The relationships and interactions between age, exercise and physiological function

by

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Abstract

This brief review focuses on the relationships and interactions between human ageing, exercise and physiological function. It explores the importance of the selection of participants for ageing research, the strengths and deficiencies of both cross-sectional and longitudinal studies and the complexities involved in understanding time-dependent, lifelong physiological processes. As being physically active is crucial to fostering healthy ageing, it **is** essential that participants in health and ageing research are defined in terms of their physical activity / exercise status as well as other lifestyle factors. Comparisons of exercisers with non-exercisers has suggested that there is a mosaic of regulation of ageing both within and across physiological systems. We suggest that four broad categories exist which encompass this regulation. These are i) systems and indices that are age-

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dependent, but activity independent; ii) systems that are age-dependent, but also malleable by exercise; iii) systems that are not age affected but are altered by exercise and iv) systems that are neither age nor activity dependent. We briefly explore the concept of a mosaic of regulation in a selection of physiological systems that include skeletal muscle, the immune and endocrine systems and cognitive function and how these categories fit within the broad framework of understanding the physiology of human ageing.

Introduction

As a pioneering experimental human physiologist Michael Rennie appreciated the difficulties involved in understanding the relationships between events studied at the molecular, cellular, tissue and whole systems levels. In particular, he grasped the limitations in understanding the regulation of muscle protein metabolism that could be gleaned from studying snapshots of complex temporal processes initiated by feeding and exercise. In this brief review we explore similar concepts, about the inter-relationships between exercise and ageing in a variety of human physiological systems. We highlight both inter and intra-system differential responses to these two challenges. Whilst acknowledging that some of the issues about our understanding of human ageing have been raised before, we revisit them in order to explore how physiological systems respond in differing degrees to these two major influences of physiological function

It is not possible here to expand in great detail on the nuances of all of the different terminologies that are widely used in ageing research. For example, to differentiate "gerontology" from "geriatrics", "healthy ageing" from "inherent ageing", or "primary" versus "secondary" drivers of ageing (Booth et a. 2011, Seals et al. 2016). This review takes a more biogerontological perspective to the study of the human ageing process. We define inherent ageing as the inherited and intrinsic biological process of change that occurs over time, unencumbered by confounding and distorting negative lifestyle factors which when present ultimately lead to increased risk of disease and death (Harridge & Lazarus 2017). Interestingly, seventy years ago The World Health Organization defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1948) and now defines healthy ageing "as the process of developing and maintaining the functional ability that enables wellbeing in older age" (WHO 2015). An extension to this is the concept of "intrinsic capacity" which comprises all the mental and physical capacities that a person can draw on and includes their ability to walk, think, see, hear and remember (WHO 2015). Thus, the concept of healthy ageing is a broad and holistic one involving both mental and physiological components and remains difficult to precisely define from a purely physiological perspective. That said, the common requirements needed for a healthy physiology to be maintained during ageing are broadly understood, these include sufficient levels of physical activity, a well-balanced diet among other lifestyle factors (e.g. lack of smoking, low alcohol consumption etc), which themselves can be influenced by multiple socio-economic factors. Cardio-respiratory fitness as determined by maximal/peak oxygen consumption ($VO2_{max/peak}$) is arguably the best index of healthy ageing with a large amount of data relating health and age across the life course being available (ACSM 2013). However, as we go on to discuss, the heterogeneity of physiological function

for any given age, even for "healthy" people makes the relationship between a physiological value and a specific chronological age poor, at best, when measured in cross-sectional studies.

Ageing and performance decline

It has previously been suggested that in addition to a decline in the capability of individual organs, tissues and cells, healthy or inherent human ageing is distinguished by a synchronous, co-ordinated diminishment of integrative physiological function (Lazarus and Harridge 2017). The fundamental mechanisms underlying these changes in humans are not fully understood, though studies in a range of model organisms have begun to identify the core drivers of the ageing phenotype at the molecular and cellular level (Lopez-Otin et al, 2013). A further concept underpinning ageing is that of reduced stress resilience and resistance (Miller et al. 2017). With resilience needed to maintain or recover appropriate function in response to a physical stressor (e.g. slower wound healing and recovery from surgery), whilst resistance being the ability of preventing something from imposing damage in the first place (e.g. increased risk of hip fracture after a fall age-related impairment to heat-related exposure). Due to the gradual and progressive nature of ageing, experiments that follow only physiological regulation over short time periods can give only limited insight into the long-term evolving regulatory processes and how the continued integration of physiological function is maintained during the ageing process. This is also true for intervention studies, including those using exercise in previously inactive people, where short-term adaptations demonstrating improvements have functional and health benefits. These do not necessarily inform about ageing *per se* but give insight into the adaptability of a suboptimal physiology when subjected to an imposed intervention.

In order to chart the changes brought about by inherent ageing on integrative physiological function, it is also necessary to identify appropriate indices or biomarkers that will reflect this (Lara et al, 2015). This in itself is a challenge. One measure which arguably captures the diminishment of this global and integrative function are the changes seen in competitive performance times as athletes age (Donato et al 2003, Rittweger et al. 2009, Baker and Tang 2010, Tanaka & Seals 2003, Lazarus & Harridge 2017). Here, whether running, cycling or swimming, numerous physiological systems have to be integrated and, in some systems (e.g. neuromuscular and cardiorespiratory systems), have to perform at, or close to, their maximal capability. It is interesting that whilst in the main these world record performances are cross-sectional in nature (different individuals hold the record for a given event in different age groups), they can, occasionally, be longitudinal (the same individual holds a record across different age groups). We have previously suggested that the shape of these curves

may represent the trajectory of change in integrative physiological function due to the inherent ageing process (Lazarus and Harridge 2018). This hypothesis supported by the concept that these curves are generated by populations of master athletes and vigorous exercisers who may represent the best model in whom to study the inherent ageing process as they are both free from the negative effects of disuse and because they reflect an activity pattern which reflects our evolutionary biology (Booth et al. 2002, Tanaka and Seals 2003, Harridge and Lazarus 2017, Lazarus and Harridge 2017, 2018). That said, it must be noted that further research on such individuals is needed to eliminate potential confounders, genetic traits and the potential for reverse causality.

Tests of athletic performance are impractical to perform in the broader population, although exercise tests which involve the measurement of cardiorespiratory performance during incremental exercise (leading to, VO_{2max}), or the Wingate sprint cycle test of anaerobic power, are examples of laboratory tests which involve multiple systems and which may reflect this integrated functional decline with age. Ideally, measures of integrated performance should be made regularly and repeatedly across the life course of an individual if the trajectory of decline in global function with ageing is to be captured.

At the other end of the continuum of "performance tests" there are clinical measures such as the 6 Minute Walk, Hand grip strength, or the Timed Up and Go tests, which provide challenging tests of integrative function for individuals with a low intrinsic capacity (Beard et al. 2016). However, because they are constrained by a plateau effect many of these tests are of limited value for those with better maintained functional ability. Therefore, it is important not to conflate these clinical tools with measures, such as athletic performance times, that can encapsulate the range of physiological functions required for the study of ageing in the healthiest and fittest of older individuals.

In reality, athletic performance curves for the same individual, champion or otherwise, are almost impossible to obtain, as are laboratory-based indices over the life course. The time scales involved, logistics and funding all play their part in limiting the number longitudinal studies. There are some notable examples of longitudinal studies (e.g. Medical Research Council National Survey of Health, Helsinki Birth Cohort Study, and the Baltimore Longitudinal Study of Ageing), but these often include only a limited range of physiological indices.

Approaches to the study of the physiology of human ageing

Across the spectrum of athletic performance and clinical functional tests, researchers rely heavily on data from cross-sectional studies and more rarely on longitudinal studies to investigate the effects of ageing. Cross-sectional studies have their own inherent problems (Hennekens and Buring 1987), but when used in healthy ageing studies other difficulties arise such as identifying the trajectory of ageing that may be applicable for any single or specific groups of individuals. In addition, most ageing studies generally concentrate on single physiological systems, whilst the heterogeneity in physiological function of participants across the age range makes it virtually impossible to assign with certainty any one physiological functional value to any given age (Lazarus and Harridge 2011, Harridge and Lazarus 2017). Thus, it appears that there is no single physiological index which indicates a particular age with any degree of certainty across the human physiological spectrum (Pollock et al. 2015). Indeed, a recent systematic review of biomarkers related to ageing recommended a range of serum measures as well as physical and cognitive assays in order to cover the full spectrum of ageing across body systems (Lara et al. 2015). In contrast to physiological indices, there is growing interest in the utility of molecular markers, specifically in regard to DNA methylation (Horvath et al. 2013). This epigenetic marker across a range of tissues has been shown to be predictive of the chronological age of the tissue donor, but the interaction between these "biological clocks" and laboratory measures of physiological function remains to be determined (Quach et al. 2017).

Cross-sectional studies do, however, have utility in that certain indices can be used to differentiate between populations (e.g. exercisers from non-exercisers) and can also be used to predict the probability of onset of clinical symptomatology. $VO_{2\ max}$, grip strength, lung function and walking speed being examples (e.g. Beauchet et al. 2016, Blair et al 1989, Desrosiers *et al.* 1995, Leong et al. 2015, Metter *et al.* 2002). What they do not do reliably is relate symptomatology and age.

There exists a further important confounding factor when investigating healthy human ageing (whether cross-sectional or longitudinal design) and that is the physical activity / exercise status of the individuals studied. This is because despite much experimental data showing that inactive people have compromised physiological indices when compared to the active, many studies either fail to study physically active people, or do not define sufficiently the exercise status of the individuals under investigation (Blair et al 1995, Booth et al 2014, Lazarus and Harridge 2010). The use of defined populations in ageing studies are needed if the confounders of inactivity and other lifestyle factors (e.g. smoking, poor nutrition, alcohol consumption etc.), on physiological function are to be understood and controlled for. Indeed, in many studies of ageing, physical activity /exercise status is largely ignored, and participants are regarded as exemplifying healthy ageing, if

they are simply free from overt clinical symptoms of ill health (Woods et al 2015). When participants are poorly defined as regards their physical activity, it becomes not only difficult to reproduce the findings of studies, but the study of the inherent ageing process is lost.

When physically active men and women are studied they are found to have superior physiological values when compared to non-exercisers across a spectrum of indices, including skeletal muscle, cardiovascular/respiratory and immune function (e.g. Klitgaard et al. 1990, Grassi et al. 1991, Wilson and Tanaka 2000, Arbab-Zadeh et al. 2004, D'Antona et al. 2007, Bhella et al. 2014, Duggal et al. 2018). The absence of clinical symptomatology provides insufficient information of physiological status. Both health and physiological status are dependent on numerous controllable lifestyle factors including; exercise, diet, smoking, alcohol intake, as well as those that may be loss controllable, such as socio-economic factors and access to health-care (Rowe and Kahn 1997). While acknowledging the importance of all of these factors, our focus here is on the role of exercise. In exercisers the period of healthspan, the functional and disease-free period of life (Fries 1980, Hansen and Kennedy 2016) is likely increased and the period of morbidity before death decreased (Lazarus and Harridge 2017). Inactivity induces a different ageing trajectory and path to old age (Hanlon et al 2018). Even at a young age physiology is compromised by inactivity (Mountjoy et al. 2011) and although physiological deficiencies may not yet be sufficiently advanced to show overt negative symptoms of health, it is possible, in certain cases, to uncover physiological dysfunction under stress testing (Miller et al. 2017). Indeed, this approach underlies the established clinical thinking when using exercise stress testing to detect underlying cardiac problems not discernible at rest (Jelinek and Lown 1976). The increasing prevalence of obesity and type 2 diabetes in inactive children with high caloric diets (Foster et al. 2018) is testament to the general prediction that poor lifestyle results in increased periods of morbidity across the lifespan. If the appearance of disease symptoms is the result of thresholds of function being breached then non–exercisers, when compared to exercisers, are well on the path to crossing these thresholds much earlier (Fried et al. 2000). Due to human physiological heterogeneity, accurately predicting which system will be the first to fail, or the age at which that failure will take place, is difficult (Lazarus et al. 2018). The alignment of the study of healthy ageing with the clinical field of geriatric medicine is often unhelpful, in that it perpetuates the idea that poor health, disease and progression through to frailty are inevitable consequences of the ageing process.

Inter and intra-System relationships between exercise, ageing and physiological function

As the effects of the ageing process and the effects of exercise are global, first intimations may be that both ageing, and exercise affect all physiological processes in all systems. However, there appear to be four broad categories of response of systems to age and exercise (Lazarus and Harridge 2018). The first contains those indices that appear to be only age-dependent (Category A), the second contains those that are age-dependent, but whose values are malleable by activity (Category B), the third comprising indices that are not affected by ageing but remain affected by exercise (Category C) and finally those indices and functions that are independent of both age and activity (Category D). The subtlety of regulation so physiological systems can be exemplified from an exercise physiologist's perceptive by resting and maximum heart rate. At rest heart rate is unaffected by age but is modifiable by exercise training across the life-course (Category C). By contrast maximum heart rate is not malleable by exercise but is highly age-dependent (Category B). Below we briefly explore, in a range of different systems, a few of these inter and intra-system relationships. This concept of the interaction between ageing and exercise to determine physiological phenotype is depicted in Figure 1.

i. Skeletal muscle mass and function

A loss of skeletal muscle mass and decline in function is one of the defining features of ageing, being a large contributor to the decline in physical function and increased risk of falls (Morley et al. 2011). Muscle is highly sensitive to both the metabolic and mechanical signals provided by exercise and feeding on the one hand and disuse on the other (Rennie et al. 2004, Wackerhage and Rennie 2006, Distefano and Goodpaster 2018). Thus, a decline in skeletal muscle mass, quality and function in later life cannot be seen as an ageing phenomenon without viewed in the context of disuse (Category B). Because master athlete records show a decline even in the most highly trained of older people, there is no doubt that there is an ageing effect on muscle size and performance. But crossing a threshold to being "sarcopenic" may not be a phenomenon experienced by all elderly people (at least not until very old age). Furthermore, a "thin and wiry" endurance athlete when young, may well be defined as sarcopenic, if the definition is based on measures of muscle mass alone. Fortunately, sarcopenia definitions do now include muscle function measures (Cruz-Jentoft et al. 2010).

Michael Rennie's enormous contribution to the study of muscle protein metabolism has recently been documented (Millward et al. 2017). Of pertinence here was work in regard to the complexity of interaction between exercise, nutrition and ageing. His group identified that there was a failure in older individuals to increase rates of muscle protein synthesis (MPS) to those achieved by young individuals in response to both high resistance exercise (Kumar et al. 2008) and amino acid feeding

(Cuthbertson et al 2005). This was termed "anabolic resistance", with the muscle-full anabolic set-point being lower in the muscles of older men than in young men in response to protein feeding (Atherton et al. 2011). A similar anabolic resistance was observed when the muscles of young individuals were immobilised (Glover et al. 2008). Thus, the relation between ageing and activity in regard to the regulation of muscle mass in later life and whether anabolic resistance can be ameliorated in life-long exercisers remains an important question.

Of further note here is recognition that the methods for quantification of muscle protein synthesis (e.g. [(^{13}C)] amino acid tracers) have until recently had to be time-restricted (~12 hours) due to the requirements of sustained bed rest and intravenous cannulations. However, more recently the first stable isotope tracer used in metabolic research, deuterium oxide (D_2O, or "heavy water") has been re-introduced. D_2O can be orally ingested negating the need for intravenous administration and allow participants to administer tracer while performing normal activities and for quantifying changes in MPS over the longer term (Previs et al. 2004, Busch et al. 2006, Robinson et al. 2011, Gasier et al 2012, Wilkinson et al. 2014). This technique is thus likely to produce greater insight into the longer-term regulation of habitual muscle metabolism in health and ageing.

An additional complexity in muscle mass regulation with ageing and exercise is the loss (reduction in number) and remodelling (enlargement through partial reinnervation) of motor units (Campbell et al. 1973). How these changes couple to changes in protein metabolism described above is unclear. There is evidence for motor unit loss and a potential impairment of remodelling in older people who are sarcopenic (Piasecki et al. 2018), whilst interestingly there is evidence both for (Power et al. 2012) and against (Piasecki et al. 2016) exercisers being better able to maintain motor unit number in their lower limb muscles. These results might put motor unit loss in either Category A or Category B (Figure 1). What is clear is that exercisers have superior muscle function, muscle quality, better maintenance of type II fibre size, whilst mitochondrial complex protein content and capillarity have all been shown to be well maintained in master cyclists over the age range 55 – 79 years (Pollock et al. 2018).

As regards metabolic health, genetics, ethnicity and socio-economic factors all play a role in its maintenance across the lifespan, but extrinsic influences are primarily a function of two core factors - levels of physical activity (often insufficient) and diet (usually too highly calorific). In both male and female master runners (Wiswell *et al.*, 2001) and long-distance cyclists (Pollock et al 2015) metabolic indices are well maintained in later life. Furthermore, Lanza et al (2008) showed that insulin-induced glucose disposal and suppression of endogenous glucose production were higher in endurance exercisers compared to sedentary subjects. This was irrespective of being a young or old exerciser.

Reduced insulin sensitivity is thus likely to be related to a reduction in physical activity rather than being an inevitable consequence of ageing (Category B). These workers also found that an age-related decline in mitochondrial oxidative capacity was absent in endurance trained individuals, once again emphasising the interdependence between exercise status and biomarkers of ageing. The molecular basis of this observation is also starting to be being unravelled. Through the deacetylation and acetylation of mitochondrial enzymes, NAD-dependent deacetylase sirtuin-3 (SIRT3) regulates energy demand during stress conditions such as fasting and exercise as well as playing a role in general metabolism. This enzyme is known for its ability to eliminate reactive oxygen species and to prevent the development of cancerous cells and / or apoptosis. SIRT3 is lower in older people but is elevated regardless of age in endurance trained subjects (Lanza et al. 2008), thus it is placed in Category B. A protein involved in oxidative phosphorylation and maintenance of mitochondrial DNA and apoptosis is OPA1. This has been shown to be downregulated during age-related sarcopenia, but this downregulation has recently, not been found in older sportsmen (Tezza et al. 2017). Interestingly, the downregulation of OPA1 in mice can also be prevented by exercising mice during ageing (Tezze et al. 2017) supporting the notion that it belongs in Category B.

In the Baltimore longitudinal study of aging ex vivo mitochondrial respiration was shown to parallel the decline in cardiorespiratory fitness (Gonzalez-Freire et al. 2018) whilst in a study of non-vigorous exercisers, mitochondrial function was found to be associated with walking performance in the higher functioning, active older adults, but not lower functioning, sedentary people. (Santanasto et al. 2016). Taken together, we conclude that these indices are decreased by the ageing process, but are also malleable by levels of physical activity and as such fall in Category B.

ii) Immune System

The immune system is essential for our survival, defending the body against bacteria, viruses and parasites. It is generally viewed as undergoing major remodelling with age which increases susceptibility to infections and reduces the ability to respond to vaccines (Del Giudice et al. 2017). Key features of immune ageing include atrophy of the thymus, the organ that produces new T lymphocytes required to respond to vaccines and new pathogens, an increase in functionally senescent immune cells, loss of regulatory T and B lymphocytes that help to prevent autoimmunity, and an increase in systemic inflammation termed “inflammaging” (Dorshkind and Swain 2009). In a wide-ranging study of the interaction of exercise and age with the immune system, Duggal et al (2018) found a high frequency of recent thymic emigrants suggestive of maintained thymic output in both male and female master cyclists. These regular exercisers also had higher levels of IL7 and IL15 compared to age-matched non-exercisers. The cyclists showed evidence of reduced systemic inflammation (and were thus not “inflammaged”), lower Th17 polarization and higher B regulatory

cell frequency than inactive elders, all of which would produce a more anti-inflammatory environment. Suggesting this component of immune function belongs in Category B. Importantly, physical activity did not protect against all aspects of immune senescence: $CD28^{-ve}CD57^{+ve}$ senescent CD8 T-cell frequency did not differ between cyclists and inactive elders. This may well indicate a Category A feature, but some caution is required as the frequency of these senescent cells is also influenced by the subject's infection history. The immune system is thus interesting in that there is a distinction between those aspects of immune function that are malleable by exercise and those that do not respond to exercise and may represent intrinsic ageing. Furthermore, the frequency of both central memory and effector memory CD4 T cells was no different between the young and old groups, putting this in Category D (not influenced by ageing or exercise).

iii. Cognitive Function

The maintenance of cognitive function is essential for independent living and age-associated diseases of the brain (e.g. dementia) can have devastating consequences for independent living and quality of life, with incidences rising along with increased life expectancy (Brayne and Miller 2017). However, there is growing evidence that exercise can maintain cognitive and brain plasticity well into old age (Clarkson-Smith and Hartley 1989, Hillman et al 2008) but, as for many indices, questions about the type, intensity and length of exercise that are necessary to produce optimum effects remain. In a recent longitudinal study physical function, physical inactivity, as well as smoking, were associated with faster rates of decline in specific cognitive domains in both men and women (Zaninotto et al. 2018). Whilst a study of 1,400 participants aged 19–94 years revealed significant longitudinal associations between baseline VO_{2max} and the trajectory of performance on multiple measures of verbal and visual memory, as well as on a cognitive screening test. With individuals having a lower VO_{2max} demonstrating accelerated trajectories of cognitive decline over time. (Wendell et al. 2013). In the study of mature cyclists (Pollock et al 2015), in which many of the confounding factors mentioned previously were ameliorated, an examination of cognition as assessed by a test of verbal fluency (animal naming) and speed and concentration (timed letter search), showed no clear association with age (Pollock et al 2015). However, efficiency of information processing declined with age at a similar rate (5–10% per decade) to that seen in the general population (Huppert, 1987). Thus, this information might suggest that efficiency of information processing belongs in Category A, while verbal fluency and timed letter search belong in Category B. It appears that different mental abilities may exhibit differential response to exercise. Although the positive effects of exercise on brain function have been recognized for many years, it is perhaps a testimony to the schisms between specialties that there is, as yet, no study in which a wide range of brain functions and physiological indices have been tested in the same individuals. It

may be that wider recognition of this brain: body interdependency which is a cornerstone of healthy ageing, could allow for improved models for the study of human ageing.

iv) Endocrine system

The endocrine system is made up of numerous organs and tissues that produce hormones which are released into the bloodstream to be used by other target organs and systems. Like other body systems its various components are differentially affected by ageing and exercise. Here we discuss just a few aspects of endocrine activity which change with advancing age and where these changes may be differentially mediated by declining physical activity levels. Testosterone levels are typically found to be 10 fold higher in males than females (Harman *et al.*, 2001; Sowers *et al.*, 2001). An age-related decline in testosterone levels in men, known as the andropause, has been reported, but was not apparent in the Pollock et al. (2015) study of master cyclists. Exercise training in sedentary older men can increase testosterone levels (Hayes *et al.*, 2013) therefore the exercise status of the cyclists may have helped in their preservation. If this was so this would suggest that previously reported declines in testosterone may also be related to declining physical activity levels (Category B).

Growth hormone (GH) and insulin-like growth factor one (IGF-I) also decline rapidly with age, termed the somatopause (Junnila et al. 2013). As is the case for many indices, data are lacking which directly compare exercisers and inactive people in the same study are lacking. The fact that IGF-I and GH levels fell in the study of master cyclists suggest that the somatopause is probably an intrinsic ageing process occurring independent of physical activity putting these hormones in to Category A.

The third major age-related endocrine adjustment is the adrenopause which describes the decline in production of the androgenic hormone dehydroepiandrosterone (DHEA) from the third decade (Orentreich et al. 1992). Currently there is little evidence that the age-related reduction in DHEA can be ameliorated by exercise. Although DHEA levels in male and female master cyclists (aged 55 – 79 years) did not decline across the cohort (Pollock et al. 2015), the levels were similar to those reported for the population as a whole and much of the decline had probably already taken place by the 6th decade. In a unique study, three groups of older individuals who were defined by their exercise status (sedentary, moderately active and endurance trained) and studied for DHEA levels at both rest and following exercise (Heaney et al, 2013), showed no difference between groups at rest or post-exercise, suggesting that the adrenopause would be in category A - an intrinsic effect of ageing.

v) Gut Health

There appear to be many small changes in gastrointestinal function with ageing such as hypochlorhydria in the stomach, changes in swallowing in the oesophagus, reduced microbiome diversity and prolonged transit times in the colon which can give rise to a number of negative effects, including malnutrition. Indeed, malnutrition is one of the most commonly implicated factors in a decline in independence, well-being and health in older people (Britton and McLaughlin 2013). However, the small bowel which is the primary site for nutrient absorption appears unaffected by age (Britton and McLaughlin 2013). Although the exercise status of the participants on which these findings are based are not described, we can conclude that the absorption functions of the small bowel are both age and exercise independent (Category C). However, the other gastrointestinal findings cannot be assigned a category until all these indices are measured in populations whose exercise status is defined. Indeed, the study by Britton and McLaughlin (2013) is a good example of the confusion that can arise when the exercise status of the participants is not defined.

Conclusion

In this short review we have attempted to explore some concepts in regard to ageing, exercise and physiological function. We have highlighted an interesting addition to the already complicated physiological regulation of ageing. This is exemplified by the differential responses occurring both within systems and between systems during ageing. We have assigned four categories to reflect this non-uniformity of response (Figure 1). By paying particular attention to the physical activity of people used for ageing research, two salient facts have emerged. Firstly, the conclusions drawn that there are differential responses to exercise both within and between systems could only have been obtained from studies in which the physical activity / exercise status of the participants was defined. It is perhaps ironic that studies in which the activity status of subjects has not been defined allow us to identify those indices and physiological actions that are both age and exercise independent. Previous ageing studies in which the activity status of the population under study has not been made clear should prove a useful library in which to uncover systems and functions that are both age and exercise independent (Category D). Secondly, although these observations have complicated the study of ageing we suggest that the uncovering of differing categories of physiological regulation may allow opportunities for the introduction of different perspectives of ageing that will open new avenues of experimentation on the ageing process in humans. For example, there must be specific genes controlling systems that are impervious to ageing and exercise (category D). Identifying those physiological functions that belong in this category might make the identification of such genes easier. To what extent are disease processes initiated by the imposed negative effects of inactivity

on exercise malleable systems (Category B)? These categories can also give added focus to initiating and directing studies on the effects of epigenetic factors acting on human ageing. Clearly, more data are needed which compare the phenotypes of those who exercise and those who do not. In an ideal situation this would be measured in longitudinal studies.

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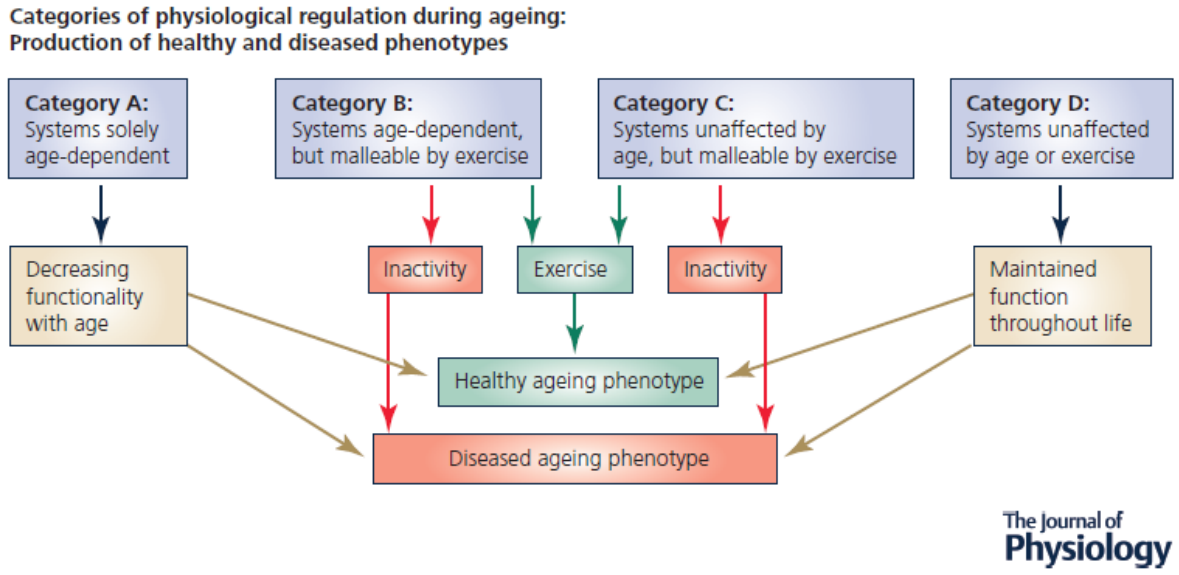
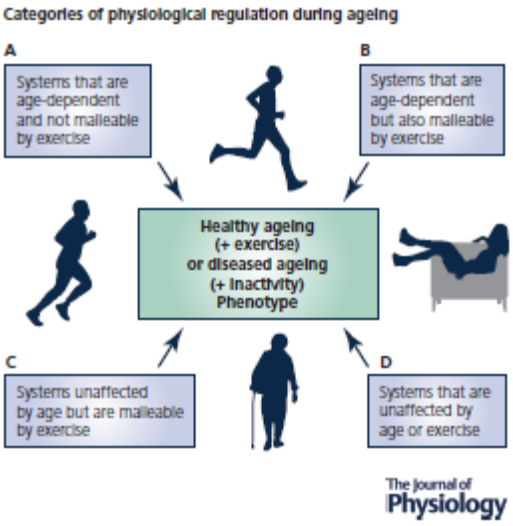
Figure Legend

Figure 1: A schematic overview showing the hypothesized regulation of healthy or diseased older phenotypes through the interaction of ageing an exercise.



Abstract Figure Legend

Schematic to depict how healthy or diseased ageing phenotypes are the product of the interaction and regulation of physiological systems that can broadly be grouped into 4 categories on the basis of their malleability or otherwise to exercise and to the ageing process.



Norman Lazarus has a medical degree from South Africa and a PhD from the State University of New York. He has worked in academia and in the pharmaceutical industry. Since 2006 he has been Emeritus Professor at the Centre for Human and Applied Physiological Sciences at King's College London. His particular interest is in trying to unravel the interactions between exercise, healthspan and ageing in humans.