic stress define allostatic load [40]. When prolonged, this multisystemic response exerts 'wear and tear' on various cellular components, accelerating age-related functional decline and susceptibility to disease affecting multiple organ systems – colloquially termed 'multimorbidity'. Together, these systems interact with energy-producing mitochondria, represent the cellular basis for 'multimorbidity', and constitute the mechanisms of vulnerability and resilience to environmental challenge [41].

Personal context – psychosocial mediators in 'multimorbidity'

Subjective and objective stress experiences, depression and social support [42–45] are all potent mediators of the stress and mitochondrial bioenergetics systems and emerged as biobehavioural factors affecting disease pathogenesis and related disease heterogeneity. Individuals with lower socio-economic status in every country [46] have significantly worse health [47] and increased likelihoods of developing 'multimorbidity' [48]. Lower socio-economic status is linked to emotional/physical abuse, less education, greater financial worry, reduced leisure time and negative health behaviours. Substance abuse, a diet high in processed foods and sedentary lifestyle [47] are risk factors and/or markers for chronic activation of the stress system, which together drive the 'emergence of multimorbidity' [49]. In line with this, various stress management approaches aimed at reducing activation of stress systems such as improving coping skills and enhancing social support [50] are associated with reduced inflammation [51–55], indicating the potential to impact disease by improving physiological dysregulation and addressing individual's psychosocial factors/needs. Enhanced support for patients' multimorbidity and frailty shows promise for future health care strategies [56,57].

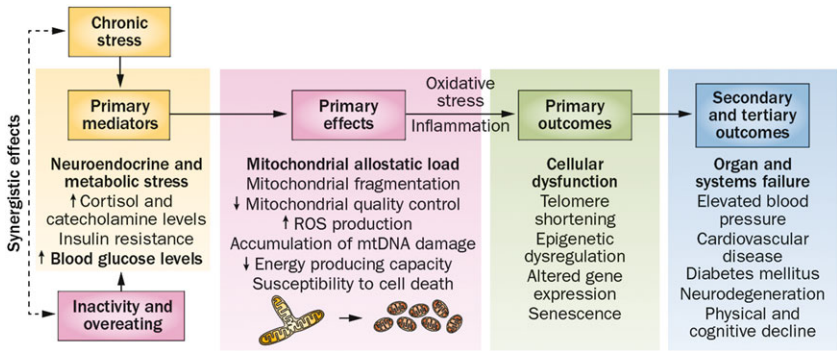

Figure 5 The stress–disease cascade and mitochondrial allostatic load. Allostatic load is a pathophysiological process in which multisystem biological dysregulation caused by chronic stress synergizes with unhealthy behaviours. Chronic stress perturbs adaptive glucocorticoid signalling and glucose levels (primary mediators) that in turn alter mitochondrial structure and function (primary effects), generating oxidative stress and cellular damage (primary outcomes). This process cumulatively worsens risk factors (secondary outcomes), which consequently leads to disease (tertiary outcomes). In this multilevel cascade, mitochondrial dysfunction is depicted as an early event mediating the relationship between primary mediators of chronic stress and disease trajectories. mtDNA, mitochondrial DNA; ROS, reactive oxygen species. (reproduced with permission: Picard M, Juster R-P, McEwen BS. Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. Nat Rev Endocrinol. 2014;10(5):303-310).

© 2016 John Wiley & Sons, Ltd.

'Multimorbidity' – highly variable clinical pictures, same underlying physiology

Osler already was aware about the variability in expression and behaviour of diseases in different people conveying – without any detailed knowledge about physiological networks – that their causes and our responses as health professionals ought to be tailored to the individual.

The outlined internal (biological) and external (social/environmental) perturbations of the genomic, proteomic and metabolomic networks modulate individuals' immune function leading to different phenotypic expressions of the same underlying disease processes. *Theoretically*, this leads to the conclusion that much observable 'multimorbidy' results from a *common underlying physiological disease process* – the chronic activation of the stress systems [39,44,45,58]. These processes affect the *whole person* across molecular, personal and social domains [59,60] and physiologically leads to a new state of *objective and subjective homeokinetic adaptation*. While the emergence of the new *stable physiological state* may entail characteristics that enable better adaptation, it also can lead to a variety of 'diagnosable diseases'. Additional diseases may or may not be associated with worse experiential or disease-specific outcomes. A person's adaptation to changes in morbidity is best reflected through his health perceptions as measured by *self-rated health* (glossary). S*elf-rated health* is a robust predictor of future morbidity, mortality and associated health service utilization and does so independent of the person's 'objective disease state' [61–64].

These insights appear to have been lost in most health systems; research suggests that people experience illness as unique and multifaceted while health professionals invariably respond in linear and prescriptive ways focused on each identifiable condition in turn [65–67]. Ultimately, such a response fails the patient's holistic needs, causes iatrogenic disease and wastes scarce health care resources.

Implications for a fairly typical person with 'multimorbidity'

Now, we can appreciate Jim's condition as a state emerging from the integrated network interactions throughout his biography. He lives in a stress-inducing environment with limited social networks, and he has been exposed to environmental toxins throughout most of his adult life; his ability to manage his daily life is limited by the resulting consequences of his lung, heart and endocrine malfunction, and he is at high risk of medication mishaps and falls.

Managing Jim's 'disease manifestations' demands a cautious approach. At his age, homeokinetic stability is more easily compromised with changes in physiological parameters like blood pressure or blood sugar levels. Lowering his blood pressure aggressively to meet a particular target value often results in cerebral hypo-perfusion causing dizziness and confusion; when combined with muscle weakness, osteoarthritis of the hip/knee and increasing frailty, falls occur more frequently, increasing the risk of fractures and intracranial bleeds. Seeing the *bigger picture* may not only help avoid iatrogenesis but also promote more individualized care [68]. Thus, continuing to focus on the management of the 'biomedical parts of multimorbidity' as 'multiple single morbidities' based on 'single-disease best-practice guidelines' is misguided and potentially dangerous [69,70].

Implications for health professionals

Person-centred care works by identifying and addressing all triggers or sources that over-stimulate the stress system – be they physical, social or experiential in nature. All stressors can potentiate the inflammatory load and thereby further deteriorate physical and mental well-being.

Addressing the sources activating the stress response is of major importance in managing a person like Jim. The aim of caring for Jim is to reduce both the sources and the consequences of the stress response and improve his immune and bioenergetic functions. Person-centred health care is only in part biomedical care; many of the other facets of the patient's illness can be more effectively and efficiently addressed utilizing the expertise of social workers, psychologists, community health workers or volunteers.

As the external environment stimulates neuroendocrine, inflammatory and bioenergetics pathways, 'multimorbidity' management needs to focus more closely on environmental factors like personal health behaviours (e.g. diet and exercise), emotional support and stress management. 'Multimorbidity' management no longer can avoid engaging in building stronger and more equitable communities focusing on housing, transportation, education, social support infrastructures and work as they are essential for good health [71–73].

Our enhanced understanding of how factors both internal and external to the person influence the physiological mechanisms of their health [74] should form the basis for designing much more comprehensive and sophisticated biomedical, social and environmental interventions for people affected by 'multimorbidity'.

'Multimorbidity' management necessitates a broad perspective asking: *Is this person in a stable or unstable health state*? followed by: *How can stability be regained or maintained*? This approach puts equal emphasis on all the objective and subjective manifestations underlying the person's health/illness [60,63,69,75]. Such a complex adaptive approach to health care adjusts to the *emergent* nature of a person's care needs in flexible ways, at one point providing simple direct interventions for a single disease aspect (*e.g.* disabling hip arthritis or acute stroke) and at others *muddling through the vagaries of the person's illness experience* [76–78] and its contextual interdependencies, especially those resulting from disability, frailty, poverty and social exclusion, which exacerbate 'brittleness' and reduce resilience (Fig. 6).

The future of 'multimorbidity' management

The future of 'multimorbidity' management might become much more discerning by combining the balancing of physiological dysregulation with targeted personalized biotechnology interventions such as small molecule therapeutics targeting specific cellular components of the stress response, with community-embedded interventions addressing psycho-socio-cultural impediments that would aim to strengthen personal/social resilience and enhance social capital.

The rapid developments in 'multimorbidity' 'omics' technologies aim to provide sensitive assays to quantify people's personalized health status reflecting whole person immune and bioenergetics states far more sensitively and specifically than currently available biomarkers of specific diseases [63]. These assays have the potential to refine clinical decision-making and guide therapeutic interventions that address the underlying molecular and cellular networks to restore balance among complex genomic, proteomic,

 © 2016 John Wiley & Sons, Ltd.

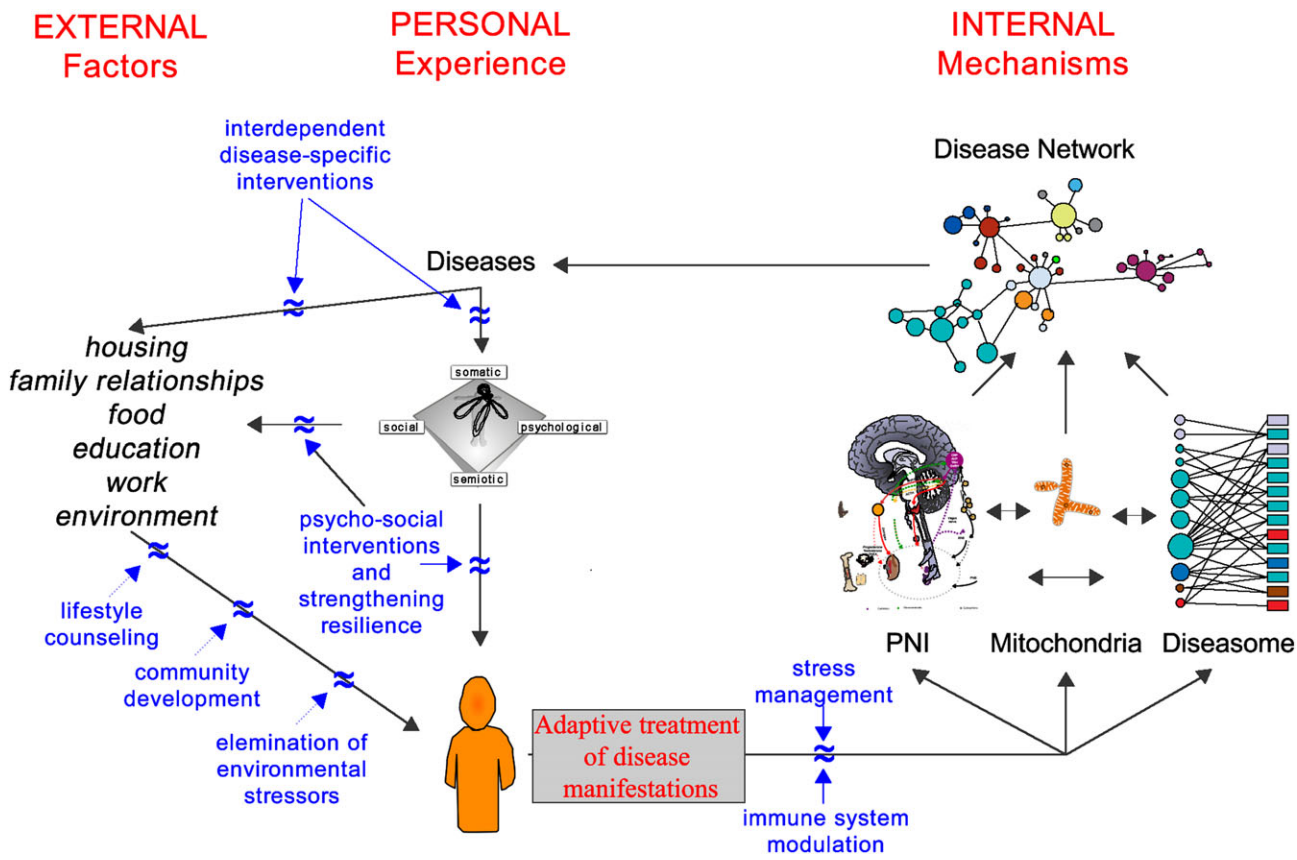

Figure 6 Approaching the dynamics of 'multimorbidity'. Links between the external and internal factors that affect the person's experience of health. His health experiences positively and negatively modulate gene, bioenergetics and immune network functions, which modulate disease network expression and result in the 'phenotypic' manifestation of disease/s. Disease/s impact as much on self-rated health as on social status and engagement, closing the feedback loop of health, illness and disease. Of note, there are numerous opportunities to strengthen a person's overall health in his physical and social environments other than disease-specific interventions. Psychoneuroimmunology (PNI) indicates potential interventions that can restore homeokinetic network stability.

metabolomic, neuroendocrine, immune and bioenergetic networks. Nevertheless, it is important to continually balance the individual's needs and wants in their personal health journey with biomarker trajectories. Clinicians need to partner with their patients to identify person-centred care that optimizes highly complex and sometimes conflicting information from multiple knowledge sources.

At a maco-level, 'multimorbidity' management needs organizational restructuring that links health professional interventions with personalized social support services and community-oriented improvements of the physical and social infrastructure in local communities. Optimal health outcomes – at the subjective and objective levels – are most likely to be achieved if biomedical and psychosocial interventions go hand in hand.

Conclusions

'Multimorbidity' is an *integrated systems state* to perturbation and feedback of the person's genomic, proteomic, metabolomic, neuroendocrine, immune and bioenergetics networks. Recognizing that 'multimorbidy' reflects an underlying disturbance \in a network of interlinked neuroendocrine, immunological and cellular processes have two important implications for health professionals. First, it invites them to explore all potential internal and external 'stressors'; over-stimulation of the stress systems (HPA axis and sympathetic nervous system) results in a proinflammatory state and persistently exhausts bioenergetics capacities and hampers resilience. Second, it warrants the seeking of person-centred holistic strategies aimed at restoring and maintaining physiological network homeokinesis. An integrated understanding of 'multimorbidity' invites health professionals to consider the multiple consequences of any biomedical intervention and underscores the potential beneficial effects of implementing stress-reducing biobehavioural interventions for patients and communities alike.

Conflict of interest

The authors declare no conflict of interest.

References

1. Loscalzo, J., Kohane, I. & Barabasi, A.-L. (2007) Human disease classification in the postgenomic era: a complex systems approach to human pathobiology. *Molecular Systems Biology*, 3, 124.
2. Sturmberg, J. P. & Martin, C. M. (2016) Diagnosis – the limiting focus of taxonomy. *Journal of Evaluation in Clinical Practice*, 22 (1), 103–111.
3. van den Akker, M., Buntinx, F. & Knottnerus, J. A. (1996) Comorbidity or multimorbidity. *European Journal of General Practice*, 2 (2), 65–70.

© 2016 John Wiley & Sons, Ltd.

4. Goh, K.-I., Cusick, M. E., Valle, D., Childs, B., Vidal, M. & Barabási, A.-L. (2007) The human disease network. *Proceedings of the National Academy of Science*, 104 (21), 8685–8690.
5. Tracey, K. J. (2007) Physiology and immunology of the cholinergic antiinflammatory pathway. *Journal of Clinical Investigation*, 117 (2), 289–296.
6. Glaser, R. & Kiecolt-Glaser, J. K. (2005) Stress-induced immune dysfunction: implications for health. *Nature Reviews Immunology*, 5, 243–251.
7. Cole, S. W. (2013) Social regulation of human gene expression: mechanisms and implications for public health. *American Journal of Public Health*, 103 (S1), S84–S92.
8. Picard, M., Juster, R. P. & McEwen, B. S. (2014) Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. *Nature Reviews Endrocrinology*, 10 (5), 303–310.
9. Wallace, D. C. (2013) A mitochondrial bioenergetic etiology of disease. *Journal of Clinical Investigation*, 123 (4), 1405–1412.
10. Barabási, A.-L. (2007) Network medicine – from obesity to the "diseasome". *New England Journal of Medicine*, 357 (4), 404–407.
11. Moynihan, R., Glasziou, P., Woloshin, S., Schwartz, L., Santa, J. & Godlee, F. (2013) Winding back the harms of too much medicine. *British Medical Journal*, 346 f1271.
12. Tinetti, M. E. & Fried, T. (2004) The end of the disease era. *American Journal of Medicine*, 16 (3), 179–185.
13. Heng, H. H. Q., Liu, G., Stevens, J. B., Bremer, S. W., Ye, K. J., Abdallah, B. Y., Horne, S. D. & Ye, C. J. (2011) Decoding the genome beyond sequencing: the new phase of genomic research. *Genomics*, 98 (4), 242–252.
14. Cannon, W. B. (1935) Stresses and strains of homeostasis. *American Journal of Medical Science*, 189, 1–14.
15. Goldberger, A. L., Amaral, L. A. N., Hausdorff, J. M., Ivanov, P. C., Peng, C.-K. & Stanley, H. E. (2002) Fractal dynamics in physiology: alterations with disease and aging. *Proceedings of the National Academy of Sciences of the United States of America*, 99 (Suppl 1), 2466–2472.
16. Billman, G. E. (2013) Homeostasis: the dynamic self-regulatory process that maintains health and buffers against disease. In Handbook of Systems and Complexity in Health (eds J. P. Sturmberg & C. M. Martin), pp. 159–170. New York: Springer.
17. Que, C.-L., Kenyon, C. M., Olivenstein, R., Macklem, P. T. & Maksym, G. N. (2001) Homeokinesis and short-term variability of human airway caliber. *Journal of Applied Physiology*, 91 (3), 1131–1141.
18. Remick, D. G. & Friedland, J. S. (1997) Cytokines in Health and Disease. New York: M. Dekker.
19. Petrovsky, N. & Harrison, L. C. (1998) The chronobiology of human cytokine production. *International Reviews of Immunology*, 16, 635–649.
20. Sapolsky, R., Rivier, C. & Yamamoto, G. (1987) Interleukin-1 stimulates the secretion of hypothalmic corticotropin-releasing factor. *Science*, 238, 522–526.
21. Dantzer, R. (2004) Innate immunity at the forefront of psychoneuroimmunology. *Brain, Behavior, and Immunity*, 18 (1), 1–6.
22. Dantzer, R. & Kelley, K. W. (2007) Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*, 21 (2), 153–160.
23. Watkins, L. R. & Maier, S. F. (1999) Implications of immune-to-brain communication for sickness and pain. *Proceedings of the National Academy of Sciences of the United States of America*, 96, 7710–7713.
24. Banks, W. A. & Erickson, M. A. (2010) The blood–brain barrier and immune function and dysfunction. *Neurobiology of Disease*, 37 (1), 26–32.
25. Lazarus, R. S. & Folkman, S. (1984) Stress, Appraisal, and Coping. New York: Springer.
26. Galli, S. J., Tsai, M. & Piliponsky, A. M. (2008) The development of allergic inflammation. *Nature*, 454 (7203), 445–454.
27. Kargi, A. Y. & Iacobellis, G. (2014) Adipose tissue and adrenal glands: novel pathophysiological mechanisms and clinical applications. *International Journal of Endocrinology*, 2014 (3), 614074. doi: 10.1155/2014/614074.
28. Kershaw, E. E. & Flier, J. S. (2004) Adipose tissue as an endocrine organ. *The Journal of Clinical Endocrinology & Metabolism*, 89 (6), 2548–2556.
29. Reaven, G. M. (1988) Role of insulin resistance in human disease. *Diabetes*, 37 (12), 1595–1607.
30. Bastard, J.-P., Maachi, M., Lagathu, C., Kim, M. J., Caron, M., Vidal, H., Capeau, J. & Feve, B. (2006) Recent advances in the relationship between obesity, inflammation, and insulin resistance. *European Cytokine Network*, 17 (1), 4–12.
31. Getz, G. S. (2005) Thematic review series: the immune system and atherogenesis. Immune function in atherogenesis. *Journal of Lipid Research*, 46 (1), 1–10.
32. Hansson, G. K. & Hermansson, A. (2011) The immune system in atherosclerosis. *Nature Immunology*, 12 (3), 204–212.
33. Berenbaum, F. (2013) Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis and Cartilage*, 21 (1), 16–21.
34. Haseeb, A. & Haqqi, T. M. (2013) Immunopathogenesis of osteoarthritis. *Clinical Immunology*, 146 (3), 185–196.
35. Scanzello, C. R. & Goldring, S. R. (2012) The role of synovitis in osteoarthritis pathogenesis. *Bone*, 51 (2), 249–257.
36. Picard, M. (2011) Pathways to aging: the mitochondrion at the intersection of biological and psychosocial sciences. *Journal of Aging Research*, 2011, 11.
37. Naik, E. & Dixit, V. M. (2011) Mitochondrial reactive oxygen species drive proinflammatory cytokine production. *Journal of Experimental Medicine*, 208 (3), 417–420.
38. Picard, M. & McEwen, B. S. (2014) Mitochondria impact brain function and cognition. *Proceedings of the National Academy of Science*, 111 (1), 7–8.
39. McEwen, B. S. (2012) Brain on stress: how the social environment gets under the skin. *Proceedings of the National Academy of Science*, 109 (Supplement 2), 17180–17185.
40. McEwen, B. S. (1998) Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338 (3), 171–179.
41. Juster, R.-P., Seeman, T., Bruce, S., *et al.* (2016) Social inequalities and the road to allostatic load: from vulnerability to resilience. In Developmental Psychopathology. 4 – Risk, Resilience and Intervention (eds D. Cicchetti & D. J. Cohen), 3rd edn. Hobeken, NJ: John Wiley & Sons.
42. Patterson, T., Shaw, W., Semple, S., Cherner, M., McCutchan, A., Atkinson, H., Grant, I. & Nannis, E. (1996) Relationship of psychosocial factors to HIV disease progression. *Annals of Behavioral Medicine*, 18, 30–39.
43. Leserman, J. (2003) HIV disease progression: depression, stress, and possible mechanisms. *Biological Psychiatry*, 54 (3), 295–306.
44. Slavich, G. M. & Cole, S. W. (2013) The emerging field of human social genomics. *Clinical Psychological Science*, 1 (3), 331–348.
45. Slavich, G. M. & Irwin, M. R. (2014) From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin*, 140 (3), 774–815.
46. Cohen, S., Doyle, W. & Baum, A. (2006) Socioeconomic status is associated with stress hormones. *Psychosomatic Medicine*, 68 (3), 414.
47. Wilkinson, R. G. & Pickett, K. (2009) The Spirit Level: Why More Equal Societies Almost Always Do Better. London, UK: Allen Lane.
48. Adler, N. & Rehkopf, D. (2008) US disparities in health: descriptions, causes, and mechanisms. *Annual Review of Public Health*, 29 (1), 235.
49. Novack, D., Cameron, O., Epel, E., Ader, R., Waldstein, S., Levenstein, S., Antoni, M. H. & Wainer, A. R. (2007) Psychosomatic medicine: the scientific foundation of the biopsychosocial model. *Academic Psychiatry*, 31 (5), 388–401.
50. Kemeny, M. (2011) Psychoneuroimmunology. In Oxford Handbook of Health Psychology (ed. H. Friedman), pp. 138–161. New York: Oxford University Press.

© 2016 John Wiley & Sons, Ltd.

51. Shapiro, D., Cook, I. A., Davydov, D. M., Ottaviani, C., Leuchter, A. F. & Abrams, M. (2007) Yoga as a complementary treatment of depression: effects of traits and moods on treatment outcome. *Evidence-based Complementary and Alternative Medicine*, 4 (4), 493–502.
52. Bower, J. E., Greendale, G., Crosswell, A. D., Garet, D., Sternlieb, B., Ganz, P. A., Irwin, M. R., Olmstead, R., Arevalo, J. & Cole, S. W. (2014) Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. *Psychoneuroendocrinology*, 43, 20–29.
53. Kiecolt-Glaser, J. K., Bennett, J. M., Andridge, R. R., Peng, J., Shapiro, C. L., Marlarkey, W. B., Emery, C. F., Layman, R., Mrozek, E. E. & Glaser, R. (2014) Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *Journal of Clinical Oncology*, 32 (10), 1040–1049.
54. Mols, F., Vingerhoets, A. J. J. M., Coebergh, J. W. & van de Poll-Franse, L. V. (2005) Quality of life among long-term breast cancer survivors: a systematic review. *European Journal of Cancer*, 41 (17), 2613–2619.
55. Osborn, R. L., Demoncada, A. C. & Feuerstein, M. (2006) Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. *The International Journal of Psychiatry in Medicine*, 36 (1), 13–34.
56. Kodner, D. L. (2006) Whole-system approaches to health and social care partnerships for the frail elderly: an exploration of North American models and lessons. *Health & Social Care in the Community*, 14 (5), 384–390.
57. Martin, C. M., Vogel, C., Grady, D., Zarabzadeh, A., Hederman, L., Kellett, J., Smith, K. & O'Shea B. (2012) Implementation of complex adaptive chronic care: the Patient Journey Record system (PaJR). *Journal of Evaluation in Clinical Practice*, 18 (6), 1226–1234.
58. Cohen, S., Janicki-Deverts, D., Doyle, W. J., Miller, G. E., Frank, E., Rabin, B. S., Turner, R. B. (2012) Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences of the United States of America*, 109 (16), 5995–5999.
59. Sturmberg, J. P. (2014) Health: a personal complex-adaptive state. In Handbook of Systems and Complexity in Health (eds J. P. Sturmberg & C. M. Martin), pp. 231–242. New York: Springer.
60. Holman, H. R. (2005) Chronic disease and the healthcare crisis. *Chronic Illness*, 1 (4), 265–274.
61. Idler, E. L. & Benyamini, Y. (1997) Self-rated health and mortality: a review of twenty-seven community studies. *Journal of Health and Social Behavior*, 38 (1), 21–37.
62. Jylhä, M. (2009) What is self-rated health and why does it predict mortality? Towards a unified conceptual model. *Social Science and Medicine*, 69 (3), 307–316.
63. Picard, M., Juster, R. & Sabiston, C. (2013) Is the whole greater than the sum of the parts? Self-rated health and transdisciplinarity. *Health Affairs*, 5 (12A), 24–30.
64. Jarczok, M. N., Kleber, M. E., Koenig, J., Loerbroks, A., Herr, R. M., Hoffmann, K., Fischer, J. E., Benyamini, Y. & Thayer J. F. (2015) Investigating the associations of self-rated health: heart rate variability is more strongly associated than inflammatory and other frequently used biomarkers in a cross sectional occupational sample. *PLoS One*, 10 (2e0117196).
65. Bower, P., Macdonald, W., Harkness, E., Gask, L., Kendrick, T., Valderas, J. M., Dickens, C., Blakeman, T. & Sibbald, B. (2011) Multimorbidity, service organization and clinical decision making in primary care: a qualitative study. *Family Practice*, 28 (5), 579–587.
66. Gill, A., Kuluski, K., Jaakkimainen, L., Naganathan, G., Upshur, R. & Walter, P. W. (2014) "Where do we go from here?" Health system frustrations expressed by patients with multimorbidity, their caregivers and family physicians. *Healthcare Policy*, 9 (4), 73–89.
67. Trikalinos, T., Segal, J. & Boyd, C. (2014) Addressing multimorbidity in evidence integration and synthesis. *Journal of General Internal Medicine*, 29 (4), 661–669.
68. Heng, H. H. Q. (2008) The conflict between complex systems and reductionism. *JAMA*, 300 (13), 1580–1581.
69. Salisbury, C. (2012) Multimorbidity: redesigning health care for people who use it. *The Lancet*, 380 (9836), 7–9.
70. Fernandez, A., Sturmberg, J., Madden, R., Lukersmith, S., Torkfar, G., Colagiuri, R., & Salvador-Carulla, L. (2015) Evidence-based medicine: is it a bridge too far?. *Health Research Policy and Systems*, 13, 66. doi: 10.1186/s12961-015-0057-0.
71. Virchow, R. (1941) Die Medizinische Reform, 2. In Medicine and Human Welfare (ed. H. E. Sigerist), pp. 93. New Haven, CT: Yale University Press.
72. Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S. & Guthrie, B. (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*, 380 (9836), 37–43.
73. Economos, C. D. & Curtatone, J. A. (2010) Shaping up Somerville: a community initiative in Massachusetts. *Preventive Medicine*, 50 (Suppl 1), S97–S98.
74. Sturmberg, J. P., Bennett, J. M., Picard, M. & Seely, A. J. E. (2015) The trajectory of life. Decreasing physiological network complexity through changing fractal patterns. *Frontiers in Physiology*, 6, 169.
75. Starfield, B. (2006) Threads and yarns: weaving the tapestry of comorbidity. *Annals of Family Medicine*, 4 (2), 101–103.
76. Sturmberg, J. P. (2012) Caring for people with chronic disease: is 'muddling through' the best way to handle the multiple complexities? *Journal of Evaluation in Clinical Practice*, 18 (6), 1220–1225.
77. Husserl, E. (1975) Experience and Judgment. Chicago: Northwestern University Press.
78. Scott, J. G., Cohen, D., DiCicco-Bloom, B., Miller, W. L., Stange, K. C. & Crabtree, B. F. (2008) Understanding healing relationships in primary care. *Annals of Family Medicine*, 6 (4), 315–322.
79. Della Mea, V., Vuattolo, O., Celik, C. & Ustun, B. (2013) Social network integration of the ICD11 revision platform. *Studies in Health Technology and Informatics*, 192, 1110.
80. Scadding, J. G. (1996) Essentialism and nominalism in medicine: logic of diagnosis in disease terminology. *Lancet*, 348 (9027), 594–596.
81. Tikkinen, K. A. O., Leinonen, J. S., Guyatt, G. H., Ebrahim, S. & Järvinen, T. L. N. (2012) What is a disease? Perspectives of the public, health professionals and legislators. *BMJ Open*, 2 (6).
82. Gems, D. (2015) The aging-disease false dichotomy: understanding senescence as pathology. *Frontiers in Genetics*, 6, 212. doi: 10.3389/fgene.2015.00212.
83. Soodak, H. & Iberall, A. (1978) Homeokinetics: a physical science for complex systems. *Science*, 201 (4356), 579–582.
84. Waddington, C. & Egger, D. Integrated Health Services – What and Why? Geneva: WHO Working Group on Service Delivery. Technical Brief No.1, 2008.
85. Shaw, S., Rosen, R. & Rumbold, B. (2011) What is Integrated Care? London: Nuffield Trust.
86. Feinstein, A. R. (1970) The pre-therapeutic classification of co-morbidity in chronic disease. *Journal of Chronic Diseases*, 23 (7), 455–468.
87. Australian Institute of Health and Welfare (2012) Risk Factors Contributing to Chronic Disease. Canberra. Contract No.: Cat. no. PHE 157. Available at: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737421546 (last accessed 22 June 2016).
88. Sturmberg, J. P. (2014) Multimorbidity and chronic disease: an emergent perspective. *Journal of Evaluation in Clinical Practice*, 20 (4), 508–512.
89. Martin, C. M. (2016) Multimorbidity – through a glass darkly. In The Value of Systems and Complexity Sciences for Healthcare – Proceedings of the 1st International Conference of Systems and Complexity in Health (ed. J. P. Sturmberg), pp. 121–131. New York: Springer.
90. Schwartz, S. S., Epstein, S., Corkey, B. E., Grant, S. F. A., Gavin, J. R. & Aguilar, R. B. (2016) The time is right for a new classification system for diabetes: rationale and implications of the β-cell–centric classification schema. *Diabetes Care*, 39 (2), 179–186.

© 2016 John Wiley & Sons, Ltd.

Glossary of terms

Disease. Objective disease definition is central to the health care frameworks and essential for service delivery. Yet, disease is 'socially' constructed via international classification systems such as International Classification of Disease (ICD) and continually under review [79]. There are two schools of thought – essentialism and nominalism in disease classification. Essentialists regard diseases as objective causes of illness; the role of a physician, in this view, is to identify the cause and treat it appropriately. Nominalists see diseases as constructs that humans create to bring order to a disorderly world. [80]

Diseases are classified by diverse historical systems. Classical classification of human disease derived from 'observational correlation between pathological analysis and clinical syndromes'. Causation or aetiology is considered central to the exercise, but classifications are based on divergent premises, including those based on pathogenesis, or by symptoms, or the organ system involved [1]. It is increasingly recognized that social perceptions of individual responsibility or blame for their condition are important [81]. For example, senescence is being proposed as a disease [82].

Homeokinesis, first described and defined by Soodak & Iberall [83], is the state of *dynamic regulation* that allows an organism *to move to different stable* states. Cannon's concept of homeostasis refers to the ability of an organism to regulate its internal environment *to maintain* a *stable or constant* state by means of multiple dynamic equilibrium adjustments, controlled by interrelated regulatory mechanisms.

Integrated care is another term with many different connotations – see definitions later.

The current understanding of integrated care is flawed, because it is based on an outdated model of discrete diseases within an individual, despite person-centric goals. The individual is a complex adaptive system, and no disease or social problem is discreet but integral to that individual's 'health system'. Individual health is an ongoing emergent phenomenon from internal and personal adaptation to life's trajectories. Understanding this requires a total shift in the paradigm of service versus individual centric interconnected adaptive care.

The World Health Organization defines integrated care as the organization and management of health services so that people obtain the care they need, when they need it, in ways that are user-friendly, achieve the desired results and provide value for money [84].

'Integrated care' is a term that reflects a concern to improve patient experience and achieve greater efficiency and value from health delivery systems. The aim is to address fragmentation in patient services and enable better coordinated and more continuous care, frequently for an ageing population, which has increasing incidence of chronic disease.

1 Integrated care is best understood as a strategy for improving patient care. Integrated care is concerned with improving patient care through better coordination. A decision about the intensity of integration is essential, starting with links across services, coordinating teams or pooling resources. Where there is a strong history of partnership working, further steps to amalgamate into a single integrated organization may be more feasible (although integration that is focused largely on bringing organizations together is unlikely to create improvements in care for patients).
2 The service user is the organizing principle of integrated care. Careful analysis of the goals of integration is critical in order to establish what might help or hinder progress. There is a need for a shared vision in which the service user perspective and patient experience are central. This will then shape how, when and where to integrate services in order to improve patient care.
3 One form of integrated care does not fit all. There is no one model of integrated care that is suited to all contexts, settings and circumstances. Careful analysis is needed about the different integrative processes that can support integration within a particular care setting. Decisions about which approaches are most relevant to a particular setting will be guided by the goals of the project, the needs of service users and other stakeholders involved, existing provision and available resources.
4 It is only possible to improve what you measure. There is a shortfall in evidence of the impact of integrated care. What evidence there is tends to be drawn from a limited range of settings and initiatives, which focus on structures and processes and involve limited assessment of outcomes or costs. Further work is urgently needed to identify what integrated care initiatives work best for whom and in what circumstances. As integration is an ongoing process, evaluation can facilitate continual refinement.

Nuffield Trust 85. The NC Integrated Steering Committee (Foundation for Health Leadership & Innovation http://www.ncfahp.org/definition-of-integrated-care.aspx) defines integrated care as both an orientation to and a model of providing health care that encompasses the goals of the Triple Aim (improving the individual experience of care, improving the health of populations and reducing per capita costs of care for populations [Berwick, Nolan, & Whittington, 2008]) while following these core concepts: Integrated care as a practice is as follows:

- person-centred and team-based;
- coordinated across systems of care and professions;
- comprised of shared information systems;
- longitudinal and evolves to meet patient needs;
- evidence-based;
- comprehensive; and
- cost-effective.

Multimorbidity is defined as 'the co-occurrence of multiple chronic or acute diseases and medical conditions within one person' [3]. Multimorbidity must be distinguished from *co-morbidity* – defined by Feinstein as 'any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study' [86] – and *chronic disease* – defined as 'Chronic diseases are illnesses that are prolonged in duration, do not often resolve spontaneously, and are rarely cured completely. … Features common to most chronic diseases include: complex causality, with multiple factors leading to their onset; a long development period, some of which may have no symptoms; a prolonged course of illness, perhaps leading to other health complications; [and] associated functional impairment or disability' [87]. For a detailed discussion, see [88].

Personalized medicine (or precision medicine, stratified medicine and P4 medicine are terms interchangeably used) is defined as 'the capacity to predict disease development and influence decisions about lifestyle choices or to tailor medical practice to an individual'. It is a highly biomedical concept aimed at (1) diagnosing a disease (and possibly the subtype) in an individual, (2) assessing an individual's risk of disease, (3) identifying whether an individual will benefit from particular interventions and/or (4) tailoring dosing regimens to individual variations in metabolic response. Evidence exists that personalized medicine is in fact emerging as 'biomarker-based' medicine rather than whole person medicine [89].

A recent paper looking at the underlying mechanisms in the spectrum of diabetes, while limited to one disease manifestation of a multimorbid state, suggests a pragmatic approach to translating systems understanding of disease mechanisms with multilevel interventions [90].

Self-rated health (SRH) is a global assessment by a person about his own overall health. Most commonly assessed with the question: *How do you rate your overall health on a scale of excellent, very good, good, fair or poor.*

Self-rated health is an independent predictor of mortality, independent of other medical, behavioural or psychosocial risk factors [61]. Explanations for the validity of SRH are as follows: (1) SRH is more inclusive than the covariates used in many studies; (2) SRH is a dynamic evaluation, judging the trajectory of health and not only current health at a defined point in time; (3) SRH influences behaviours that subsequently affect health status; and (4) SRH reflects resources that reflect or even affect ones' ability to cope with health threats [61,62].

© 2016 John Wiley & Sons, Ltd.