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REVIEW

The Biological Rationale for Integrating Intrinsic Capacity Into Frailty Models

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Abstract: The assessment and management of two function-centered clinical care models, frailty and intrinsic capacity decline have been proposed to achieve healthy aging. To implement these two care models, several different guidelines have been advocated by different health organizations, which has resulted in confusion and cost-ineffective results in healthcare practice. Although there are various operational definitions and screening tools of frailty, the most accepted operational definitions are based on the recognition of frailty phenotypes or deficit accumulation-based frailty indexes. Intrinsic capacity, referred to as the total physical and mental capacities for individual to undertake daily tasks in everyday life, is another care model, including five domains. Similar or identical instruments have been used to assess frailty and intrinsic capacity. In the present narrative review, we outlined the biological rationale for integrating intrinsic capacity into frailty models and highlighted the hierarchical and energy-dependent order of the intrinsic capacity domains. The vitality domain or energy metabolism-related capacity, is the highest order dimension and the basis of other intrinsic capacity domains. Vitality vulnerability manifests as a pre-frailty status in function-centered healthy aging. We provided a conceptual framework of frailty phenotypes and frailty indexes based on the hierarchical and energy-dependent order of the intrinsic capacity domains, particularly vitality capacity. To facilitate the clinical translation of the framework, some potential energy metabolism-related biomarkers have also been proposed as critical components for assessing and screening vitality capacity in older age. The integrating framework not only provides testable theoretical hypotheses, particularly about vitality as a foundational element in aging, but could serve as a starting point for further research to unravel the mechanisms of frailty. It also improves cost-effectiveness for optimizing aging interventions in clinical healthcare and public health policies of healthy aging.

Keywords: frailty, vitality, intrinsic capacity, frailty phenotype, frailty index, biomarkers

Introduction

Healthy aging emphasizes to develop and maintain the functional ability, enabling well-being of individuals in older age without regard for the presence of chronic diseases and multimorbidity.[1,2] The World Health Organization (WHO) proposed that achieving or recovering functional ability is a priority goal. To achieve healthy aging, two clinical care models, frailty and intrinsic capacity (IC), have been constructed to change traditionally disease-centered to function-centered care model and to extend individuals' health span without dependence. Frailty is characterized by the decline in capacity reserve of multiple physiological systems to maintain homeostasis, resulting in function decline, resilience decrease to stressors, and a remarkable risk of adverse outcomes, including disability, dependence, and even mortality.[3–5] IC, introduced by the WHO in 2015, is referred to as all the physical and mental capacities to undertake the physical and mental tasks at any time of everyday life.[6,7] IC, environmental factors, and their interactions determine individual's

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functional ability.[6] Obviously, frailty represents the results of interactions between environmental factors and IC, and a decline in IC to a vulnerability threshold that is not enough to maintain homeostasis across multiple physiological systems under endogenous and exogenous minor stressors. The recovery from this decline in IC and the reversal of frailty status can delay the occurrence of adverse health-related outcomes.

Frailty and IC are two multidimensional and dynamic concepts that reflect opposite sides of capacity reserves. IC mainly includes five dimensions: locomotion, vitality, cognition, psychosocial, and sensory dimensions.[7] Capacity reserve is increased during development and reaches a peak value at maturity period.[8] After the maturity period, IC and capacity reserve decline with increasing age and individual differences but indicating a typical pattern, including three stages: a relatively high and stable, a declining, and an accelerated decline period.[9] IC has been validated given its association with adverse health-related outcomes and poor quality of life.[10–13]

Similarly, frailty also includes physical (organ-specific, sensory, and mobility), cognitive, social, psychological, and nutritional dimensions. Frailty is a dynamic, and potentially reversible process, and its prevalence increases with the increase of age.[3–5] There are more than 70 different operational definitions despite various consensus guidelines have been proposed. The two most commonly and widely recognized frailty models are the physical frailty phenotype[14] based on biologically interconnected symptoms and signs, including weakness, slow gait speed, low physical activity, exhaustion, and unintentional weight loss, and the frailty index model[15] based on age-related deficit accumulation, indicating a continuous score of symptoms, signs, disabilities, and diseases. Population-level frailty prevalence varied by models, age, and sex. The prevalence was 12% using physical frailty measures, and 24% using frailty index models, ranging from 11% among those who were 50 to 59 years of age to 51% among those who were 90 years of age or older.[16] The prevalence was higher among females than males using two frailty models.[3,5,16] Demographic and sociocultural factors, multimorbidity and chronic disease, and lifestyle factors not only affect capacity reserve,[17] but also are the risk factors for the onset of frailty or frailty progression.[5,18–20]

In recent years, the concept of frailty phenotypes has evolved constantly. Multidimensional frailty phenotypes, such as physical frailty,[14] cognitive frailty,[21,22] psychological frailty (encompassing the concepts of mood and motivational frailty),[23] social frailty,[24] biopsychosocial frailty,[25] oral frailty,[26] and nutritional frailty[27] have been widely defined and validated. Moreover, some subtypes of the physical frailty phenotype, strictly linked to some IC domains such as mobility[28] and sensorial frailty[29] have also been proposed. Physical frailty is the basal component of the construct of some other frailty phenotypes, such as cognitive, biopsychosocial, and nutritional frailty phenotypes. However, other phenotypes, including social and psychological frailty, mobility, sensorial, and oral frailty, only correspond to the organ (system)-specific, cognitive, social, and psychological domains. An evident drawback of these classifications is the difficulty in differentiating organ (system)-specific, cognitive, social, and psychosocial frailty phenotypes from organ (system)-specific, cognitive, psychiatric, and late-life depression, or anxiety. Thus, to establish a common biological basis for different frailty phenotypes is required. Although age-related deficits of IC domains are already being integrated into frailty indexes,[30,31] frailty indexes contain more dependence-related components such as disability and multimorbidity, and less the components of pre-frailty.

Vitality, defined as energy homoeostasis, is speculated to be one of the higher hierarchical levels of physiological systems, and may serve as a biological basis for the other IC domains.[7,12,13] The assessment of vitality might be useful for the explanation of the trajectory from the pre-frailty to frailty status.[32] Energy homoeostasis system is the highest hierarchical level of physiological systems that mediates other energy-dependent stress response, immune, and metabolic regulation systems.[33,34] Ageing-related biological mechanisms, such as chronic inflammation, mitochondrial dysfunction, cellular senescence, resilience-related hormonal changes, and nutrient sensing dysfunction are thought to be involved in frailty.[3,4,35] For example, nutrient sensing system AMPK, sensing energy stress, interconnecting with other aging pathways,[36] might play an important role in IC and frailty. Thus, we hypothesized that energy deficits or vitality under a critical threshold may constitute a pre-frailty status. Integrating vitality into the constructs of frailty phenotypes or frailty indexes will not only make it easy to identify the early frailty risk but also to separate frailty from the presence of chronic diseases or multimorbidity. To standardize diagnosis of vitality and frailty based on validated assessment of vitality and multisystem dysregulation, will improve clinical management of both IC impairment and frailty by developing new personalized interventions. The biology of IC and frailty could provide help to identify the modifiable

risks. Frailty risk and the impairment of IC could be reduced through the strengthening of resilience and weakening vulnerability in physical, cognitive, social, and psychological domains.

Several practice guidelines of frailty from different countries or health organizations have been proposed.[35,37] All kinds of rapid screening and diagnostic tools for frailty phenotypes[38,39] or frailty indexes[40,41] based on biomarkers, electronic tools or wearable devices, and iPhone Apps have been developed. However, a single operational definition, the identification of frailty in different clinical settings, and personalized interventions are still lacking. Evidence of all interventions, such as (multicomponent) physical activity programmes, nutrient supplementation, social support, and modify home environment for community-dwelling older adults with frailty, and comprehensive geriatric assessment, polypharmacy reduction, and frailty-specific care pathway for frail patients in hospital are weak.[35] At the same period, the guidance for person-centered assessment of IC[9] and integrated care for older people (ICOPE) implementation framework[42] also were proposed. From a cost-effective point of view, these two clinical care models were not integrated well to implement them in clinical practice, although guidelines or consensus for frailty and IC care models have been proposed to achieve healthy aging.

In the present article, we presented critical evidence to support the vitality domain of IC as the basis of the other dimensions of this construct and the pre-frailty status for a function-centered healthy aging, also reviewing the possible underlying mechanism. Additionally, we proposed a conceptual hypothetical framework of frailty phenotypes and frailty indexes based on IC. Finally, we discussed a possible approach to implement the constructs of frailty phenotypes and frailty indexes in clinical practice.

The Vitality Domain Is the Highest Hierarchical Level of Physiological Systems of Both Intrinsic Capacity and Frailty

During aging, the trajectories of functioning at the individual, organ or system, and cellular and molecular levels generally show a decline with age, resulting from the dynamic interplay of between IC domains and the external environment (such as physical, economic status, and social environments), and internal environment (genetic determinants).[43] The biochemical processes that maintain life, activities of daily life, and homeostasis under adverse stress events require energy. Vitality is the basic domain of IC and reflecting the energy metabolic capacity to maintain the optimal homeostasis level in organisms.[7,32] Vitality provides a background biological energy reserve for the other IC domains to maintain normal functional status under stressful conditions. The concept that vitality might serve as a biological basis for other clinical expressions of IC is not novel but has already been anticipated by Beard et al.[12] However, this personal hypothesis is far from being confirmed/validated by the WHO. Additionally, Beard et al proposed that vitality capacity is affected by genetic inheritance, biological aging, and higher level energy homoeostasis, stress response systems, and repair mechanisms.[13] The operationalization of IC (particularly the vitality capacity) might not be reliable and definitive today. Recently, the WHO instituted a working group to develop a consensual definition in which vitality capacity is a physiological state of energy and metabolism, neuromuscular function, and immune and stress response functions.[32] In higher physiological systems, energetic homeostasis is the highest level physiological system that mediates other higher energy-dependent regulation systems, such as neuroendocrine, immune, and metabolic regulation systems in molecular, cellular, and organ or systemic levels with epigenetic modifications by the external environment and genetic modifications by the internal environment.[33,34] Therefore, vitality may be the earliest domain to be impaired during aging among IC domains followed by other domains with high energy demand. However, the hierarchical order can be modified by environmental factors. The impairment of some dimensions may precede vitality impairment due to internal environmental factors, such as the susceptible apolipoprotein E (*APOE*) ε4 allele of cognitive impairment, or external environmental factors, such as noise-induced psychological stress and hearing impairment.

The energy constructs proposed by Schrack et al,[44] energy was divided into three levels: 1) essential energy, which is the energy essential for independent living, including energy expenditure for life maintenance at rest or resting metabolic rate and submaximal energy expenditure, which represents extra energy for unstable homeostasis and daily activities; 2) potential energy, or energetic reserve capacity that is available above essential energy (the difference of peak and essential energy expenditure); and 3) available energy that is above the resting energy (Figure 1A). Vitality is

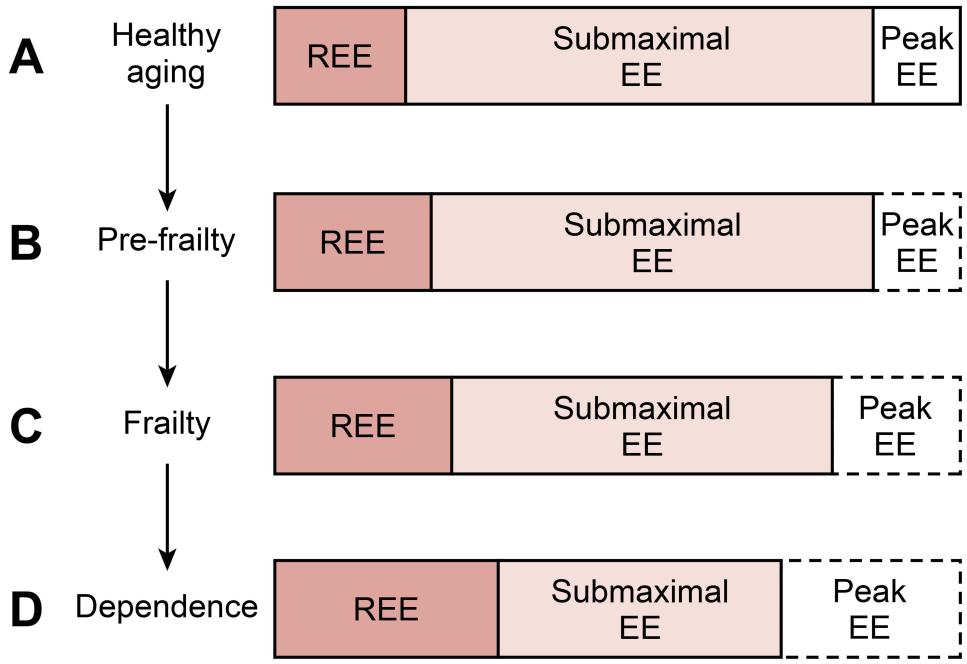

Figure 1 Schematic model of energetic capacity dynamic alterations from healthy aging to frailty and dependence. (**A**) Energetic capacity of healthy aging individuals. (**B**) Energetic capacity of individuals with pre-frailty. (**C**) Energetic capacity of individuals with frailty. (**D**) Energetic capacity of individuals with dependence. Essential energy expenditure = resting energy expenditure + submaximal energy expenditure; Potential energy expenditure = peak energy expenditure – essential energy expenditure; Available energy above resting energy.
Abbreviations: REE, resting energy expenditure; EE, energy expenditure.

the energy reserve required to the maintenance of independent living under stress. An energy reserve capacity below the essential energy demand is the vulnerability threshold for vitality. Previous studies indicated that declines in energy availability, resting, total, and peak energy expenditure.[45,46] From middle-age to late life, about 55% to 60% loss of the total available energy is lost.[44] In older individuals, it is necessary to adapt to the decline of energy availability, and the increase of essential energy for independent living with increasing age.[44,47] When aerobic energetic reserve capacity is below the essential energy limits, anaerobic metabolism is excessively activated to compensate for energetic demands for independent living,[48] which results in physical fatigue or exhaustion. Self-perceived fatigue was also identified among the WHO top attributes/biomarkers for energy and metabolism.[32] The biological, physiological, and psychological stressors during the aging process accelerate the decline in available energy and decrease in the threshold of fatigue,[49] which causes low physical activity, such as sedentary behavior and reduced endurance. The earliest symptoms and signs are ideal parameters for vitality diagnosis when frailty occurs in the physiological or psychosocial domains. Two longitudinal cohort studies showed that the first manifestation of physical components of frailty tended to be exhaustion, followed by slowness of gait, and other components.[50] However, weakness was reported the first manifestation in earlier studies.[51,52] Older individual with pre-frailty or frailty had a gradually decreased resting metabolic rate.[53,54] Frail and pre-frail older adults mediated energy requirement by the increase respiratory frequency to compensate the decreased oxygen consumption and expired volume.[54] Based on the above evidence, we speculated that the vulnerability threshold of vitality (energetic reserve capacity below the essential energy demand under stress) might be a pre-frailty status (Figure 1B).

When the decline in available energy is significantly below essential energy and not enough to maintain daily living, older individuals experience a declined physical activity,[55] slow gait,[46,47] weak grip, decreased sensory function, cognitive decline, and vulnerable psychosocial function,[33,34] apart from vitality vulnerability (Figure 1C). During exercise, the rapid decline of energy in older subjects with physical frailty was closely associated with fatigue and exercise intolerance.[56] Adaptive behaviors may be beneficial for conserving energy when available energy becomes deficient. However, further accelerated decline in fitness, such as diminished lean mass, increased body fat to lean ratio,

and chronic multimorbidity, leads to an increase in resting energy expenditure, dependence, and other adverse health-related outcomes (Figure 1D).[50]

The Critical Mechanisms of Aging-Related Decline of Intrinsic Capacity in a Hierarchical Order

During aging, the decline in IC domains occurs in a hierarchical order, depending on the energy demand under environmental stressors. Energy is mainly produced in the mitochondria by oxidative phosphorylation and is supplemented in the cytoplasm by aerobic and anaerobic glycolysis. Aging results in the downregulation of oxidative phosphorylation and antioxidant defenses, and an increase of reactive oxygen species (ROS) in mitochondria.[57] The hydrogen from fats and carbohydrates are oxidized with oxygen to generate energy [adenosine triphosphate (ATP) and heat] by β-oxidation and the tricarboxylic acid cycle (TAC) in the mitochondrial matrix. The electron transport chain pumps protons out of the mitochondrial inner membrane to create an electrochemical gradient through oxidative phosphorylation enzyme complexes I, II, and IV. When protons return the mitochondrial matrix from the mitochondrial inner membrane via a proton channel in complex V, the stored energy of the electrochemical gradient is transferred into chemical energy known as ATP in the matrix. ATP is then exchanged for cytosolic adenosine diphosphate (ADP) by the adenine nucleotide translocator. The downregulation of oxidative phosphorylation causes a chronically reduced electron transport chain, which promotes ROS production, mitochondrial deoxyribonucleic acid (DNA) mutagenesis, and premature cell death. Aging also results in the decline of nicotinamide adenine dinucleotide phosphate (NADPH) and antioxidants [glutathione (GSH))] through the pentose phosphate pathway.[57,58] Instead of the conversion from lactate to pyruvate, to produce acetyl coenzyme A (CoA) for entering the TAC, aging promote lactate production in the glycolysis pathway.[59] The decrease of ATP and antioxidant production and the increase of ROS cause the vicious cycle of energy defect or vitality below the threshold and pre-frailty status (Figure 2A). Moreover, energy defects increase vulnerability in other energy-dependent regulation systems, resulting in stress maladaptation at the molecular, organellar, organic, and systemic levels. In turn, it leads to progressive organ pathology, functional impairment in other IC domains, and clinical symptoms such as fatigue, exhaustion, slow gait, hearing and vision impairment, cognitive impairment, and frailty.

Mitochondrial function plays critical roles in the maintenance of mitochondrial bioenergetics. Mitochondrial energy exchange, and redox balance were selectively impaired by the mutation or deletion of both mitochondrial DNA (mtDNA)-encoded NADH dehydrogenase, cytochrome oxidase subunit I, and nuclear DNA-encoded nicotinamide nucleotide transhydrogenase in mice, causing psychological stress-induced abnormal neuroendocrine and metabolic function, inflammatory and transcriptional responses.[33] The decline in energy consumption during aging leads to a decreased adenosine monophosphate (AMP) or ADP/ATP and NAD^+/NADH ratio, which inactivate AMP kinase and sirtuin 1, respectively (Figure 2B). AMP kinase promotes the activity or expression of transcription factors, including peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC)-1α and forkhead box (FOXO) either directly or via elevating the activity of sirtuin 1 and its subsequent deacetylation of the two proteins.[58] AMP kinase mediates mitophagy and fission of dysfunctional mitochondria by phosphorylation of the pro-mitophagic factor UNC51-like kinase 1, and the mitochondrial fission factor (MFF), respectively,[60] which facilitates mitophagy of damaged mitochondria.[61] In addition to sirtuin 1, sirtuin 3 also regulates AMP kinase activity and glutathione antioxidant defense system by deacetylation.[62] In the nucleus, two master transcription coactivators, PGC-1α and nuclear respiratory factor 2 (NRF2) form heteromeric complexes with peroxisome proliferator activated receptor γ (PPARγ) control the levels of mtDNA polymerase and nuclear-encoded mitochondrial transcription factor A (TFAM), which promotes the expression of mtDNA-encoded proteins. Phosphorylated and deacetylated FOXO factors translocate to the nucleus and promote the transcription of target genes, including stress response genes, such as mitochondrial antioxidant manganese superoxide dismutase (MnSOD) and catalase, mitophagy and lysosome genes, and PGC-1α.[63] The down-regulation of downstream signaling pathways due to the inactivation of AMP kinase and sirtuin 1 leads to abnormal mitochondrial function, including the decline of mitochondrial biogenesis, bioenergetics, quality control, and elevation of ROS. Finally, these mechanisms result in a pre-frailty status (vitality vulnerability), dysfunction of neuroendocrine, immune, and metabolic regulation systems, such as stress response dysregulation by the hypothalamus-pituitary-adrenal (HAP) axis-

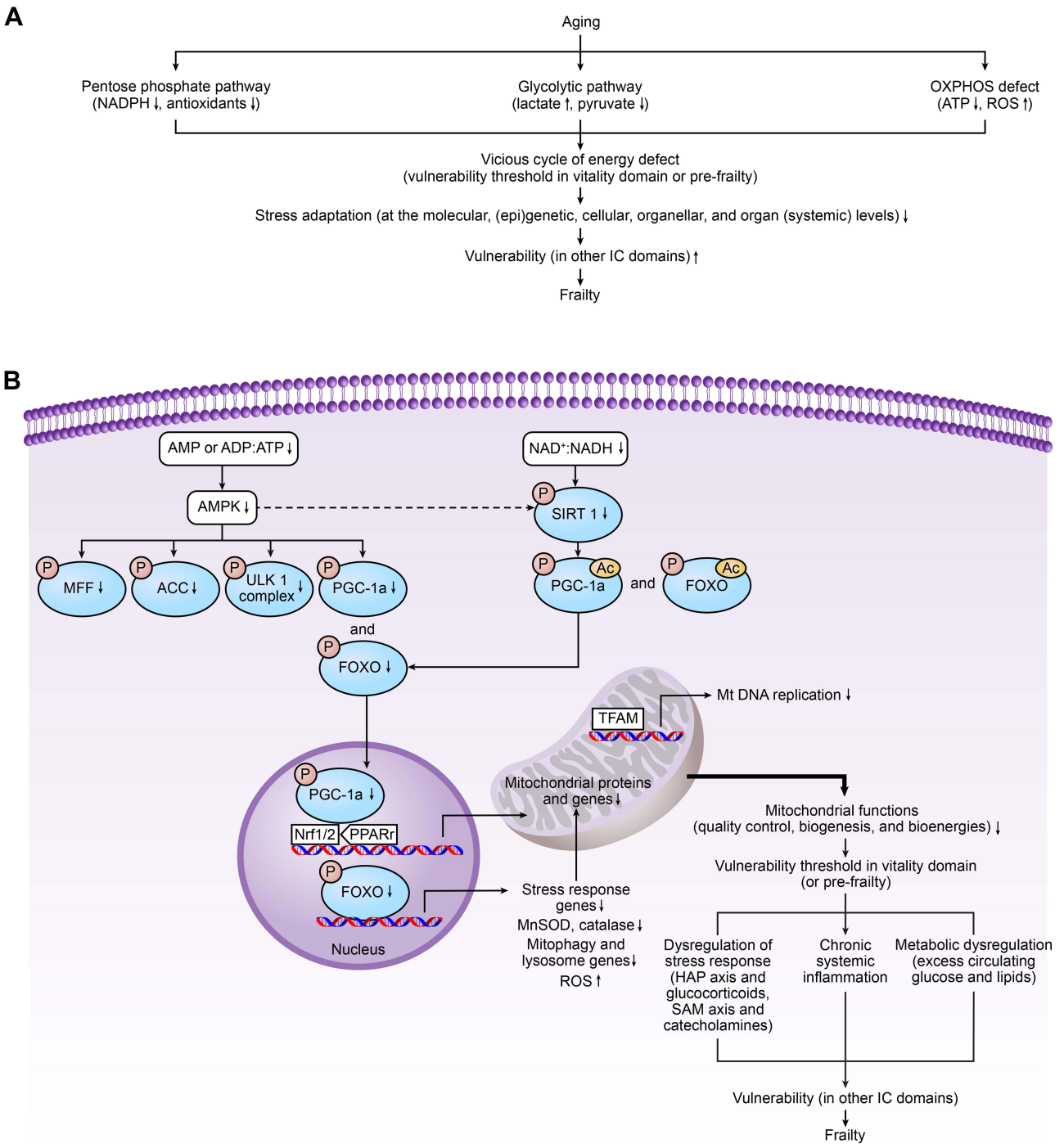

Figure 2 The consequences and mechanisms of aging-related energy defects. (**A**) Consequences of aging-related energy defects. Aging-related low resting energy expenditure causes low NADPH and antioxidants in the pentose phosphate pathway, low aerobic glycolysis, high anaerobic glycolysis, and oxidative phosphorylation defects, including low ATP production, high ROS, and a chronically reduced state of the electron transport chain. Persistent energy defects and pathological processes result in a vicious cycle of energy exhaustion (impaired vitality or pre-frailty). Energy exhaustion leads to stress maladaptation at the molecular, (epi)genetic, cellular, and organ (systemic) levels, which increases the vulnerability of other IC domains in an energy-dependent manner and, in turn, frailty. (**B**) Mitochondrial dysfunction is the major contributor to aging-related energy defects. Reduced energy consumption leads to a decreased AMP/ATP ratio, which inactivates AMP kinase, causing a decrease in β-oxidation of fatty acids by the phosphorylation of acetyl-CoA carboxylase, mitophagy by the phosphorylation of the ULK1 complex, and the activity or expression of PGC-1α and its downstream signaling pathways in the nucleus. Reduced energy consumption leads to a decreased NAD+: NADH ratio, which decreases the activity of SIRT1 and AMP kinase activity, and subsequent deacetylation of PGC-1a and FOXO. These aging-related molecular mechanisms result in mitochondrial dysfunction, including quality control, biogenesis, and bioenergetics, which cause vitality vulnerability, dysregulation of stress by HAP axis-glucocorticoids, SAM axis-catecholamine pathways, chronic systemic inflammation, and metabolic dysregulation, such as excess circulating glucose and lipids. In turn, dysregulation of these systems causes an increase in the vulnerability of other IC domains in an energy-dependent manner and frailty.

Abbreviations: IC, intrinsic capacity; NADPH, nicotinamide adenine dinucleotide phosphate; ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; AMPK, AMP kinase; ROS, reactive oxygen species; FOXO, forkhead box; ACC, acetyl-CoA carboxylase; ULK1, UNC51-like kinase 1; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; SIRT1, sirtuin 1; NRF1/2, nuclear respiratory factor; MFF, mitochondrial fission factor; TFAM, mitochondrial transcription factor A; MnSOD, mitochondrial antioxidant manganese superoxide dismutase; HAP axis, the hypothalamus-pituitary-adrenal axis; SAM axis, sympathetic adrenal–medullary axis.

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glucocorticoids, and the sympathetic adrenal–medullary (SAM) axis- catecholamines, chronic systemic inflammation, and metabolic dysregulation with excess circulating glucose and lipids. The impairment of other IC domains occurs in an energy-dependent hierarchical order. The combination of pre-frailty and impairment in different IC domains manifests as different frailty phenotypes or frailty severity. Several studies have indicated that mitochondrial dysfunction is closely related to frailty. White patients with frailty from cohorts of the Cardiovascular Health Study had a significantly low mtDNA copy number.[64] One of markers of cellular stress and damage is the circulating cell-free mitochondrial DNA, which was a significant increase in older adults with late-life depression and frailty.[65] The intermediates in energy-producing metabolic pathways, involving the TAC and glycolysis, were significantly increased in frail older adults.[66] Nrf2 deficiency could deteriorate frailty and sarcopenia in older mice further verified that the dysfunction of skeletal muscle mitochondrial biogenesis and dynamics mediate frailty progress.[67]

The Constructs of Frailty Phenotypes and Frailty Indexes Based on the Hierarchical Order of Intrinsic Capacity Domains

The concept of frailty is evolving. In clinical practice and research, the most common frailty models, including Fried et al phenotype model of frailty[14] and FI model developed by Rockwood and Mitnitski[15] were validated in a lot of clinical trials, and considered as basis for new frailty models or instruments. The main strength of the physical phenotype model is the possibility to identify the early stage of frailty after stress exposure and allostatic load of physiological systems. The limitation of this model mainly reflects physical dimension, and does not directly indicate the status of other dimensions. Compared with the physical phenotype, FI model may identify the multidimensional health deficits and frailty severity, but the model contains also frailty adverse outcomes, such as disabilities. FI model also does not strictly differentiate frailty from chronic diseases or multimorbidity. Nonetheless, different research groups are approaching frailty from multiple angles based on the two principal frailty models. Some research groups developed frameworks and diagnostic procedures for multiple frailty phenotypes, including cognitive frailty,[21,22] nutritional frailty,[27] and biopsychosocial frailty[25] and considered the physical frailty phenotype as the basic component. Other research groups extended perspectives for the two principal frailty models, including biomarkers[38,40] based on genetic, epigenetic and imaging techniques, sociocultural factors, besides multimorbidity, psychological factors, symptoms, and disabilities. New techniques,[39,41] such as wearable devices and smartphones have been also developed to improve the frailty screening and diagnostic procedures. Other research teams developed new frailty models or instruments, including multidimensional Groningen Frailty Indicator,[23] social frailty,[24] oral frailty,[26] mobility[28] and sensorial[29] frailty.

In the present review, we attempted to develop constructs of different frailty phenotypes or frailty indexes based on vitality vulnerability and capacity reserve decline in other IC domains. Several important questions must be addressed. Vitality capacity reserve, referred to as the energy metabolism reserve, maintains an individual's physiological homeostasis and is the main component of frailty. When the vitality capacity reserve (available energy reserve) is close to the level of essential energy, adaptation to adverse stressful events or homeostasis becomes difficult, and a pre-frailty status (vitality vulnerability) occurs. Following vitality vulnerability, other IC domains gradually declined in an energy-dependent hierarchical order, resulting in different frailty phenotypes and frailty severity (Figure 3A and B). However, vitality may not be the earliest impairment among IC domains, and other dimension vulnerabilities may present earlier than vitality due to internal environmental (genetic) and external environmental factors. For example, the *APOE* ε4 allele, is a risk factor for the cognitive dysfunction. With respect to external environmental factors, noise can induce psychological stress and hearing loss. In these conditions, individuals might manifest early or late multimorbidity due to the impairment of other IC domains with normal vitality reserves (Figure 3C and D).

Second, the dynamic development of frailty phenotypes and frailty indexes greatly depends on the trajectory of IC, leading to frailty heterogeneity. Frailty phenotypes and severity based frailty indexes developed dynamically with similar patterns over time. Frailty increased with increasing age, with higher rate in women and individuals with lower socioeconomic status.[5] Similar frailty patterns were found in community-dwelling older people from developed and developing countries. Several longitudinal studies indicated that the physical frailty phenotype was a dynamic process.[68–70] About 38.1% individuals retained their baseline frailty status,[70] and 36.4–36.8% had a transition in frailty status, in which transition to severe frailty was

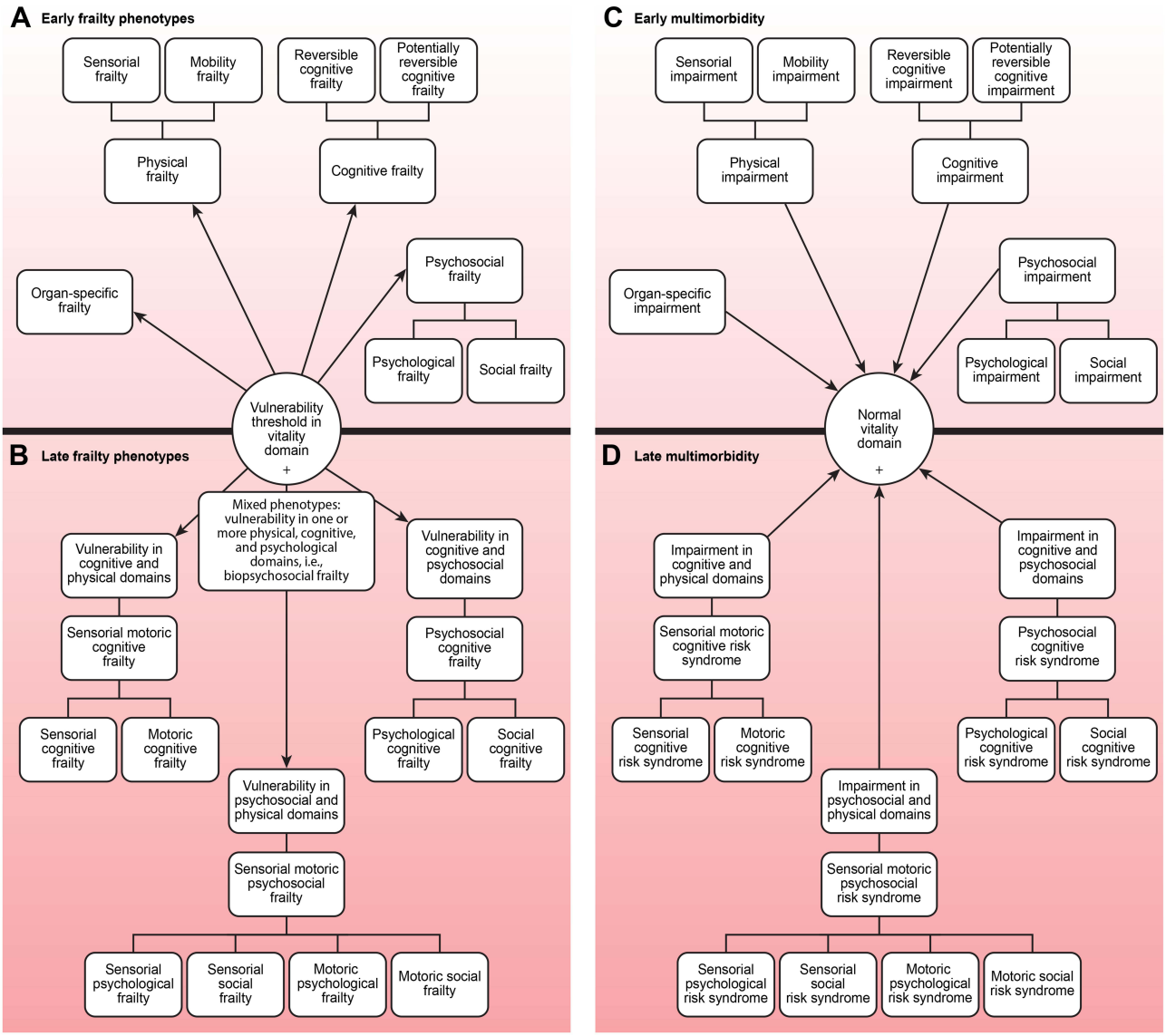

Figure 3 The classification of early and late frailty phenotypes based on the vulnerability of vitality capacity and other different intrinsic capacity domains. (**A**) Early frailty phenotypes based on the vulnerability of vitality capacity and one of the other four intrinsic capacity domains. (**B**) Late frailty phenotypes based on the vulnerability of vitality capacity and in more than one of the other four intrinsic capacity domains. (**C**) Early multimorbidity is based on vulnerability in one of the other four intrinsic capacity domains, accompanied by a normal vitality domain. (**D**) Late multimorbidity based on vulnerability in more than one of the other four intrinsic capacity domains, accompanied by a normal vitality domain.

more common than transition to lesser frailty status.[69,70] However, the rate of older individuals with physical pre-frailty converted to robust was higher than those that converted to physical frailty, and the rate of transition to frailty in men was higher than that in women.[69] Thus, at the late stage of aging, frailty phenotypes are more complex and severe.

In addition, there were interactions among the different IC domains. Women with sensory impairments had reduced muscle strength.[71] Vision/hearing loss was associated with pre-frailty and frailty in baseline; and vision/hearing loss was positively associated with frailty progression from baseline robustness.[72] Multiple impairments were related to increased risk of depressive symptoms,[73] poor performance on cognitive functions.[74] Dual sensory impairments in hearing and vision were independently and together associated with poorer cognitive, social function (social frailty), and depression outcomes.[29,74–76] Dual sensory impairment had been showed that might predict subsequent cognitive decline, and dementia.[77,78] Gait speed and handgrip are the common components of both IC and frailty. Slow gait was associated with cognitive impairment,[79] and low grip or slow gait speed could predict cognitive decline.[80] Cognitive and motor/physical dysfunctions might bidirectionally develop.[81]

The Constructs of Frailty Phenotypes Based on the Hierarchical Order of Intrinsic Capacity Domains

In the early aging stage, vitality impairment is the earliest among IC domains. When vulnerability occurring in vitality and one of the physical domains of IC (locomotion or sensory domain) may be considered physical (sensorial-mobility) frailty and its two subtypes: sensorial frailty and mobility frailty (Figure 3A). Cognitive frailty is referred to as vulnerability occurring simultaneously in the vitality and cognition domains. Based on the severity of cognitive impairment, including pre-mild cognitive impairment (MCI) and MCI, cognitive frailty may be defined as reversible and potentially reversible cognitive frailty of two subtypes.[22] Vulnerability occurring simultaneously in vitality and one of the psychosocial IC domains (psychological or social domains) may be referred to as psychological, social, and psychosocial frailty subtypes. In addition, vulnerability occurring simultaneously in vitality and organ function is referred to as an organ-specific frailty phenotype, for example, oral frailty.[26]

In the late aging stage, vitality vulnerability usually accompanies impairment of one or more other IC domains, including physical, cognitive, and psychosocial domains. We defined these as mixed frailty phenotypes, that is, biopsychosocial frailty (Figure 3B).[25] If vulnerability in other IC domains accompanies normal vitality capacity, individuals might manifest early multimorbidity, including the presence of chronic diseases related to domain-specific impairment or late multimorbidity, such as sensorial motoric cognitive risk syndrome (ie, sensorial cognitive risk syndrome and motoric cognitive risk syndrome (MCR)), sensorial motor psychosocial risk syndrome (ie, sensorial psychological risk syndrome, sensorial social risk syndrome, motoric psychological risk syndrome, and motoric social risk syndrome), and psychosocial cognitive risk syndrome (ie, psychological cognitive risk syndrome and social cognitive risk syndrome) (Figure 3C and D). However, normal vitality capacity with late multimorbidity syndromes is rare because other IC domains may also affect vitality capacity reserve.

The Constructs of Frailty Indices Based on the Hierarchical Level of Intrinsic Capacity Domains

Frailty index was based on a continuous score summing of age-related deficits, including signs, symptoms, disabilities, and diseases.[15] Following this, different constructs of frailty indexes were developed. Frailty indices can predict adverse health-related outcomes, such as developing MCR.[80] Individuals with higher scores of frailty index increased the risk of dementia even if individuals with a low level of AD pathology.[30] Compared with frailty phenotypes, it could be relatively easy to construct a new frailty index based on a score summing age-related deficits in different IC domains. However, vitality capacity is currently less reflected in frailty indexes. Vitality vulnerability or a pre-frailty status is a prerequisite for the construction of frailty indexes. Thus, frailty can be discriminated from multimorbidity by frailty indices. Moreover, vitality assessment may identify individuals who may benefit from early interventions to prolong functional ability (or slow decline). Some potentially relevant attributes/biomarkers of vitality capacity proposed by the WHO working group on vitality capacity could be integrated into frailty indices. Among these, there are prominent attributes/biomarkers for energy and metabolism, neuromuscular function, and immune and stress response functions.[32]

A real-life prospective study showed that the large-scale implementation of the WHO integrated care for older people programme through two-step care pathways, a positive screening and an in-depth assessment, were feasible for the diagnosis of IC deficits.[82] A real-world longitudinal study verified that physiological reserve was positively associated with IC domains, and individuals with better IC in different domains indicates better physical resilience, which may result in less frailty severity.[83] IC have been integrated into healthy aging model together with other environmental factors reflect the resilience. This model has been tested in clinical or community setting of European countries to improve the integrated-care of frailty phenotypes and multimorbidity.[84] These studies provided preliminary evidence for the integrating framework proposed by us.

How to Implement Frailty Screening After Integrating IC in Frailty in Real-World Clinical Practice

To assess integrated frailty through the construct of frailty phenotypes and frailty indices, there is less controversy in the rapid screening and in-depth assessment instruments of cognitive, psychological, social, and nutritional domains.[85] The inconsistency is mainly due to the assessment of the vitality domain, and the discrimination of vitality from physical domains, especially the locomotion domain. Biologically interconnected symptoms and signs that jointly express energy dysregulation, usually used for

physical frailty diagnosis, were also used to detect vitality. Some frailty biomarkers, such as unintentional weight loss or gain, abnormal BMI,[86] abdominal circumference, nutritional status by Mini Nutritional Assessment, abdominal fat,[10,11,87,88] hand grip strength,[10,88,89] and loss of appetite were used alone or in combination with other biomarkers for detecting vitality.[7,87,90] Vitality was also assessed by four simple questions from the 36-Item Short Form Health Survey (SF-36).[91] However, these instruments for vitality screening may be confused with frailty screening tools. Recently, a valid and theoretically error-free composite score for IC was created using biomarkers and self-reported measures.[12] Vitality was objectively assessed using forced expiratory volume (FEV), grip, and blood biomarkers. The construct model was validated in a longitudinal English cohort and a Chinese cohort.[13] However, these parameters did not directly reflect energy status. Grip was useful for detecting the locomotion domain of IC, and biomarkers only indicated aging-related physiological alterations. There are many similar aging-related biomarkers, such as resting metabolic rate or circulating lactate level.

The proposed construct of frailty models, both phenotypes and indexes, based on integrated IC domains, requires a simple, rapid screening tool and valid clinical research criteria for vitality. While there was a recent consensus on the WHO working definition for vitality capacity,[32] and some potential biomarkers have been identified, a further systematic review of the potential biomarkers of vitality capacity to develop an operational definition of this construct. Among these biomarkers, several direct assessment tools for energy metabolism and vitality capacity need to be investigated. Some tools are the resting, submaximal, and peak energy expenditure.[44] A 6-minute walk and peak oxygen consumption during cardiopulmonary testing may be potential instruments to assess vitality. Frail individuals with exercise intolerance are distinguished from healthy middle aged individuals by fast fatigue with a seven-fold faster energetic decline in skeletal muscle.[56] Cardiorespiratory fitness, indicated by high metabolic equivalent, is inversely related to mortality risk after adjustment by age, race, and sex.[92] Therefore, energy-dependent cardiorespiratory fitness may also be another useful parameter to assess vitality capacity.

Some simple and non-invasive attributes/biomarkers for the rapid screening of vitality dimension proposed by the WHO are easy to collect by older people themselves and professional healthcare providers in routine practice. The rapid screening instrument is composed of non-invasive attributes/biomarkers. Rapid screening of vitality can not only identify at-risk individuals with pre-frailty but also further measure the vitality domain using more objective in-depth assessment tools and identify pre-frailty individuals who may benefit from early interventions to achieve healthy aging. The in-depth assessment instruments include muscle endurance (exercise intolerance), available energy, energy-related circulating biomarkers (glycated hemoglobin), and immune-related circulating biomarkers of inflammation. Professional healthcare providers can perform an in-depth assessment of the vitality domain. Additionally, compared with rapid screening instruments, some components, such as circulating glycated hemoglobin and C-reactive protein, have been collected in routine practice. It is feasible to integrate these easily collected components from rapid screening and in-depth assessment into electronic medical records or other administrative data sources.

The implementation of the proposed integrating model into the WHO integrated care for older people programme in different settings will significantly improve the cost-effectiveness for personalized care of healthy aging. However, there are some critical challenges before the integrating model could be widely accepted and translate in real-world. Firstly, more evidence is needed to support that vitality was the top hierarchical order of different IC domains, and the earliest change in vulnerability, or pre-frailty status. Secondly, it is difficult to find the objective instruments to assess the resilience/vulnerability in physical, cognitive, psychological, and social domains. Moreover, some measures such as exercise endurance and available energy to assess vitality are difficult to collect in routine practice.

Conclusion

Vitality capacity, referred to as energy metabolic reserve, and may be the basis of other IC domains and a pre-frailty status. Additionally, based on the hierarchical order of different IC domains, particularly vitality capacity, we proposed a conceptual framework of frailty phenotypes and frailty indexes. Potential energy metabolism-related contributes/biomarkers have also been proposed as critical components for the rapid screening or objective assessment of vitality capacity in older age. The integration IC into frailty models in clinical practice will enhance healthcare cost-effectiveness and outcomes, optimizing aging interventions, and guiding public health policies.

Data Sharing Statement

Further details about the data are available from the corresponding author on reasonable request.

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Disclosure

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