Abstract

The propensity for regular and repeated physical exercise to induce and maintain a hormetic effect upon health parameters over a broad range of disorder conditions through the progression of resilience to neurodegenerative disorders, diabetes, stroke, sarcopenia, osteopenia, immunosenescence, and metabolic syndrome has been examined. Beyond the alleviation fragility, fatigue, stress-distress and selective vulnerability perturbations induced by different forms of physical exercise may induce hormesis and/or autophagy, through the disruption of homeostasis and manifestation of adaptive responses, to instigate multi-layered resilience. The hormesis challenges, accomplished through daily exercise, the promotion of resilience at molecular, cellular, tissue, e.g. muscle, and organ, e.g. brain, immune-functioning, bone material, physiological and behaviour-expressive levels, have been observed both from pathophysiological and etiogenetic dimensions. Regular exercise over extended periods (optimally years and decades, preferably lifelong) is expected to shift the inverted-U shaped hormesis curve to a sensitization' whereby the health benefits of consisting of suitable proportions of endurance and resistance type, performed daily over months, years or decades ought to instigate some manner of ‘behavioural sensitization’ whereby the health benefits of equivalent levels of exercise escalate incrementally.

The process of hormesis, which encompasses the processes of adaptation and conditioning, occurring in cells, tissues and/or organs and organisms generates biphasic responses/behaviours/activities/reactions to the exposure of, initially, low doses/amounts of a potentially/effectively harmful, yet increasing, amounts of agents or conditions or experiences; Mithridatism, a concept harking back to Mithridates IV, King of Pontus, refers to the self-inflicted exposure to toxins/radiation/nociception in order to develop 'immunity' or 'resilience' to toxin(s) applied whereby physiological resistance to a poison may be attained by gradually self-administering non-lethal amounts with mechanical and metabolic consequence for bodily tissues [75]. Adaptation and conditioning, compatible and interchangeable notions, imply that low levels of stress may mobilize and up-regulate the existing molecular and cellular pathways to promote cells and organisms to enhanced physiologic resilience to greater stress not least in providing resistance to neurodegenerative disorders [25, 24]. Within the so-called hormentic zone, in general, there arises a favourable biological and/or behavioural response to low exposures to toxins, irradiation and other biological/behavioural stressors [22]. Hormesis is derived from Greek “horiais” “rapid motion, eagerness”, in turn derived from ancient Greek word hormnaien to set in motion, impel, and urge on”. A pollutant or toxin agent that incurs hormesis would produce the opposite, but not exactly so, effect at small doses as it would at large doses. Hormentics presents the notion that involves the study and scientific basis for hormesis whereas Mithridatism implies the deliberate self-exposure to toxins/harmful agents in order to evolve immunity/resilience against these agents.

In neurotoxicological studies, hormesis manifests a ‘dose response’ phenomenon that is characterized by low dose stimulation, high dose inhibition that results in either a J-shaped or an inverted U-shaped dose response curve. Low doses of noxious environmental agents have been shown to induce autophagy, an essential adaptive response that protects all cell types globally, in addition to exerting influences both on the products of gene translation and transgenerational via epigenetic mechanisms with implications for neuropsychiatric disorders, ageing and neurodegenerative disorders and clinical interventions [2]. The selective nature of the biphasic dose responses to stressors, toxins, environmental challenges, particularly physical exercise, serves as the unique signature of hormesis, independent of inverted U- or J-curve depiction. Such environmental factors that would seem to produce positive responses have also been termed “eustress-inducing” factors. A recent notion that elaborates the hormesis theme at the expense of parsimony, is ‘adaptive homeostasis’ which has been defined as ‘The transient expansion or contraction of the homeostatic range in response to exposure to sub-toxic, non-damaging, signalling molecules or events, or the removal or cessation of such molecules or events’ [30]. The concept of hormesis has been applied increasingly to cover molecular biological processes whereby mild-moderate intermittent stressors from any source, e.g. physical exercise, calorie restriction, fasting and cognitive stimulation, may induce hormesic responses [55]. Mitohormesis refers to mitochondrial retrograde signalling causing, amongst other effects, accelerated generation of mild reactive oxygen species caused by these stressors [78, 110, 113]. Xenohormesis refers to phytochemical-induced hormesis arising from the reciprocal determinant relationships between plants and animals [31].
Thus, the distortions or disarrangement of fundamental physiological agents/nutrients acting outside their normal range, essentially hormesic processes, through the disruption of homeostasis, may instigate a wide variety of beneficial influences that eclipse the mere alleviation of stress-distress or vulnerability. In the context of physical exercise and training, each bout of exercise may be regarded, for present purposes, as a low dose of toxin exposure that is assuming that a moderate level of exercise is undertaken. With each successful bout of exercise (daily), health assets, such as anti-inflammatory cytokines and brain-derived neurotrophic factor (BDNF) are expected to increase whereas health liabilities, e.g. pro-inflammatory cytokines and stress hormone levels ought to decrease [6]. These and other assets may arise from several sources, including reactive oxygen species and cytosolic calcium functioning as common triggers of signalling pathways [88]. The particular interaction between physical exercise and oxidative stress constitutes an extremely complex reciprocity that emerges from relationships between the type, intensity, frequency and duration of exercise, as well as the ratio of endurance and resistance exertion since acute exercise culminates increased oxidative stress thereby permitting these operations (stimuli) to endow an hermetic up-regulation of the body's endogenous antioxidant defence systems [79]. Under conditions of extreme training, elite athletes under conditions of high oxidative stress may be of necessity required to consume levels of anti-oxidant supplementation. Among post-fontan, palliative surgical procedure used in children with univentricular hearts, patients, physiological resilience was obtained through endurance exercise controlled respiratory training that improved cardiorespiratory performance and greater aerobic capacity [3].

**Hormesis challenges of exercise**

According to Mattson and co-workers [14, 60, 62, 65, 68], the hormetic effects of physical both exercise and dietary energy restriction may diminish the risk of cardiovascular disease, diabetes and stroke as well as neurodegenerative disorders through the stimulation of mild transient stressors affecting cardiac and vascular cells, exercise therewith up-regulates the expression of genes encoding proteins involved in cellular stress resistance, e.g. heat-shock proteins and growth factors. Neuronal networks augur the “primary responders” to these operations (stimuli) to endow an hermetic up-regulation of the body's endogenous antioxidant defence systems [79]. Under conditions of extreme training, elite athletes under conditions of high oxidative stress may be of necessity required to consume levels of anti-oxidant supplementation. Among post-fontan, palliative surgical procedure used in children with univentricular hearts, patients, physiological resilience was obtained through endurance exercise controlled respiratory training that improved cardiorespiratory performance and greater aerobic capacity [3].

**Resilience promotion**

Hormesis pertains to the phenomenon through which a single exposure or repeated exposures of a noxious agent/stressor may evoke adaptive physiological or behavioural modifications from the organism that permit greater resistance to higher doses of the noxious agent/stressor with reduced/diminished harm/injury to the biomanisms its coeptual refinements have been extended and developed to encompass 14 areas of application [26]. In the context of physical exercise, long-term training, optimally chronic and on a daily basis, and perhaps even a single, acute bout, induce adaptive responses consisting of marked plasticity and physiological resilience in antioxidant defence capacities and metabolic functions mainly due to re-modelling of cellular mitochondria through processes involving the activation of redox-sensitive signalling pathways [52], adaptations that are of essential relevance among ageing individuals threatened by sarcopenia and fragility. Among ageing populations, lassitude and frailty increase to around two-and-a-half times that of younger populations due to reductions in electrically-evoked contractile properties of muscle fibres; the selective loss of fast myosin heavy chain II muscle has been linked markedly with age-related losses of whole-muscle strength, i.e. isometric torque and power. A sedentary life-style during ageing described by physical inactivity both accelerates sarcopenia and aggravates the survival of myocytes whereas resistance exercise counteracts inactivity-induced muscle atrophy in older adults. Contrastingly, prolonged endurance, aerobic, exercise or shorter-duration, high intensity, resistance, exercise induced heightened levels of biomarkers for oxidative stress in both blood and skeletal muscle in humans and laboratory animals [49, 50, 91], lipid peroxidation [48, 85, 112] and the immune-redox balance [5]. Among aged, immunosenescent populations, pulmonary pseudomonas aeruginosa infection may cause severe morbidity and mortality. Two-year old, aged, BALB/c mice were assigned to the exercise or sedentary, or infected or non-infected groups [96].

As evolutionary-based adaptive responses, hormesis in living organisms promotes performance and resilience through cell proliferation, reparations of cells and tissues, regional brain and CNS integrity, associative plasticity, fecundity, disease resistance, behavioural and cognitive-emotional limits and healthy ageing and longevity that are essential for endurance and thriving in challenging physical and social environments [12, 28, 63]. Small molecules, such as tomatidinepresent in unripe tomatoes generating mitochondrial hormesis by mildly causing reactive oxygen species production which produces cellular stress resistance, present an avenue to alleviate the generative effects of human laboratory rodent and human neuronalaging; the compound extended lifespan and health-span in an animal model, the worm Caenorhabditis elegans, of ageing which shares many major longevity pathways with mammal by improving many behaviours associated with health-span and muscle health, such as increased pharyngeal pumping, swimming movement, reduced percentage of severely damaged muscle cells and upsurge of cellular antioxidant response pathways [34].
the aerobic exercise condition, pulmonary pseudomonas aeruginosa colonization and lung inflammation, i.e. total cells, neutrophils, lymphocytes in bronchoalveolar lavage with significant effects upon bronchoalveolar lavage levels of IL-1ß (interleukin-1ß), IL-6, CXCL1, and TNF-a [96], as well as parenchymal neutrophils. Exercise elevated significantly the bronchoalveolar lavage levels of IL-10 and parenchymal and epithelial IL-10 expression, while epithelial and parenchymal NF-xB [83] expressions were reduced. Taken together, the aerobic exercise intervention/exposure blocked pulmonary pseudomonas aeruginosa colonization that had induced lung inflammation (pneumonia) in the aged mice, and bacterial colonization among elderly mice that involved IL-10/NF-xB, and redox signalling.

The role of physical exercise in antioxidant enzyme activity and apoptosis-related protein expression linked to diabetes has been the subject of some consideration [13, 44, 74]. Three groups of rats consisting of a LETO-control group), an OLETF-diabetes group and an OLETF + EXER group, which received resistance exercise, were studies [57]. Lipid peroxide and superoxide dismutase activity were increased significantly among the OLETF + EXER group compared to OLETF-diabetes group, whereas Gluthathioneperoxodixase activity was reduced markedly among the OLETF + EXERCompared to the OLETF-diabetes group. Caspase-3 expression within the hippocampus region was reduced markedly also among the OLETF + EXERcompared to the compared to OLETF-diabetes group. Bax protein expression indicated markedly lowerlevels in the OLETF + EXER group than in the OLETF-diabetes groupwhereas Bcl-2 expression reached notably higher levels in the OLETF + EXER group than in the OLETF-diabetes group. Finally,Homeostatic Model Assessment of Insulin Resistance levelswere reduced markedly among the OLETF + EXER group in comparison with the OLETF-diabetes group. Thus, it was demonstrated that regular resistance-type physical exercise as an intervention effectively diminished diabetes-related oxidative stress by the enhancement of antioxidant enzyme activity which in turns appears to have attenuated apoptosis-related protein, such as caspase-3, bax and bcl-2 expression in the hippocampus of diabetic populations.

![Figure 1](image-url). The hormetic effects of exercise intensity upon Cell integrity as indexed by resilience to oxidative stress concurrent with the promulgation of plasticity, autophagy and bioenergetics.

**Resilience to sarcopenia**

Maintenance of skeletal muscle mass and muscular strength throughout the lifespan presents a central determining factor for human health and well-being. Throughout the process of ageing, gradual loss of both skeletal muscle mass and strength promotes the risk liabilities linked to the propensity for exacerbated injury and impairment, likelihood of functional dependence, morbidity and mortality. Some of the causes of sarcopenia include: reductions in physical exercise and activity, loss of neuronal signals from brain to muscle thereby lowering hormone levels, a decline in the body’s ability to convert protein to energy and improper nutrition in terms of caloric and protein intake to maintain muscle mass and strength [72]. Cardiovascular fitness has been shown to be correlated strongly with peak oxygen consumption, skeletal muscle index, and first ventilator threshold and peak oxygen pulse in distinguishing between sarcopenic and non-sarcopenic elderly men [18]. An inverse association has been indicated between the hourly increments in total, moderate, vigorous, and moderate-vigorous physical exercise, the latter of which correlated with body-mass-index and waist circumference in 1539 aged men and women [92]. Among elders patients presenting combined sarcopenia and diabetes mellitus, with lower extremity muscle mass, resistance exercise therapy was shown to be beneficial [70]. Among a cohort of reasonably well-trained male subjects, aged 19-33, mean = 25, years, physical exercise, endurance-type, elevated markers of autophagy within human skeletal muscle tissue after the first 2-hours of recovery from continuous moderate cycling at 157±20 W for 60 min or continuous moderate cycling bouts that were interspersed by 30-sec cycling sprints (473±79 W) every 10-min and 8 weeks of exercise training increases the capacity for autophagy and mitophagy regulation [19]. They found that, among the participants, exercise elevated markers of autophagy in human skeletal muscle within the first 2 hours following recovery from the exercise-bouts and 8 weeks after cessation of exercise training augmented the capacity for autophagy and mitophagy regulation. Hormesis pertains to the outcome of a small amounts of damage that are inflicted upon an organism or tissue with the end-outcome of a net gain in health and function whereas autophagy, involving longevity, represents the means of recycling cells’ old, broken, or unneeded parts’ so that their components may be reutilized for synthesis of new molecules or be burned for energy. Mitophagy occurs in defective mitochondria following damage or stress and is the selective degradation of mitochondria through autophagy. Hormesis is dependent upon autophagy into to repeat its benefits.

The potentially injurious properties of hormetic exercise upon muscular tissue ought not to be doubted: during cardiomyocyte injury, stretch, and/or fibrosis, cardiac Troponins, regulatory proteins integral to muscle contraction (e.g. cTnI, cTnT), NT-proBNP, and galectin-3 (GAL-3), of cardiac and skeletal muscle present biomarkers of heart disorders that are observed. Autophagy refers to the naturally-occurring, intrinsically-regulated mechanism through which the cells, e.g. muscle cells, disassemble/dismantle the unnecessary or dysfunctional components present whereas failure of autophagy is thought to be one of the main reasons for the accumulation of damaged cells and ageing. In a study of 18 half-marathon runners (15 males, 46 ± 6 years), the above troponins were elevated transiently post-race, exceeding the diagnostic threshold, but were normalized after 24 hours, implying a temporary stress on the myocyte [103]. Nevertheless, this increase of all the cardiac troponin biomarkers was both moderate and reversible most likely representing the physiological response to acute exercise.

**Resilience to osteopenia**

Transient hormetic challenges may result in prolonged resilience. Premature physical disability due to osteoporosis, with 80% women at risk, afflicted large numbers of individuals, 10 million in the United States. The role of physical exercise in antioxidant enzyme activity and apoptosis-related protein expression linked to diabetes has been the subject of some consideration [13, 44, 74]. Three groups of rats consisting of a LETO-control group), an OLETF-diabetes group and an OLETF + EXER group, which received resistance exercise, were studies [57]. Lipid peroxide and superoxide dismutase activity were increased significantly among the OLETF + EXER group compared to OLETF-diabetes group, whereas Gluthathioneperoxodixase activity was reduced markedly among the OLETF + EXERCompared to the OLETF-diabetes group. Caspase-3 expression within the hippocampus region was reduced markedly also among the OLETF + EXERcompared to the compared to OLETF-diabetes group. Bax protein expression indicated markedly lowerlevels in the OLETF + EXER group than in the OLETF-diabetes group. Finally,Homeostatic Model Assessment of Insulin Resistance levelswere reduced markedly among the OLETF + EXER group in comparison with the OLETF-diabetes group. Thus, it was demonstrated that regular resistance-type physical exercise as an intervention effectively diminished diabetes-related oxidative stress by the enhancement of antioxidant enzyme activity which in turns appears to have attenuated apoptosis-related protein, such as caspase-3, bax and bcl-2 expression in the hippocampus of diabetic populations.

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States alone, and a further 18 million presenting low bone mass/density implying greater risk for the affliction [53, 109], with lean mass among girls and young women an essential determinant for bone strength and density [46]. In osteopenia, bone mass density is lower than normal, with bone mass density T-scores of between -1.0 and -2.5, with a higher incidence in older women, and more frequently in post-menopausal women due to the loss of estrogen [73], but a wide range of risk factors have been indicated, including excessive caffeine, alcohol, smoking, or prolonged use of glucocorticoid medications [47, 98], diabetes type 2 and HIV [1, 40], and not least a sedentary lifestyle [108]. Peak bone mass is obtained at around 18 years of age with growth maintained through the third decade and exercise offers a significant factor in bone accrual influencing markedly annual gains in bone density and mass during the ages of 13-18 years [93]. Osteopenically-inclined young women failing to attain high peak bone mineral density remain at risk for developing osteoporosis [36]. Whereas swimming and bicycling seem unlikely to inhibit osteopenia, resistance exercises such as weight-training and since ‘bone-loading’ exercise offer protection and it appears likely will increase bone mineral density [114,116]. Physical exercise classes consisting of either cardio-kickboxing or yoga improved serum osteocalcin, with higher serum-osteoalcalcin levels relatively well-correlated with bone mineral density increases, among premenopausal women, aged 18-28 years [95]. Osteocalcin, bone gamma-carboxyglutamic acid-containing protein, a non-collagenous protein/hormone in bone and dentin, also acts on myocytes to bolster energy availability and utilization thereby promoting exercise capacity. Bone-loading exercises are highly beneficial for adolescent and pre-pubertal girls whereby effective increments in peak bone mass are forthcoming through mobilization of jumping/hopping, and/or resistance training with two-to-four relatively short (30 min/day or less) exercise sessions per week over a prolonged period can maintain or improve bone mass; among older women facing risk factors that preclude them from participating in high-impact activities, other weight-bearing exercises, e.g. resistance training, weight-specific yoga postures, or walking, ought to be effective in maintaining or improving bone mass/density [99]. Dietary supplements may enhance the effects of exercise upon bone density: it was observed that regular physical exercise (physical training protocol) co-administered with red wine and resveratrol, a plant polyphenol antioxidant, solution which provide bioactive compounds, improved the beneficial effects on bone health, femoral dimensions, bone mineral density and bone mineral content, even in combination with a high saturated fat diet that induces deleterious effects on bone mineralization [27].

**Metabolic resilience**

Among both older and elder older individuals and laboratory animals, healthy ageing and the reduced risk for several disorders is linked to benefits accruing from cardiovascular exercise, i.e. aerobic/ endurance exercise of low to high intensity that depends primarily on the aerobic energy-generating process, using oxygen for exertional energy demands during exercise via aerobic metabolism [111]. The complicity of oxidative stress in a range of health- and well-being-threatening pathophysiological conditions, especially ageing, neuro-inflammatory, cardiovascular and neurodegenerative disorders is coupled to the damage inflicted upon several cellular and tissue biomarkers that include proteins, DNA and lipids. Contrarily, from an hormesic standpoint, the free radicals provoked during physical exercise comprise essential modulators of muscle contraction, antioxidant protection, and oxidative damage repair whereby reactive oxygen species, generated during exercise bouts, present the main mediators of antioxidant molecule/agent up-regulation, as assessed by the increased glutathione reductase and/or superoxide dismutation levels following endurance/resistance exercise training [5, 89, 107]. Consequently, it seems the case that regular, habitual-type physical exercise, dependent on mode, intensity, and duration, generally promotes a decreased risk for coronary heart and related disease and mortality while, on the other hand, sudden, vigorous exercise would be expected to increase the likelihood of precipitate cardiac death among sedentary individuals with pre-existing vascular disease profiles [17]. The amount of time spent sitting as opposed to time standing, walking, gardening or doing household work presents deferential effects upon cardiovascular health or cardiovascular issues as assessed through changes in endothelial functioning as marker of cardio-metabolic integrity. In a group of 61 subjects, with normal weight, overweight and type 2 diabetes, assigned to ‘exercise’, ‘light-intensity walking and standing’ and ‘sitting 14 hrs/day’ groups, it was found that endothelial dysfunction scores, soluble intercellular adhesion molecule-1 and Se-selection were lowered in the exercise group [33]; insulin sensitivity and plasma lipids, HDL-cholesterol, non-HDL-cholesterol, total cholesterol and Apolipoprotein B, were lower in the ‘light-intensity walking and standing’ group compared with the ‘sitting 14 hrs/day’, together implying that light physical activity and moderate-to-vigorous physical exercise exerted a differential effect upon risk markers of cardio-metabolic health.

The effects and outcomes may be explained by the notion of hormesis through which low doses of an agent (exercise) that is destructive at high dose levels, induces adaptive beneficial responses upon the cells/tissues or the organisms’ health. Remarkably, following the administration, into the tail-vein, of the exercise-conditioned plasma, catalase $V_{max}$ and $K_m$ values, measured in gastrocnemius muscle, were increased implying that potential adaptations stimulated by the administered exercise-plasma constituted an active fluid capable of regulating tissue homeostasis host tissues [104]. In a prospective pooled analysis of 11 population-based baseline surveys in England and Scotland between the years 1994 and 2008 that were linked with mortality records, that incorporated 50225 walkers, were studied with a particular attention to associations between walking pace (slow, average, brisk/fast) and all-cause, cancer and cardiovascular disease [94]. The notion that walking exercise benefits health parameters was supported and accepting a causality relationship their results suggested that increasing walking pace may diminish risk levels for all-cause and cardiovascular mortality.

![Figure 2](image_url)

**Figure 2.** The hormetic effects of exercise intensity upon as indexed by resilience to behavioural stress concurrent with the promulgation of cognition, positive mood and different types of performance.
Physiopathological resilience

Sedentary individuals ("couch-potatoes"), unengaged intellectually with unrestricted calorie intake and an over-nourished metabolic phenotype are uniquely vulnerable to cardiovascular disorders, stroke, Alzheimer's disease and Parkinson's disorder whereas lifestyles consisting of physical exercise, dietary restriction and social and intellectual challenges develop multilevel pathways of hormesic resilience [66]. Physical exercise, e.g., aerobic, abates the risk of morbidity and reduced mortality from cardiovascular disease and even related malignancies, as an effective, health-promoting stressor with conspicuously hormesic properties. Through this latter process, cellular and physiological adaptations, cardiovascular and muscular, to an environment enriched oxygenation drove the development of multi-layered systems of stressors that include mechanical, metabolic, oxidative components, conferred by exercise, perception followed by protection, including antioxidant and stress response proteins. These short-lived outbursts of stressor-sensations during acute bouts of exercise or exercise-training schedules, also referred to as 'preconditioning' aroused augmentation of cellular stress defences against forthcoming insults of oxidative, metabolic and mechanical stressors that may induce injury or disease pathophysiology. Exercise hormesis/preconditioning that induces the stress response and antioxidant enzyme activation safeguards against striated muscle damage, oxidative stress and injury with marked clinical protection against ischemia-reperfusion injury, Type II diabetes and the ravages of ageing [56]. In an animal laboratory study, C57/Bl6 mice were assigned to either sedentary or exercise conditions, involving either 1, 3, or 12 h of access to a running wheel per day, 5 days/weeks, beginning at 3.5-4 months of age, over an eight-month intervention period followed by a battery of neurobehavioral testing and, after sacrifice, the collection of blood and tissues for biomarker assay [84]. It was observed that the longer access to a treadmill running-wheel intervention induced markedly greater volume and higher running speed, but more breaks in running. All the exercise groups, taken together, displayed reduced body weight, increased muscle mass, improved motor function on the rotorod test for motor capacity, and reduced anxiety in the open field test. Although all the exercise groups showed improved food intake, the largest increase was shown by the 12 h group but did not differ between 1 h and 3 h mice. Whereas exercisedose-dependently increased working memory performance in the Y-maze, the 1 h and 12 h groups displayed the largest changes in the mass of many organs, as well as alterations in several functional analyses including social interaction, novel object recognition, and Barnes maze performance. Their results imply that long-term, even chronic, exercise induces far-ranging effects upon physiological markers, function, and cognition, which may diverge through "dosage/intensity" and measurement, with only relatively limited investment of small amounts of daily exercise bestowing notable benefits to cardiovascular health and performance.

Both laboratory and clinical studies have provided ample evidence for the ameliorative role of physical exercise whether endurance or resistance in the treatment of Parkinson's disease [7, 9, 10, 11]. For example, in the laboratory mouse MPTP model of Parkinsonism, using a treadmill running exercise set-up, autophagy, through autophagy flux, and dopaminergic neuronal regeneration, and reduced apoptotic cell death were observed [51]. Similarly, the influence of exercise intervention for marked benefits in both normal ageing and Alzheimer's disease happen consistently documented [6, 10]. Even 'late-running' confers benefits: even 7 months of sedentary life-style, 5 months of wheel-running that was initiated 4 months after disease-onset ameliorated aspects of complete Alzheimer's pathology in TgCRND8 mice [45], such as structural plasticity via elevated dendritic complexity, beta-amyloid (Aβ) plaque burden and enhanced amyloid clearance across the blood-brain barrier, along with attenuations of micro gliosis, inflammation, oxidative stress, autophagy deficits, that promoted better memory performance and lower levels of agitation. Dysfunctional autophagic action is implicated in physiopathology of α-amyloid deposition, a major morbidity hallmark of Alzheimer's disease. Groups of transgenic APP/PS1 mice were assigned to either the sedentary or exercise conditions as were groups of wild-type mice [115]. Both Aβ plaques and soluble forms of Aβ (Aβ40 and Aβ42) were significantly increased in transgenic sedentary mice, who displayed a decrease in autophagy activity as evidenced by a significant increase in the levels of light chain 3-II and P62, as well as an accumulation of lysosome, compared with wild type sedentary mice, whereby exercise reduced Aβ deposition in APP/PS1 transgenic mice. Exercise increased autophagy activity as evidenced by a significant reduction in the levels of P62 and Lamp1 in the transgenic exercise mice. In the autophagic influence of exercise diet, the microtubule-associated protein, tau, which promotes microtubule-associated protein contributing to the etiopathogenesis of Alzheimer's disease, was examined for the role of exercise and calorie restriction intervention in obese mice [42], with beneficial, reductive effects of exercise on tau phosphorylation and detrimental, invigorating effects of caloric restriction upon tau aggregation. Exercise is necessary for skeletal muscle homeostasis and alters autophagy and unfolded protein response. In young previously-untrained male participants, autophagosome, spherical structure with double layer membranes essential for macro autophagy, content was augmented by resistance training, and, although blunted by ageing, uncustomed resistance exercise a delayed unfolded protein response was induced. Fragility is a physiological syndrome characterized by diminished reserves and reduced resistance to stressors as a result of the cumulative decline of multiple physiological systems that increase vulnerability to adverse health outcomes, such as acute diseases, falls and their consequences.

![Figure 3](image)

Figure 3. The hormetic effects of exercise intensity upon resilience to Disorder liability to Alzheimer's disease, Parkinson's disorder, Stroke, Metabolic syndromes, ageing and mortality concurrent with the promulgation of neurogenesis.

Disease tolerance, particularly immune tolerance, as an important defence mechanism has been long recognized, incorporating the capacity to resist an infection without loss in fitness, a defence strategy as 'endurance' or 'resilience' [87]. Exercise promotes physical fitness in order to facilitate resilience to chronic diseases and ageing-related disorders. Immune cell migration, cytokine release, activity, and...
trafficking have been found to regulate the biphasic, inverted U-curve dose-response relationships [21]. The notion of hormesis implies that low-dose preconditioning by pro-inflammatory cytokines, or other harmful agents, can modify a subsequent response to the same or alternative insults [117]. The enhanced production of free radicals and reactive oxidant species and endoplasmic reticulum (ER)-stress that provided adaptive improvements by regular exercise through an hormesic action arising from mitohormesis [71]; similarly, interleukin (IL)-6, the prototypic exercise myokine is induced also by oxidative and ER-stress. Finally, the exercise-induced expression of certain myokines, as for example irisin and meteor in-like myokines are associated with the transcription factor, PGC-1α, and to all intents and purposes, not related to ER-stress whereas typical ER-stress-induced cytokines, including FGF-21 and GDF-15, are not exercise-induced myokines under normal physiological conditions (ibid).

Particularly among elder individuals, regular exercise, independent of type and form, imparts physiologic and psychological resilience against the risk for lifestyle-related diseases [15, 67], advances the lifespan [4], and elevates quality-of-life [20, 37-39] together with beneficial brain structural and functional effects pertaining to neurogenesis neurotropic and growth factor production and greater capillarization [80]. It serves to elevate glucose transporter content, GLUT4, improves insulin sensitivity with accompanying reduced risk for metabolic syndrome [29, 43, 86], together with several organs including kidney, liver, heart, skeletal muscle and testis [58, 77]. Exercise bestows a heightened cognitive integrity and self-esteem, positive mood and emotional resilience, a greater number of neurons and lower levels of apoptosis as a function of both intensity and type of training, with sedentary lifestyles driving inverse outcomes [16, 32, 97, 100, 102]. In this context, the biphasic hormesis dose response induces both positive and negative effects as a function of exercise intensity [41]. Environmental agents, like exercise, in low dose-levels promote both hormesis and autophagy, also an adaptive response; provide higher levels of protection to cells, tissues and organs in combination with Tran's generational influences through epigenetic mechanisms that enhance biological resilience [2].

Taken together, a wide range of observations present a consensus regarding the role of systemic adaptation emerging from regular exercise lifestyles for the prevention, resistance to, and recovery from a multitude of somatic and neurologic-psychiatric disorders, as well as improvements in healthy volunteers. The human body is exposed to a variety of stress forms during physical activity which include thermal, metabolic, hypoxic, oxidative and mechanical stress [76] with biochemical/molecular and functional outcomes exerting dose-dependent effects upon muscular and neurobehavioral adaptation. In this context, it has been implied that adaptive response to exercise-induced reactive oxygen species, an hormesic process, in conjunction with oxidant or antioxidant administration alters the ‘bell-shaped’ hormesis curve to influence levels of physiologic or psychological resilience whereas sedentary lifestyles, ageing or pathology alter the bell-shaped dose response curve through elevations of oxidative stress sensitivity, affecting redox biology, metabolism, and anabolic/catabolic pathways in skeletal muscle in an intensity dependent [69, 81, 105]. Furthermore, at physiologic levels, reactive oxygen and nitrogen species modulate cellular signals; exercise bestows a range of stressor upon skeletal muscle and cardiovascular tissue, mechanical, metabolic and oxidative [56]. These hormetic inductions stimulate transcription factors, up-regulate gene expression of cytosolic and mitochondrial adaptive/stress proteins. Stress-induced responses and antioxidant enzymes following exercise protect against striatal muscle damage, oxidative stress and tissue injury, as well as for the management of chronic inflammatory conditions, involving for example peroxisome proliferator activated receptor-gamma and liver X-receptor-alpha [106].

**Figure 4.** The hormetic effects of exercise intensity upon resilience to disorders of sarcopenia, osteopenia and metabolic syndrome concurrent with the promulgation of immune function.

**Exercise-Hormesis-Epigenetic links**

The forces of epigenetics allow heritable phenotypic alterations to transpire without the involvement of changes in the DNA sequence. Epigenetic alterations, which are manifestly adaptive, seem to be more likely to arise than genetic alterations and through which the environmental fluctuations may induce specific and predictable epigenetic-related molecular changes, thereby ensuring adaptive epigenetic phenomena. Adaptive epigenetic rearrangements may be expected to occur during infancy and throughout the lifespan, developing hormesis-reinforced functional ability and resilience of cells and organisms functional ability of cells and organisms [101]. In this context, the hormetic properties of phytoestrogens, such as is flavones, maintain vascular function, protecting against cardiovascular diseases activation of signalling pathways and elevating nitric oxide bioavailability and regulation of phase II with antioxidant enzyme expression via the redox sensitive transcription factor Nrf2 [90]. Physical exercise contributes effectually to hippocampal neuroprotection combined with up-regulation of BDNF expression and epigenetic regulation while concurrently the chronic inhibition of GABA, receptor potentiates exercise-induced behavioral activity [59]. Furthermore, it was observed that exercise-induced, treadmill-running) memory improvements were bolstered by changes in hippocampal miRNA-mRNA regulatory network [35]. The offspring of voluntary-exercised mouse mothers, running-wheel access, normalized Nrf1 methylation and gene expression and ameliorated the negative effects of maternal high-fat feeding on obesity, diabetes and insulin sensitivity [54].

**Conclusions**

The inception/induction of processes involving hormesis, autophagy and/or mitophagy have been observed to render consistently more-or-less profound assets not only for health, well-being and longevity among healthy young, middle-aged and elderly individuals but also those presenting neurodegenerative disorders, diabetes, stroke, sarcopenia, osteopenia, immunosenescence, and metabolic syndrome. Hormesis conferred by physical exercise procures several dimensions...
of resilience, physiological, anti-stress propensity, cognitive-emotional, against liability to the above disorders and others conditions such those associated with ageing. Chronic, regular and moderately strenuous exercise, ideally suitable combinations of endurance and resistance will produce shifts of the inverted-u shaped curve to the right thereby implying that, over time, exercise intensity levels that were at situated at descending portion of the curve would be placed at the ascending portion: this shift implies, not only that with repetitive, small-interval training episodes strength and tolerance levels shall increase, but also that resilience to disorder liability would be enhanced. The chronic, repetitive schedule of exercise training is predicted also to promote the eventual advent of a form of ‘behavioural-sensitization’ expression from which similar exercise levels may induce greater resilience linked to the months and years over which the performance of training has persevered. One possible metaphor for this phenomenon may be: comparison hormesis to regular savings in the bank whereby the longer the time one has saved money in the bank, the greater one's existing capital, which in its turn induces bank officials to arrange higher interest rate for oneself as a customer; this implies that for an unchanged level of savings a higher savings income accumulates in one's savings bank account, and so on.

**Figure 5.** The hormetic effects of exercise intensity upon resilience to pro-inflammatory cytokines and cortisol with BDNF and anti-inflammatory increase.

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**References**


