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Department of Health Sciences

Physical behaviors, sarcopenia and adverse events in the Toledo Study of Healthy Ageing

Doctoral thesis

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June 2020

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“Let everything happen to you: beauty and terror.
Just keep going. No feeling is final.”

Book of Hours, I 59

Rainer Maria Rilke

"Lo mismo con las canciones
los pájaros, los alfabetos,
si quieres que algo se muera
déjalo quieto".

Movimiento, Salvavidas de Hielo

Jorge Drexler

Agradecimientos

Pienso en la vida como una serie de casualidades que se suceden una tras otra. Necio aquel que piensa que la parte que le toca es de algún modo sustancial en relación a la que no.

En mi caso, hacer una tesis doctoral y lo que de ella resulta fue una de esas casualidades. Hablo desde mi perspectiva (quizá alguno nació siendo doctor). Una cosa llevó a la otra. Quiero aprovechar estos párrafos para reconocer a esas casualidades que han contribuido positivamente de una u otra forma a que me encuentre hoy aquí.

En primer lugar, a mis padres, Juan Luis e Isi, por su amor inconmensurable, por su fe ciega en sus hijos, por alegrarse más cuando vienen buenas y sufrir más que nosotros cuando vienen malas. Por estar SIEMPRE ahí.

A mis hermanos. A María, por ser siempre un espejo en el que mirarse. A Alberto (más compañero de vida no se puede ser), por enseñarme que existe la telepatía. Os quiero hermanos. Y a los que los acompañan, Jordan y Carmen, por introducir mucho más que acentos exóticos en mi familia (que también).

A mi abuela Joaquina, que hoy estará más ancha que larga, porque "una madre y una capa *tó* lo tapan". Imagínate la madre de otra madre. Por todo lo que te hubiera gustado cogernos y no nos pudiste coger.

A mis abuelos, Luis y Carmen, por su eterna lucha por una vida mejor y ser mis conejillos de indias preferidos.

A mis tíos y primos, por ser padres, amigos y hermanos.

Especialmente a María, mi compañera de vida. Por transformar a un pintas en lo que hoy soy. Por el tiempo que te robo cuando mi sueño me lleva lejos. Por apuntalar la viga cuando parece que todo se derrumba. Esto también es tuyo.

A mis amigos, por ser casualidades que llegaron para quedarse. A Tyces, por la portada y por ser el tercer gemelo. A Pancho, porque mi alegría se correlaciona con la tuya. A Rocío, por tu amor por la ciencia de la vida y por el que nos das a nosotros. A Kalvi, Yusta, Peli y demás, por vaciar el pueblo cuando vas y no están. A Tetín, a Laura. A los de Getafe por esa maravillosa certeza de que nada ha cambiado, nada cambia y nada cambiará.

Y a más casualidades que aparecieron por el camino. A mis compañeros de la Fundación y del Servicio de Geriatría del Hospital de Getafe, por descubrirme la pasión por todo lo que tenga más de 70 años. A los sujetos de los estudios en los que he participado, porque yo les puse a hacer sentadillas, pero ellos me brindaron mucho más. A los que aparecieron en Navarra: a Isa, por sus recetas y su amistad; a Miriam, por los cafés y su sempiterna lucha por despertar en mí su amor por los bichos intestinales (algún día lo conseguirás). A la gente del Servicio de Geriatría del Complejo Hospitalario de Navarra y de Navarrabiomed, por tener siempre una sonrisa y hacerme sentir parte de ellos. A los Santamaría Agudo, mi familia adoptiva al norte del Sadar.

A Bati, por presentarme Stata, por tu excepcional manera de sobreestimar mis cualidades. Por tu apoyo y amistad.

A los coautores de mis trabajos, por su inestimable contribución, imprescindible para que el barco llegase a buen puerto. Especialmente a Stefan y a José Antonio, por nuestras peleas estadísticas. Al personal del Estudio de Toledo, a Franjo, por los datos y su entera disposición.

A Leo, por confiar en mi cuando rompía el cascarón y por seguir haciéndolo después de todo. Por pisarme el freno cuando hace falta y por tus siempre acertados consejos (jamás me perdonaré haberlo contrastado). Por ser mejor persona que investigador.

A todos vosotros, gracias por haberos quedado e incorporaros a mi vida durante este proceso. Sólo os pido que sigáis ahí.

¡¡GRACIAS!!

Juanlu.

List of abbreviations

ACSM: American College of Sports Medicine

ADL: Activities of Daily Living

AHA: American Heart Association

BADL: Basic Activities of Daily Living

BMI: Body Mass Index

CDCP: Center for Disease Control and Prevention

COPD: Chronic Obstructive Pulmonary Disease

CRP: C-Reactive Protein

CVD: Cardiovascular Disease

DHEA: Dehydroepiandrosterone

DHHS: Department of Health & Human Services

EU: European Union

EWGSOP: European Working Group on Sarcopenia in Older People

FI: Frailty Index

FNIH: Foundations of the National Institutes of Health

FP: Frailty Phenotype

FRADEA Study: Fragilidad y Dependencia en Albacete

GBTM: Group-Based Trajectory Modelling

GH: Growth Hormone

HF: Heart Failure

HIC: High-Income Countries

HT: Hypertension

HRQoL: Health-Related Quality of Life

IGF-I: Insulin-like Growth Factor-1

IADL: Instrumental Activities of Daily Living

ICD: International Classification of Diseases

IL-6: interleukin 6

LMIC: Low- and Middle- Income Countries

LPA: Light Physical Activity

£: United Kingdom Pounds Sterling

MET: Metabolic Equivalent

MHC-I: Myosin Heavy Chain-I

MHC-II: Myosin Heavy Chain-II

MI: Myocardial Infarction

MIC: Middle-Income Countries

MM: Muscle Mass

MPA: Moderate Physical Activity

MVPA: Moderate-to-Vigorous Physical Activity

PA: Physical Activity

PPM: Physical Performance Measures

RMR: Resting Metabolic Rate

SB: Sedentary Behaviour

SC: Satellite Cell

SPPB: Short-Physical Performance Battery

TNFα: Tumor Necrosis Factor Alpha

TSHA: Toledo Study of Healthy Ageing

T2DM: Type 2 Diabetes Mellitus

UN: United Nations

US: United States of America

USD: United States Dollars

VPA: Vigorous Physical Activity

WHO: World Health Organization

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Summary-Resumen

Summary

Ageing population is a worldwide occurrence and this phenomenon poses substantial burden on individuals and healthcare systems. Life expectancy increases have not been accompanied by parallel healthspan expansions, which have led to higher rates of disability among a growing share of the population. Primary ageing, lifestyle factors and comorbidities interact to shape the functional trajectories along late-life. Healthy ageing refers to the maintenance of functional ability that guarantees wellbeing in older persons and is believed to occur in the absence of pathologies. In contrast, the presence of diseases and deleterious lifestyle factors might drive an accelerated ageing and premature disability.

The loss of muscle mass and function, termed sarcopenia, has recently being proposed as a key factor leading to disability and adverse events in older adults. Physical exercise has been proposed as the best strategy for maintenance and development of functional ability. Nevertheless, few older adults partake in structured exercise regimes and the best dosage and intensity remains unclear in such a heterogeneous population. In this scenario, free-living physical activity and sedentary behaviour might constitute the differential factor determining functional ability trajectories. Recent availability of objective physical activity measures that allow better characterization of physical behaviours together with novel statistical methods have allowed to address open research questions regarding this relevant health determinant in older adults, such as the role of light physical activity and sedentary behaviour and the dynamic nature of physical activity on disability-related conditions and adverse outcomes.

The current Ph.D. dissertation intends to add insight into the associations between physical activity and sedentary behaviour and healthy ageing, overcoming limitations identified in previous research, through two scientific works using data from the TSHA, an ongoing population-based study.

Study 1 (Chapter 1)

In the first study (Chapter 1), we explored the associations between objectively assessed free-living physical activity and sedentary behaviour and sarcopenia and its determinants. A common methodological limitation of physical activity epidemiology when using accelerometers is the overlooking of the fact that the time in which a subject can partake in physical activity and sedentary behaviour is limited. Isotemporal substitution models allowed us for the mathematical estimation of the effect of reallocating certain amount of time in one physical activity intensity category by the same amount in other on the odds of sarcopenia and its determinants. Furthermore, we used age-specific cut-points for physical activity intensity categorization, avoiding underestimation due to energy cost differences in older adults. The results pointed to the unique dose-response association between moderate-to-vigorous physical activity and sarcopenia and its determinants, both substituting sedentary behaviour and light physical activity, and an insufficient effect of the latter for promoting skeletal muscle health. Our results support previous evidence of protective role of moderate-to-vigorous physical activity on sarcopenia and suggest the presence of an intensity threshold below which little benefit is obtained. These findings might guide interventions tailored at preventing or reverting sarcopenia.

Study 2 (Chapter 2)

Despite substantial unequivocal evidence relating physical activity and healthy ageing has been accumulated, physical activity is a dynamic behavior that changes along time and its evolution might be associated to adverse events distinctly to cross-sectional estimates. The main purpose of this study was to investigate the presence of different late-life physical activity trajectories within the TSHA sample and their associations with adverse outcomes. We found 5 physical activity trajectories within our sample. Belonging to the trajectories prospectively maintaining/increasing baseline physical activity levels was associated with a lower risk of mortality, hospitalization and onset and worsening of disability compared to those presenting with low baseline physical activity levels and reducing physical activity along follow-up. In addition, increasing physical activity trajectory was associated with lower risk of disability outcomes in comparison with decreasing physical activity levels despite similar low baseline values. These findings support the beneficial effect of late-life physical activity maintenance for adverse events prevention and the potential of increasing physical activity for activities of daily living disability prevention, even in the most inactive older adults.

Consequently, the research results included in this thesis dissertation reinforce the role of physical behaviors as modulators of the physiological reserve loss with ageing, both captured through a single organic system and outcome levels.

Resumen

El envejecimiento de la población es un fenómeno global que puede tener unas implicaciones relevantes tanto a nivel de la salud individual como en los sistemas sanitarios. Esto se debe a que los aumentos en la esperanza de vida observados en los últimos siglos no se han visto acompañados concurrentemente de aumentos de los años vividos sin enfermedad. El desarrollo de enfermedades crónicas y su aparición en forma de comorbilidad unido a los efectos del envejecimiento primario ha derivado en la progresiva pérdida de función y el desarrollo de discapacidad.

El envejecimiento saludable se define como el mantenimiento de la capacidad funcional que garantiza el bienestar en el adulto mayor. En contraposición, la acumulación de patologías y la presencia de estilos de vida no saludables pueden condicionar un envejecimiento acelerado y la emergencia prematura de la discapacidad.

La pérdida de masa y función muscular que acompaña al envejecimiento (sarcopenia), constituye una de las piedras angulares en el desarrollo de la discapacidad en el anciano. El ejercicio físico ha sido propuesto como la herramienta de elección para mantener y aumentar la función física en ancianos y, por ende, prevenir el deterioro funcional asociado con la sarcopenia.

Sin embargo, muy pocos sujetos ancianos participan en programas estructurados de ejercicio y los parámetros óptimos de esos programas se desconocen. En ese contexto, los comportamientos físicos espontáneos (comportamiento sedentario y actividad física), podrían ser determinantes relevantes de la capacidad funcional en el anciano. La incorporación de medidas objetivas en la epidemiología de la actividad física y el reciente desarrollo de nuevos métodos estadísticos ha permitido atender preguntas de investigación como las asociaciones del sedentarismo y distintos niveles de intensidad de actividad física con parámetros de salud e incorporar la naturaleza dinámica de los comportamientos físicos como factor determinante de salud.

La presente tesis doctoral pretende profundizar en las asociaciones entre los niveles de actividad física y sedentarismo e indicadores de envejecimiento saludable (sarcopenia y eventos adversos), superando algunas limitaciones identificadas en la evidencia previa. En la misma se han incluido dos trabajos realizados con datos del Estudio de Toledo del Envejecimiento Saludable, un estudio poblacional en curso.

Estudio 1 (Capítulo 1)

El primer estudio tuvo como objetivo el explorar las asociaciones entre la actividad física espontánea y el sedentarismo y la sarcopenia y sus determinantes. Una limitación común de la epidemiología de los comportamientos físicos es la omisión de la finitud del tiempo en el que un sujeto puede participar en actividad física. Recientemente, los modelos de sustitución isotemporal han permitido estimar matemáticamente los efectos de aumentar el tiempo en uno de los niveles de comportamiento físico (sedentarismo, actividad física ligera, moderada y vigorosa) a expensas de reducir el tiempo en otro, simulando cambios comportamentales. Además, en la clasificación del tiempo en cada uno de los niveles de intensidad se emplearon puntos de corte a la señal del acelerómetro validadas en sujetos ancianos, evitando la subestimación de la intensidad derivada del empleo de umbrales validados en población joven.

Los resultados indicaron una asociación única entre los niveles de actividad física de moderada a vigorosa y la sarcopenia y sus determinantes, tanto en modelos clásicos de regresión, como sustituyendo a la actividad física ligera y al sedentarismo en los modelos de sustitución isotemporal.

Nuestros resultados expanden la evidencia previa de la asociación entre la actividad física y la sarcopenia, con la presencia de un umbral de intensidad por debajo del cual el beneficio es mínimo.

Estas observaciones podrían dirigir el desarrollo de intervenciones orientadas a la prevención y a la reversión de la sarcopenia.

Estudio 2 (Capítulo 2)

Pese a que la evidencia acumulada sobre el rol de la actividad física como determinante del envejecimiento saludable es inequívoca, la naturaleza dinámica de la actividad física, especialmente volátil en los últimos años de vida, ha despertado el interés sobre el papel de la evolución en los patrones de actividad física como determinante de salud.

El objetivo del Estudio 2 fue el de evaluar la presencia de distintas trayectorias de actividad física en la población del estudio de Toledo de Envejecimiento Saludable y sus asociaciones con eventos adversos (mortalidad, hospitalización, discapacidad y progresión de la discapacidad).

Se identificaron 5 trayectorias de actividad física que diferían tanto en los niveles de actividad física inicial como en su progresión. La pertenencia a trayectorias de actividad física de mantenimiento o aumento de la actividad física a lo largo del envejecimiento se asoció con reducciones en la probabilidad de morir, ser hospitalizado, presentar alguna limitación o empeoramiento en el estado funcional al seguimiento, en comparación a aquellos presentando bajos niveles de actividad física iniciales y reducciones a lo largo del tiempo.

Además, el aumento de la actividad física se asoció con reducciones en el riesgo de limitación funcional incidente en aquellos sujetos con muy bajos niveles basales de actividad física, en comparación con aquellos que la redujeron desde niveles similares. Los resultados de este estudio contribuyen a la evidencia previa indicando el efecto beneficioso del mantenimiento de la actividad física en los últimos años de vida en la prevención de los eventos adversos y el potencial de obtención de beneficios con incrementos de la actividad física, incluso en los sujetos ancianos más inactivos.

Declaration

I, Juan Luis Sánchez Sánchez do hereby declare that scientific papers included in this thesis dissertation have been published in international peer reviewed journals.

In order to adhere to the requirements of a thesis, the formats of the papers have been adjusted accordingly. This edition did not change the content of the published articles.

The Ph.D. candidate was involved in study conception, data analysis, results interpretation and the drafting of the manuscripts.

Financial Support, List of Publications and Conference Papers

Financial Support

All the scientific publications embedded in this Ph.D. dissertation were produced using data from the Toledo Study of Healthy Ageing (TSHA), which is funded by grants from the Spanish Ministry of Economy, Industry and Competitiveness, co-financed by the European Regional Development Funds (RD120001/0043) and the Centro de Investigación Biomédica en Red en Fragilidad y Envejecimiento Saludable—CIBERFES (CB16/10/00464). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
The student did not receive any funding for the production of the research presented.

List of Publications

[1] Sánchez-Sánchez JL, Mañas A, García-García FJ, et al. Sedentary behaviour, physical activity, and sarcopenia among older adults in the TSHA: isotemporal substitution model. J Cachexia Sarcopenia Muscle 2019; 10: 188–198.

[2] Sanchez-Sanchez JL, Izquierdo M, Carnicero-Carreño JA, et al. Physical activity trajectories, mortality, hospitalization, and disability in the Toledo Study of Healthy Aging. J Cachexia Sarcopenia Muscle. Epub ahead of print 12 March 2020. DOI: 10.1002/jcsm.12566.

Scientific Communications at International Congresses

Oral Communication at the 15th International Congress of the European Geriatric Medicine Society. "Longitudinal Physical Activity Trajectories and Mortality In The Toledo Study Of Healthy Ageing". Eur Geriatr Med (2019) 10 (Suppl 1):S1–S325-O-04.

Poster Communication at the International Conference on Frailty and Sarcopenia Research: "Associations between physical activity levels, sedentary behavior and sarcopenia in the Toledo Study using population-adapted cut-points", J Frailty Aging (2017) 6 (Suppl 1): S1-P-170.

General Background

General Background

1. Population Ageing

1.1 Population projections in the World, Europe and Spain

Population ageing is a worldwide occurrence. The reduction of fertility rates together with increases in life expectancy across the second half of the 20th and first decades of 21st century stand out as the main drivers of this demographic transition. Exceptional life expectancy increases are the result of improvements in life conditions and considerable advancements in medical science that have taken place during this period [1].

During the period 1980-2019 the overall >65 years population has almost tripled, from 262 to 727 million persons worldwide. The increases in the proportion of octogenarians has been especially appealing, since the number of people above 80 years of age have grown from less than 36 to 143 million people [2, 3].

Notwithstanding these notable figures, this global demographic transition is an ongoing process, believed to continue in the coming years, in which every country in the world is expected to experience an increase in the share of population aged 65 or over (Figure 1). According to the UN 2019 World Population Prospects, it is expected that by 2050, the share of the population above 65 years of age will rise from 9.3% in 2020 to 16% (1,5 billion people) of the total population. In addition, the number of very old people (i.e. those above age 80) having tripled from 1990 to 2019, will grow even faster, and is expected to triple again by 2050, reaching 426 million people worldwide [4].

This population aging demographic transition has led to a reshaping of the age distribution of our populations, with the narrowing of the bottom of population pyramids in most of developed countries (Figure 2), with children and young age groups becoming progressively smaller relative to aged groups. By 2045 it is projected that people over 65 will outnumber the 15-24 age group (1.41 *vs* 1.35 billion people) and that of children (0-14 years) by 2075 (2.1 billion *vs* 2.0) (Figure 3) [4].

Although the EU lies on an advanced stage of the ageing population process compared to developing or low-income countries, life expectancy trends are expected to keep up, with increases of 7.8 years and 6.6 years on average in the period 2016-2060 for men and

women, respectively [5], which would make Europe the most aged geographical region in the world.

Figures are especially remarkable in the case of Spain, due to the combination of sharp fertility rate reductions, together with exceptional longevity achieved in the last decades. From 1960 the total fertility rate has dropped from 2.7 to 1.34 [6] whereas life expectancy at birth evolved from 71.98 to 83.6 in both sexes. It is estimated that by 2060 one third of the population will be 65 years of age or above, and more than 50% of these will exceed the age of 80 [7], placing Spain as the second oldest country in the world.

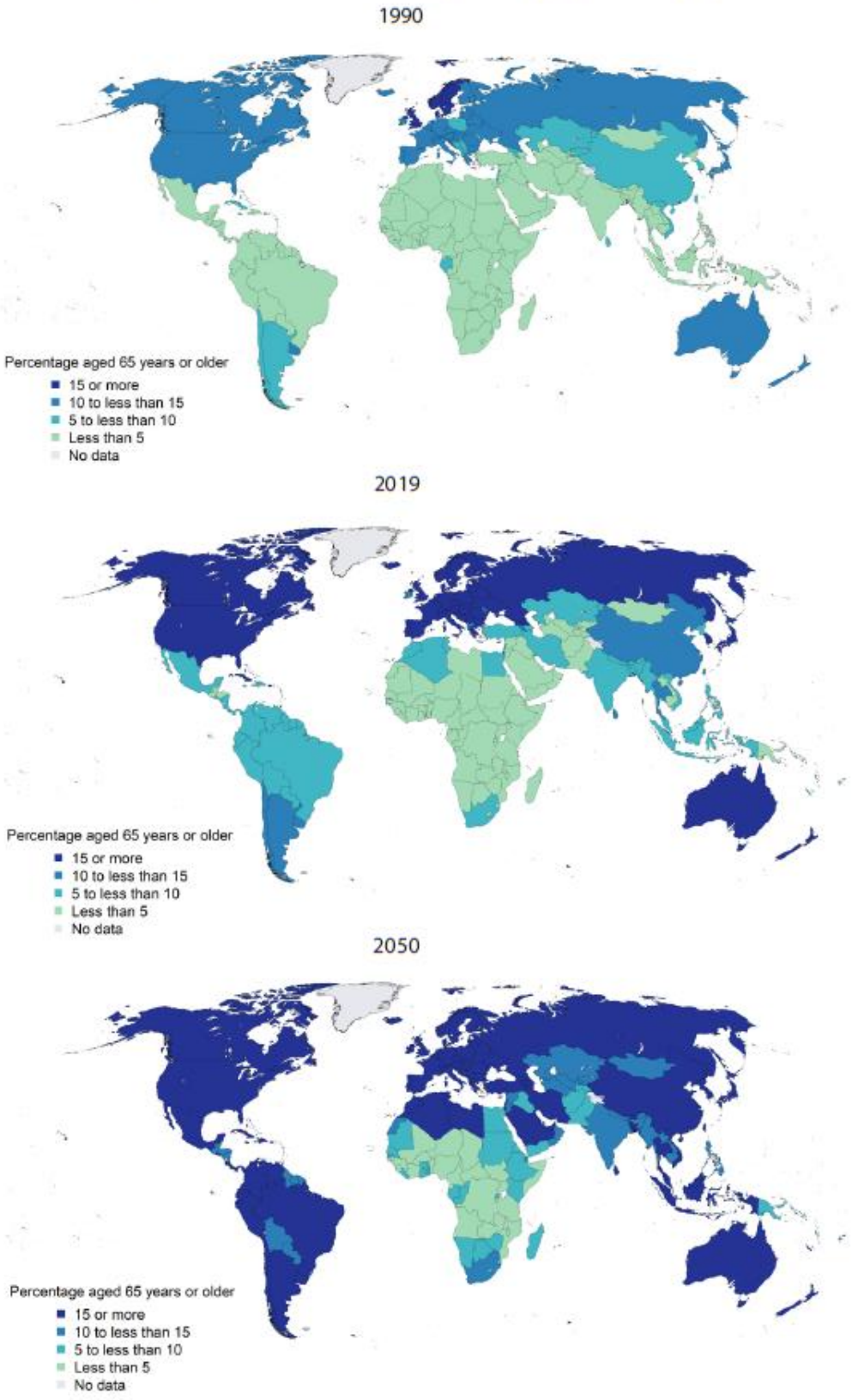


Figure 1. Global population by broad age group demographic evolution of the different age population segments from 1980 to 2050.

Data source: UN (2019). World Population Prospects: the 2019 Revision [4].

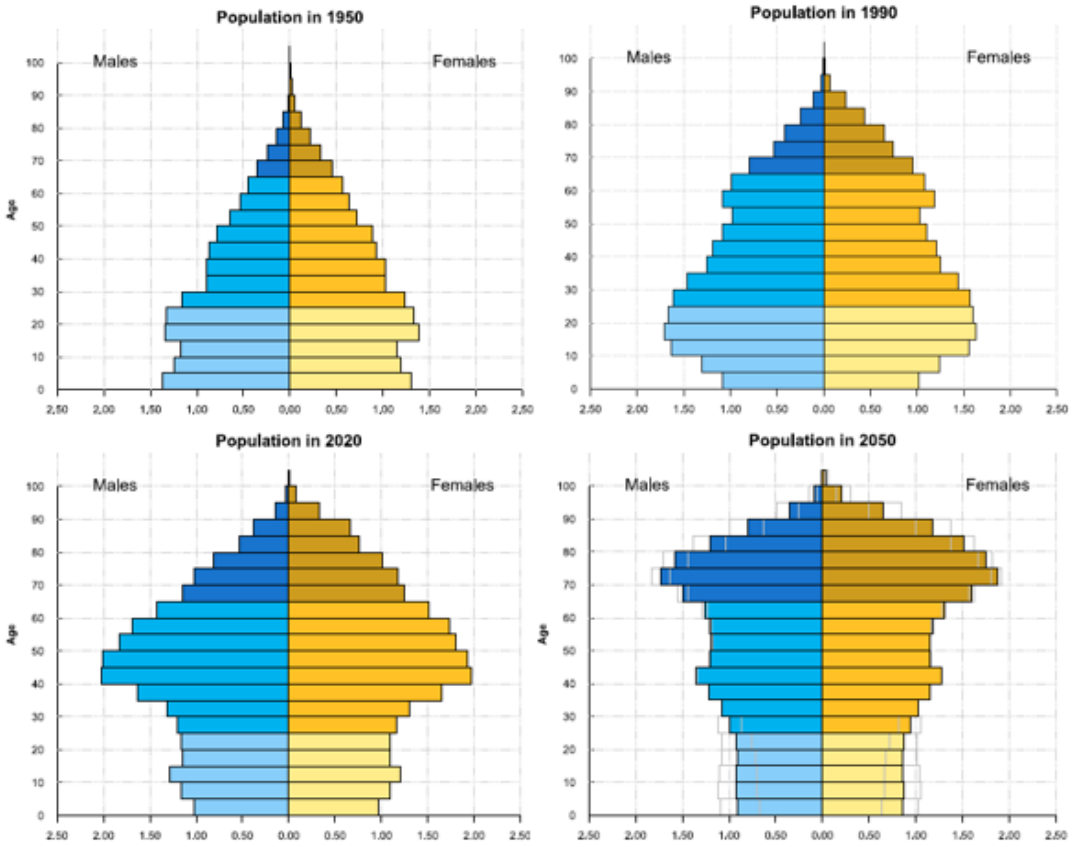


Figure 2. Population pyramid in Spain in the years 1950, 1990, 2020 and 2050 (projection)*

*Uncertainty is shown in lighter shades for 95 per cent prediction intervals

Data source: UN (2019). World Population Prospects: the 2019 Revision [4].

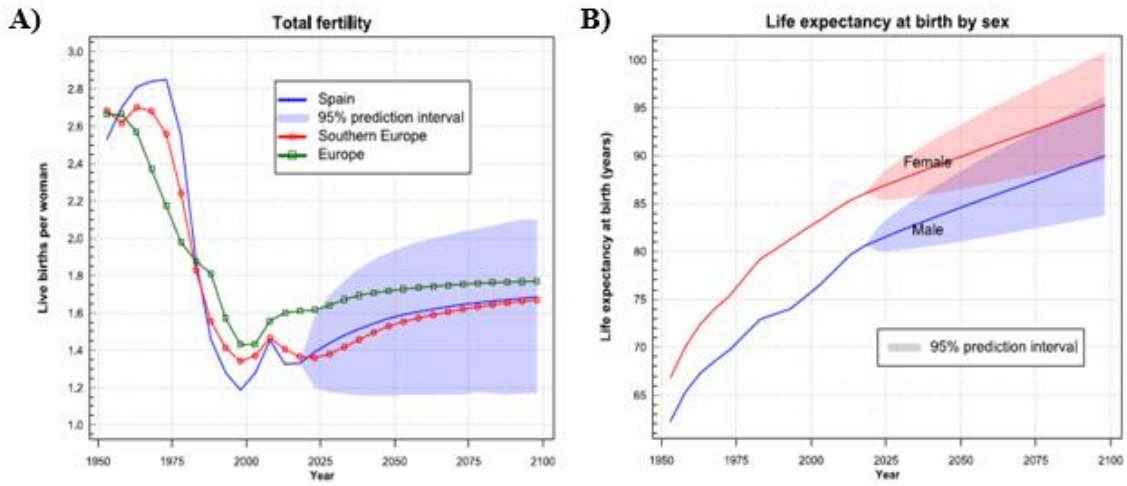


Figure 3. Total fertility rate (A) and life expectancy (B) evolution and projections in the period 1950-2100 in Spain*.

*Medium-variant projections for 2020-2100 are shown as thin colored lines.

Data source: UN (2019). World Population Prospects: the 2019 Revision [4].

1.2 The demographic transition: a challenge for older adult's care

Although lifespan increase should undoubtedly be perceived as an important accomplishment of modern societies comprising both improvements in life conditions and fundamentally to the advances in medical science, this phenomenon has not been accompanied with a concomitant increase in years of healthspan due to the development of the so-called age-related pathologies. Whereas global life expectancy at birth increased by 5.5 years between 2000 and 2016, the healthy life expectancy (mean years lived without functional limitations and disability) did by 4.8 in the same period (Figure 4) [8].

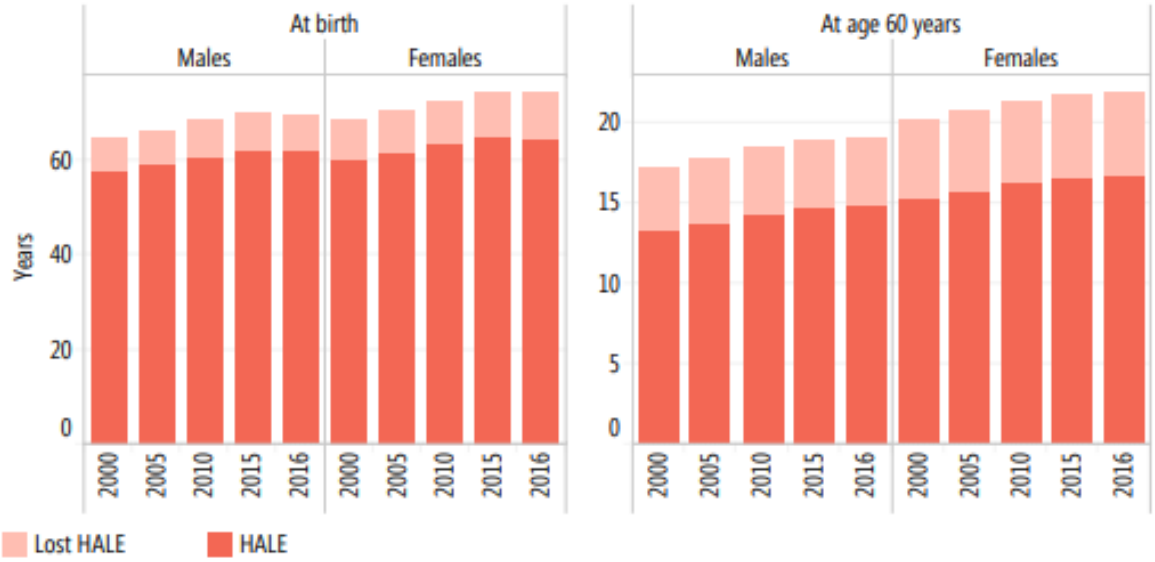


Figure 4. Global life expectancy and Healthy Life Expectancy (HALE) at birth and at age 60 in the period 2000-2016

Data source: WHO (2019). World Health Statistics 2019: Monitoring health for the SDG [8].

In recent decades and from an epidemiological point of view, the burden of disease has shifted from infectious diseases to morbidity from chronic non-communicable diseases (cardiovascular diseases, cognitive disorders, T2DM, cancer, kidney disease, COPD, etc.) [9]. These chronic conditions tend to accumulate (pluripathology), interact negatively in a synergistic way with each other (comorbidity) and manifesting mainly as functional decline rather than premature death.

An increasing proportion of the population is living with multiple diseases and sub-clinical impairments that together lead to disability and poor quality of life [1, 10]. Consequently, the entire society has become tasked with the care of a greater share of persons characterized by high clinical complexity, the presence of disabling conditions and social issues, drivers of increased financial and personal burden on healthcare and social welfare systems, which finally might jeopardize their short-term sustainability [1, 5].

Among a constellation of issues, disability, the extreme end of the functional decline, is the most appealing consequence of ageing populations [11]. The WHO has defined disability as "an umbrella term for impairments, activity limitations and participation restrictions".

In the US, 3 out of 5 adults ≥ 65 years present with some kind of functional limitation [12], whereas in Spain disability for IADL and ADL figures lay in 31,9% and 11,1% among community-dwelling older adults. Disability prevalence is associated to female sex and rockets in the oldest old, since 70% and 35% present with disability in IADL and BADL, respectively [13].

Hence, a relevant question when judging the effect of ageing populations from the individual and the entire society point of view, is whether increases in life duration might in fact contribute to years lived in good health or being translated in a greater number of years lived with disability [14, 15].

From a general point of view, incapacity for performing the ADLs in older people decreases their quality of life, increases sanitary costs and contributes to premature death [16–18]. Recent studies have shown that requiring major dependence on others for ADL is a risk factor for elder abuse [19].

Although functional disability rates obviously increase in older and specially in the very old people, disability is not arguably the unavoidable end of the ageing process [20] and since its development rely on a myriad of not-fully understood factors, some of which are surely modifiable (obesity, T2DM, smoking, alcohol consumption, physical activity, cultural engagement and diet, among others) [21, 22]. In fact, some evidence has estimated the share of disability potentially preventable through risk factors elimination/reduction [23], and results points toward an hypothetical substantial

reduction in disability rates if the burden of deleterious lifestyle factors was curbed (Figure 5).

Therefore, the prevailing biomedical strategy has evolved from increasing longevity, to the "compression of morbidity" paradigm, and finally to the increase of healthspan. Increasing longevity is no longer a major concern of medicine, and the focus has moved into the maintenance and prolongation of function along the ageing process [24] as a mean of guaranteeing free-of-functional disabi ageing (i.e. optimal longevity).

To this end, the design and implementation of strategies for disability prevention and postponement relies on the identification of target modifiable contributors to the development and worsening of chronic conditions and functional decline.

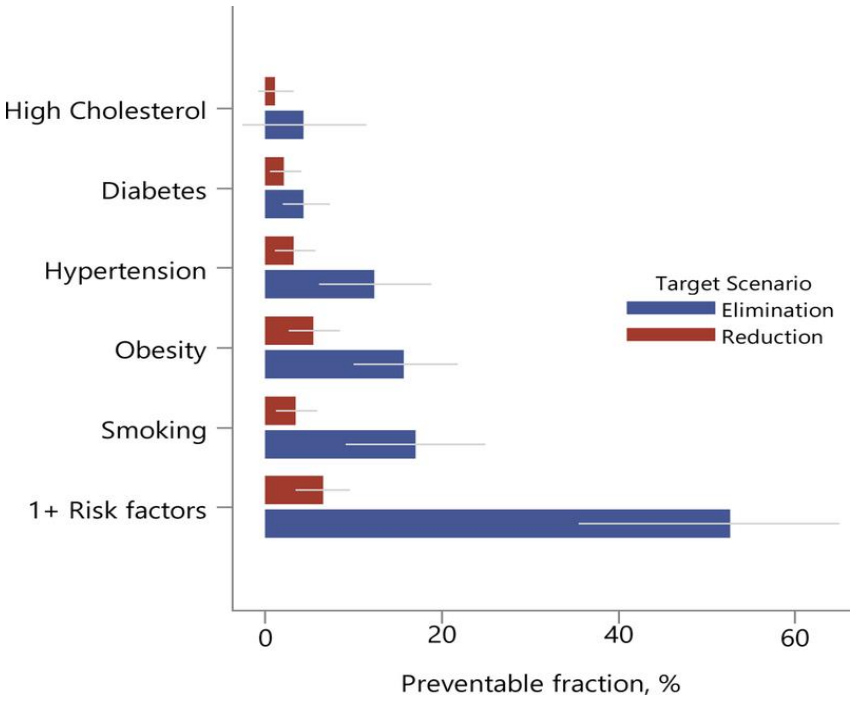


Figure 5. National-level preventable fractions (expressed as percentages) of disability associated with risk factors under elimination and reduction scenarios for adults ages 18–74, 2013

Disability is defined as difficulty walking or climbing stairs; bathing; or independently conducting errands. 1+ Risk Factor category indicates the presence of at least one of the five risk factors.

Data source: Mehta et al., 2017 [23].

2. Healthy vs. Accelerated Ageing

In response to the demographic and epidemiological transitions, The WHO recently defined a model of ageing termed "Healthy Ageing" as the ideal process of fostering and maintaining the functional ability that enables wellbeing in older age. Functional ability of an individual (health-related attributes that enable people to be and to do what they have reason to value), by its part, is comprised by the intrinsic capacity (physical and functional capabilities) and its interaction with the environment [25]. Intrinsic capacity is the manifestation of the integrated function of different body functions and its operationalization rely on 5 domains (locomotor, sensory, vitality, cognitive and psychosocial) [26] (Figure 6).

From this perspective, older adult's health is considered from a functional (intrinsic capacity) rather than disease-based perspective. This has the potential to substantially modify the way in which clinical practice is currently conducted, shifting from a reactive disease-centered toward proactive functional ability-centered paradigms (with the aim of preservation and promotion of intrinsic capacity and disability prevention), addressing and adapting to the undergoing demographic and epidemiological transitions.

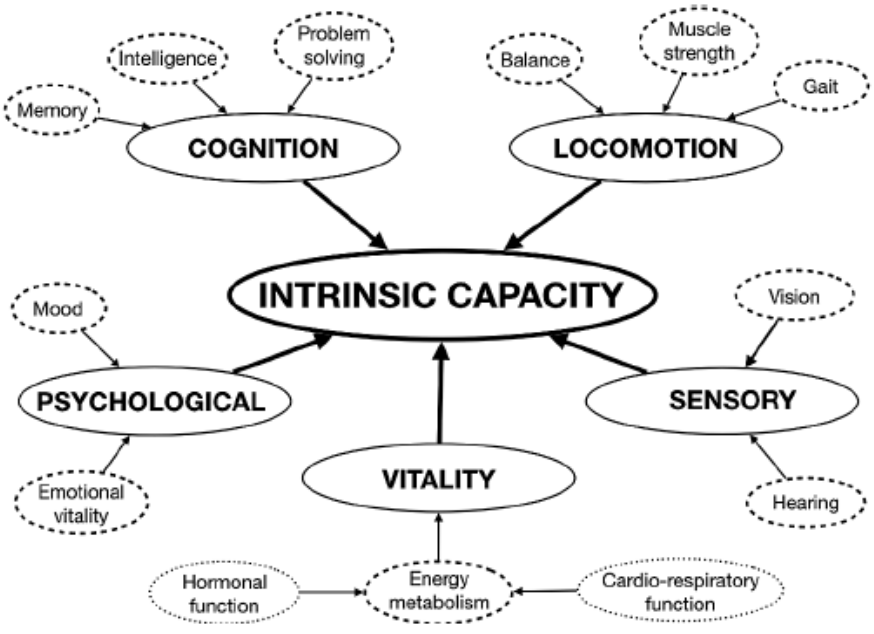


Figure 6. Domains of the intrinsic capacity construct.

From Cesari et a., 2018 [26]

2.1 What is beneath intrinsic capacity decline?

Mechanisms underlying the decreased physiological reserve of different body systems mediating intrinsic capacity declines in ageing have been extensively researched [27–29]. A newly named area of biological research, geroscience, is devoted to the identification of biological mechanisms determining trajectories of physiological ageing and the strategies for healthspan expansion [30, 31]

Gradual declines in physiological reserve contribute to body system functions impairment and functional decline along ageing. It has been suggested that these changes could be the result of inherent (or primary) aging, secondary to health behaviors (such as physical activity and nutrition) and the presence of comorbidities (obesity, T2DM, CVDs, respiratory conditions such as COPD, etc.) and their interaction [11].
Harridge and Lazarus defined inherent (or primary) ageing as "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" [32]. Hence primary ageing, envisioned as a free-of-disease and adverse health behaviors model of ageing, could the ideal target of the healthy ageing paradigm prompted by the WHO in most of the individuals [24].

At the cellular and organ levels, chronic pro-inflammatory states, cellular senescence, impaired proteostasis, hormonal changes, immunosenescence, insulin-resistance and mitochondrial dysfunction drive changes that mediate reduced homeostatic responses [33, 34], impaired function of integrated systems, such as musculoskeletal, vascular, respiratory, endocrine, immune and nervous systems [28] and reduced intrinsic capacity at the whole-body level.

When certain degree of decline is reached homeostatic mechanisms start failing [35], a process that is overtly evident when the intrinsic capacity reserves are insufficient to cope with requirements of ADLs [36] and the breaching of the disability threshold ensues. Ideally, adverse events occur at the very end of life, but importantly, the presence of deleterious life-long or late life-limited lifestyle factors (poor nutrition, inactivity, alcohol and tobacco use among others) might lead to the development or aggravation of comorbidities, such as respiratory (COPD) diseases, CVD (HF, HT, MI), obesity and T2DM, that potentially condition an accelerated physiological reserve loss [37, 38].

The result is that in the presence of exhausted physiological reserves an otherwise small insult (e.g. a new drug, minor infection, hospitalization or surgery) might result in catastrophic and disproportionate change in health state (i.e. disability, death and institutionalization), occurring early in life in the context of an accelerated ageing [11, 27] (Figure 7).

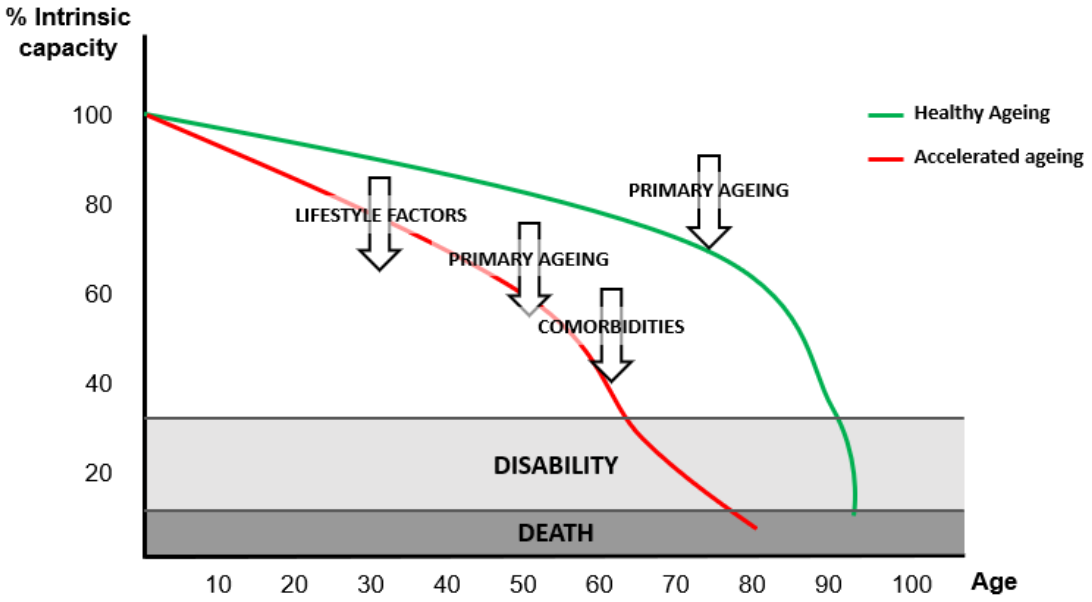


Figure 7. Physiological Reserve/Intrinsic Capacity Trajectories Associated and influence of comorbidities in the disabling cascade.

2.2 Healthy Ageing Phenotypes

Extensive research has been carried out and several mechanisms have been identified for explaining intrinsic capacity loss of ageing. As stated in previous sections, most are ageing-inherent processes whose magnitude and pace are believed to be importantly modulated by behaviors (such as PA, sedentarism, nutrition, smoking and alcohol consumption) and co-occurrence of comorbidities. Unfortunately, the dissociation of mechanisms being exclusively the result of primary ageing from those associated with lifestyle and disease contributing to further impairment (and to what extent) or resulting solely from disease remains a challenging enigma in the field of ageing physiology [39, 40].

Nevertheless, some evidences have been accumulated in this regard. As an example, loss of muscle proteostasis has been putatively associated with normal ageing. Despite both reduced protein synthesis and catabolic processes have been described in muscle ageing, reduced anabolic responses following stimulus such as feeding and muscle contractions is believed to occur in the healthily-ageing muscle (despite being greatly influenced by the presence of factors such as inactivity and metabolic syndrome through insulin resistance), whereas increased muscle protein breakdown has mostly been shown to be present in extreme disuse and pathologic conditions [41, 42].

Master athletes as a healthy ageing model

In the study of different intrinsic capacity decline trajectories, senior master athletes have arisen as an extreme primary ageing model lacking the influence of deleterious lifestyle factors and comorbidities. Overt reductions in CRF [43–45], and MM at the single-physiological system levels [46, 47] and progressive worse performance in sports (as marker of integrative physiological function of multiple systems) [48], have been described among senior athletes. These age-related declines in body systems function occurring even in ideal aging conditions, such as high levels of PA, good nutrition and absence of alcohol and tobacco consumption, can be consequently attributed to inherent ageing *per se*.

Notwithstanding the age-declines in physiological systems seen also in master athletes, these studies have also shown that CRF, strength and power are higher among active

persons across all age groups, and that master athlete's values remain probably well above those sued by ADLs, being equal to 20 or 30 years younger inactive counterparts [32], supporting that disability is not an irremediable end of ageing.

These findings suggest that factually there exist models of healthy ageing, in which intrinsic capacity decrease does occur, but later in life and at a slower pace than "pathologic/accelerated" ageing, solely as a result of inherent ageing, preventing or postponing the breaching of the disability threshold.

Therefore, the understanding of the determinants of inter-individual variability in functional changes with ageing and establishing effective strategies to enhance function at the population level are among the research priorities moving forward.

3. Frailty

In the process of understanding disability late-life development, the term frailty was coined more than 20 years ago to designate a pre-disability state characterized by reduced capacity to respond to stressors. The most common definition of frailty is that of "an age associated, biological syndrome characterized by decreased biological reserves, due to dysregulation of several physiological systems, which puts an individual at risk of adverse events when facing minor stressors and is associated with poor outcomes" [27].

Despite poor agreement exist regarding its operational definition [49, 50], experts concur in that frailty is syndrome of decrease functional reserve and resistance to stressors, that precedes disability and with a multidimensional and dynamic nature [50]. Frailty is an independent construct distinct to comorbidity or disability. In fact, poor overlapping between these three entities has been described (Figure 8) [49].

Frail individuals are more likely to require assisted living, susceptible to suffer adverse events (hospitalization institutionalization, disability) and to die when compared to age-matched counterparts [51, 52].

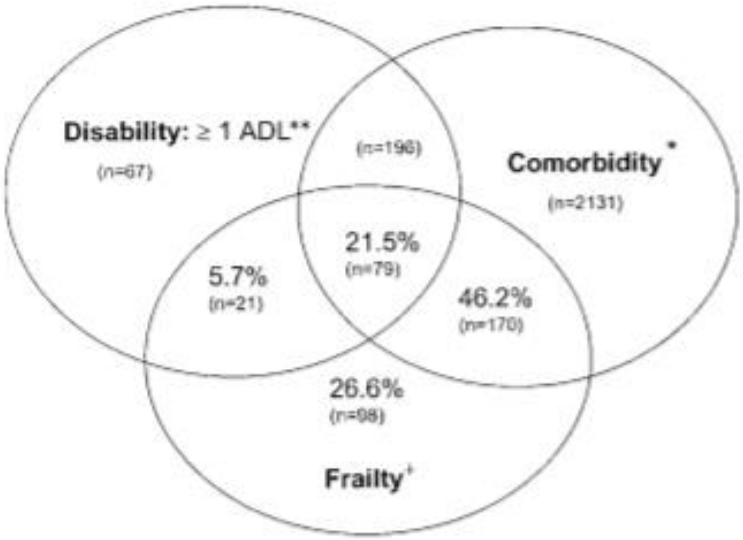


Figure 8. Venn diagram displaying the overlap between frailty, comorbidity (presence of ≥2 diseases) and disability (difficulty in ≥1 ADL).

From Fried et al., 2001 [49].

Two school of thought have prevailed in relation to frailty definition: The FP Model by Fried and colleagues and the Deficits Accumulation Model by Rockwood and colleagues. Whereas the Fried's FP envisions frailty as a geriatric syndrome of diminished functional reserve, captured as the empirical manifestation of a specific biological model of energy dysregulation (i.e., the mismatch between energy uptake and energy utilization) (Figure 10), in the accumulation of deficits model individual contributors to frailty (including disability itself) constitute the drivers of frail subject's poor prognosis [53]. While these two frailty definitions present important conceptual differences mainly in relation to the relationship between frailty and nosographically classified conditions (non-necessarily present in the FP conception) and disability (frailty envisioned as the precursor of disability from the FP perspective and possibly present in the FI) [54], current evidence about a relevant convergence between the two principal models of frailty should reinforce the validity of the concept [55].

Wide discrepancies exist in terms of frailty prevalence between studies. In a systematic review and meta-analysis of 21 studies, Collard et al. observed a prevalence of frailty ranging between 4.0% and 59.1% among community-dwelling older adults, with an overall estimate of 10.7% for frailty and 41.6% for PF status. They also found higher frailty prevalence among women (9.6 vs 5.2%) and with increasing age (from less than 5% among those aged 65-69 to 15.7% in the 80-84 and 26,1% in those ≥85 years of age) [56] (Figure 11).
This huge variation in frailty prevalence estimations might be the result of the use of different frailty operationalization across studies, the use of population-specific vs. reference cut-off points, features of single-studies populations and settings (community, primary care settings, nursing homes…).

For instance, among community-dwelling older adults, frailty prevalence has been estimated to lay around 10% globally [56, 57], whereas rates are much higher among institutionalized older adults, where figures approach 50-60% [57, 58], primary care settings and geriatric units (30%) and hospitals (54%) [57].

Despite substantial heterogeneity in frailty distribution in different studies, frailty has consistently been associated with older age, female sex and socioeconomic status [27, 59].

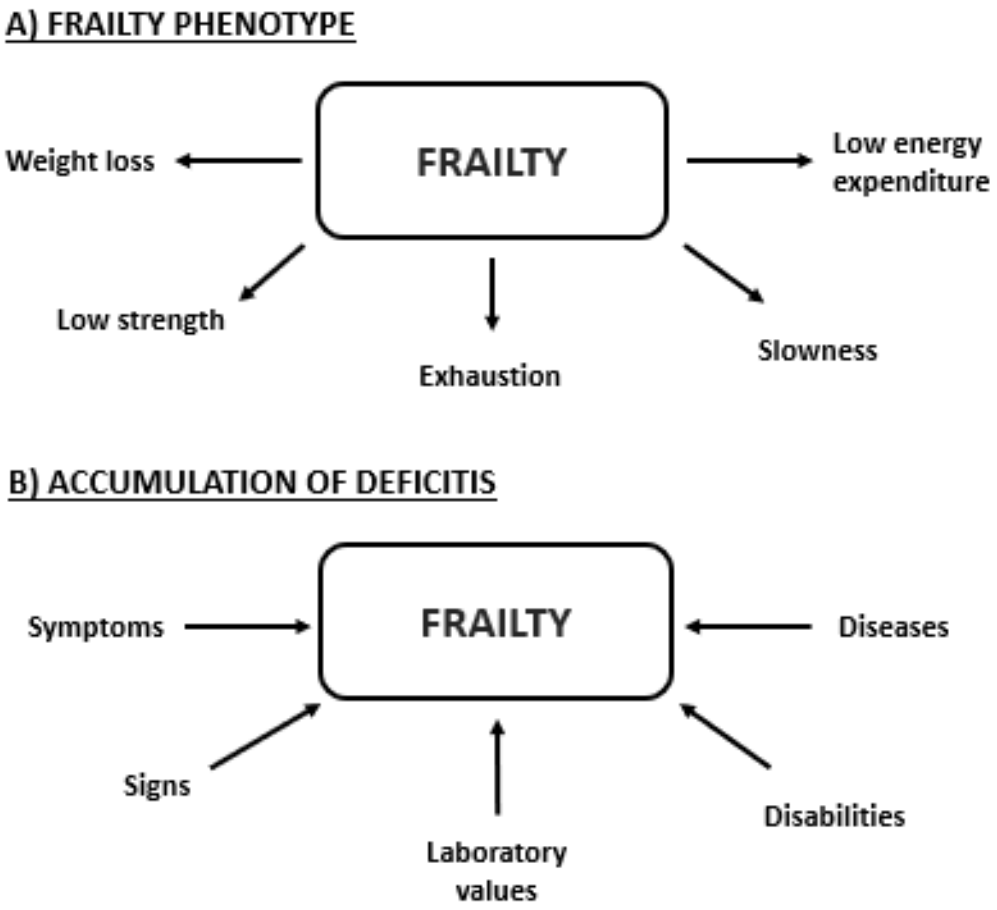


Figure 9. Frailty conceptual definitions.

A) Frailty Phenotype: Frailty as the manifestation of physiological dysregulation.

B) Frailty Index: Frailty as the accumulation of deficits.

Adapted from Xue and Varadhan, 2014 [53].

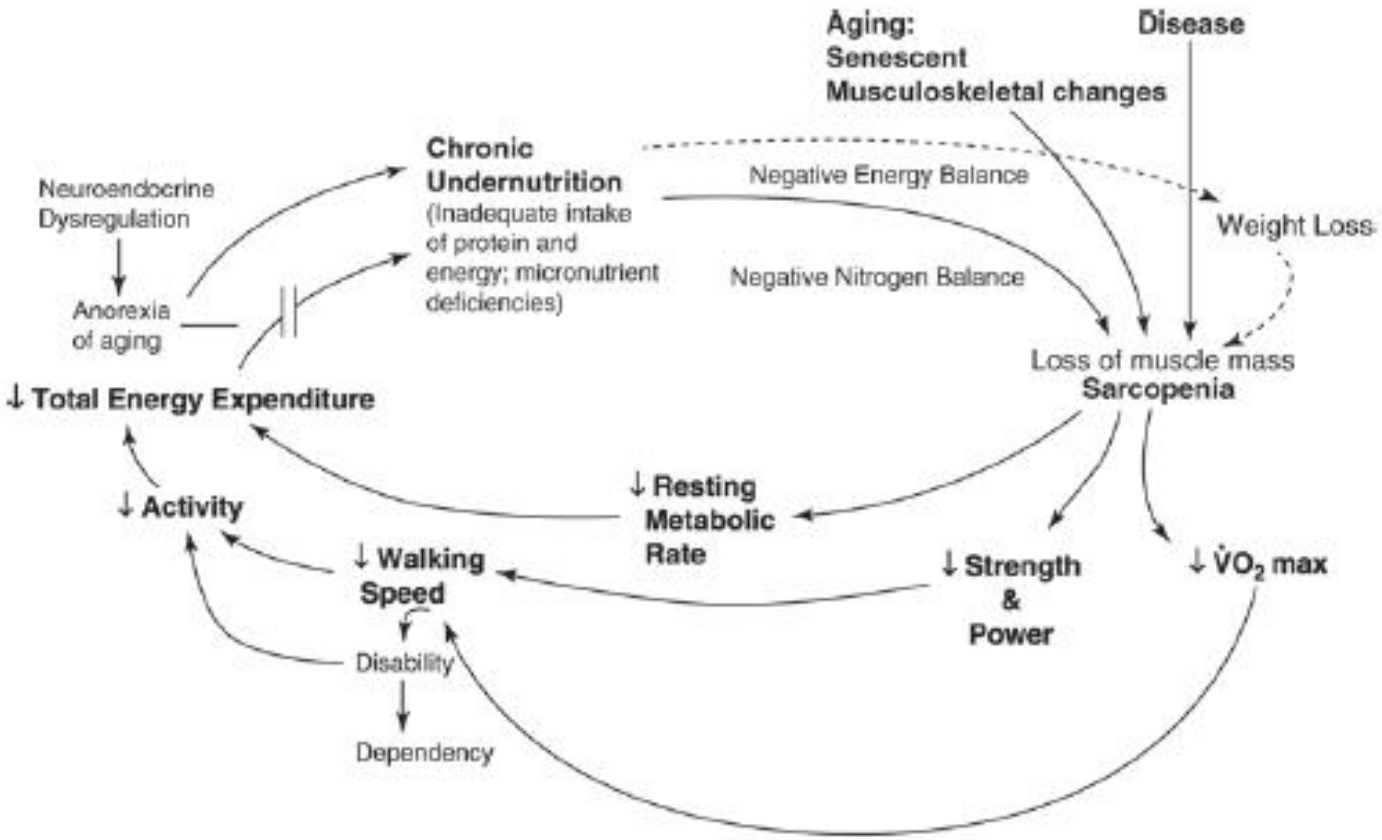


Figure 10. Cycle of frailty according to Fried's conception From Fried et al., 2001 [49]

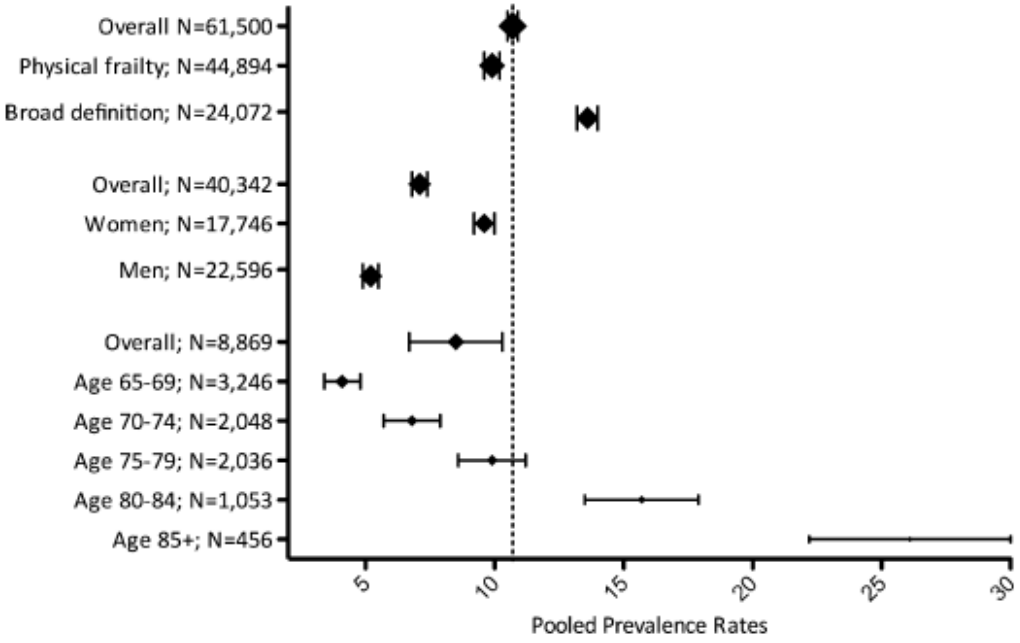


Figure 11. Frailty prevalence in older adults (>65 years), according to physical frailty and broader definitions and stratified by sex and age-groups.

From Collard et al., 2012 [56]

3.1 Frailty relevance in the clinical scenario

Once disability in older adults is established, functional recovery is unlikely, whereas frailty is a reversible dynamic process that offers an opportunity to gain functionality [60], delaying or impeding the appearance of disability [61, 62]. Since frailty might precede by several years the development of disability and other adverse events [63], its detection, assessment and management at the individual level might lead to the identification of its contributors and allow for the onset of interventions aimed at preventing and/or postponing adverse events in older adults [64, 65]. Furthermore, frailty status, by assuming the role of a biological age marker, is believed to add prognostic value and assist at individually tailoring interventions among older adults for which chronological age or the number of comorbidities are poor prognostic indicators [66–73].

Hence, the value of frailty screening and assessment goes beyond the simple risk stratification of the older person, and is rooted in the potential of providing added and valuable information to define optimal care pathways by guiding clinical decisions [74–76].

4. Sarcopenia

In the mediation between frailty and disability, a prominent role is played by sarcopenia [77, 78], whose development might be envisioned as a paradigmatic example of the interaction of primary aging/diseases/lifestyle behaviors on a body system.

4.1 Sarcopenia definition

Sarcopenia (from Greek: "sarcos" referring to flesh and "penia,": a lack of) was first described by Rosenberg in 1989 [79]. Whilst originally referred just to the exclusively age-related loss of lean mass, recent definitions have been expanded to include measures of muscle function (strength and power) and physical performance [80].

The recent recognition of sarcopenia as an independent condition by an ICD code [81] represents the increasing awareness regarding this entity as a relevant syndrome driving important outcomes in older adults. However, there remains substantial controversy regarding how sarcopenia should be defined and operationalized [82] (Table 1). The inclusion of muscle function and physical performance in at-first exclusively MM-centered construct and the selection of the best one among the existing operational definitions are current glowing matters of discussion [83, 84].

4.2 Sarcopenia epidemiology

The relevance of sarcopenia arises from being relatively common condition and being associated with short-term and long-term adverse effects but, regrettably, the lack of a standardized sarcopenia definition hampered the accurate estimation of the burden of disease, the study of its etiology and potential therapeutic options, which in the end has preclude its translation into the clinical practice [85].

This fact becomes overtly evident given the disparate prevalence estimates yielded by the use of different definitions (ranging from 9.9 using 40.4 % among community dwellers in Mayhew et al., recent meta-analysis) [86], which suggests that different operationalizations might not be interchangeably and might identify different at-risk groups of older adults.

Table 1. Sarcopenia operationalizations and cut points proposed

Diagnosis definition	Muscle mass	Muscle strength	Physical Performance
Baumgartner et al., 1998	ALM < 2SD young values of the same ethnic group	-	Not applicable
Cruz-Jentoft et al., (EWGSOP), 2010	Women: SMI ≤5.50 kg/m² Men: SMI ≤7.26 kg/m²	Women: handgrip strength<20 kg Men: handgrip strength<30 kg	SPPB ≤8 Gait speed<0.8 m/s
Fielding et al., (IWGS), 2011	Women: SMI ≤5.67 kg/m² Men: SMI ≤7.23 kg/m²	-	Gait speed<1.0 m/s
Morley et al., (SSCWD), 2011	ALM < 2SD young values of the same ethnic group	-	Gait speed<1.0 m/s
Chen et al., (AWGS), 2014	Women: SMI ≤5.40 kg/m² Men: SMI ≤7.00 kg/m²	Women: handgrip strength<18 kg Men: handgrip strength<26 kg	Gait speed<0.8 m/s
Studenski et al., (FNIH), 2014	Women: ALM/BMI<0.512 Men: ALM/BMI<0.789	Women: handgrip strength<16 kg Men: handgrip strength<26 kg	Gait speed<0.8 m/s
Cruz-Jentoft et al., (EWGSOP) 2019	Women: SMI < 5.50 kg/m² Men: SMI < 7.00 kg/m² Or Women: ALM < 20 kg Men: ALM < 15 kg	Women: handgrip strength<16 kg Men: handgrip strength<27 kg Or 5-times chair stand test >15 s	SPPB ≤ 8 Or Gait speed < 0.8 m/s Or TUG ≥ 20 s Or 400-m walk ≥ 6 min

ALM: appendicular skeletal lean mass; BMI: body mass index; SMI: Skeletal Muscle Mass Index; EWGSOP: European Working Group on Sarcopenia in Older People; IWGS: International Working Group on Sarcopenia; SSCWD: Society of Sarcopenia, Cachexia and Wasting Disorders; AWGS: Asian Working Group for Sarcopenia; FNIH: Foundations of the National Institute of Health; TUG: Test Up-and-Go; SPPB: Short Physical Performance Battery.

Focusing on recent and more comprehensive sarcopenia definitions (including muscle strength and physical performance measures), a lower proportion of older adults present with sarcopenia, with overall prevalence around 10% for both community-dwelling men and women [87].

Notwithstanding the differences in sarcopenia definitions and methodologies in the studies, sarcopenia appears to be more prevalent in clinical settings such as nursing homes (51% in men and 31% in women) [88], hospital (23% in men and 24% in women) [88], post-acute care (56%) [89] and in populations of older adults presenting with conditions (COPD [21.6%], CVD [31.4%], dementia [26.2%], T2DM [31.1%]) [90, 91].

Similarly to frailty, sarcopenia is more prevalent among oldest old subjects [86] whereas the absence of clear sex-differences observed might be the result of the use of sex-specific cut-points in most of the instruments.

4.3 Sarcopenia: a public health issue

From the clinical sense, sarcopenia might be the result and contribute to the aggravation of several age-associated conditions (diabetes [92, 93], cancer [94], CVDs [95]). Moreover, age-related muscle function losses mediate the deterioration of the physical domain of intrinsic capacity [96], deriving in poor outcomes such as mobility and ADL disability, severely impacting HRQoL [97, 98]

Sarcopenia has been associated with adverse outcomes such as mortality [99], falls and fractures [100], functional decline and hospitalization [97] in older adults populations.

Consequently, sarcopenia poses a huge financial stress on healthcare systems. In the US, the costs associated with sarcopenia (defined only through MM) were estimated at $18,5 billion in 2000 [101]; and the differential hospitalization-related healthcare costs between sarcopenic and non-sarcopenic individuals in the same country reached USD $2315 [102]. Recently, an analysis of the Hertfordshire Cohort Study the presence of low HS resulted in an estimated excess economic burden for health and social care of £2,5 billion [103].

Sarcopenia is considered a major public health issue, requiring correct assessment, identification, prevention and if present, interventions to reverse or attenuating its progression with the aim of avoiding its burdensome consequences [97].

4.4 Sarcopenia evolution and physiopathology

Regarding the natural history of sarcopenia, MM and function have been shown to peak around the fourth decade of live, to be maintained across adulthood and to decrease thereafter in both sexes [104]. Importantly, losses in muscle function (i.e. in muscle strength and power) precede and are steeper than those in MM [105], indicating a decline in specific force area and in peak power per unit volume, usually referred as "muscle quality" [106]. In a seminal study, Lauretani et al., showed that MM, strength and power values at age >85 years were 25, 50 and 75% lower than that observed in men 20-29 years old in the InChianti study (Figure 12) [107].

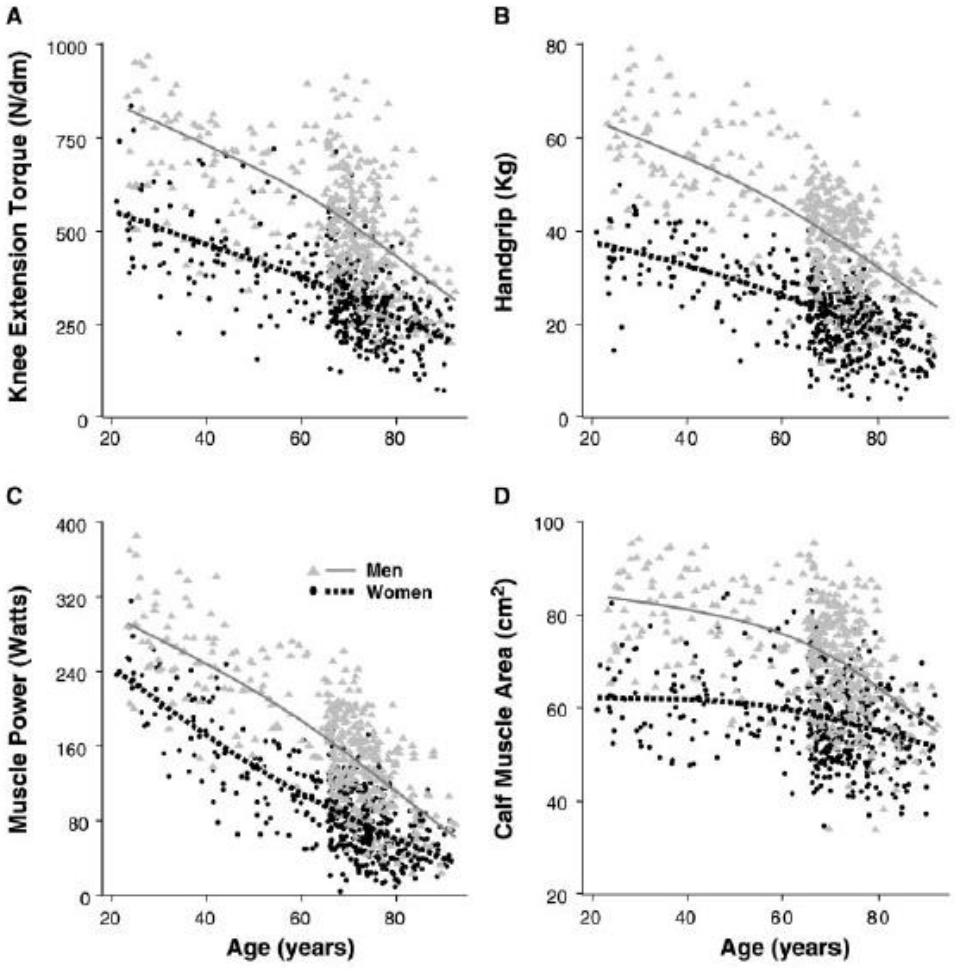


Figure 12. Adulthood trajectories in maximum knee extension torque (A), maximum handgrip strength (B), lower extremity muscle power (C) and calf muscle area (D) in the InChianti Study.

From Lauretani et al., 2003 [107].

Of note is the evidence showing that skeletal muscle function, especially power, is more strongly associated with physical function [96] and adverse outcomes in older populations than measures of MM alone [108].

At the muscle histological level, sarcopenia is characterized by the loss of motor neurons and motor units enlargement (due to partial reinnervation) of denervated fibers [109], reduction in the number of both type I and II muscle fibers, accompanied by type II fiber-specific atrophy [110], higher presence of mixed-fibers (co-expressing both MHC-I and MHC-II) [111], muscle fat and fibrous tissue infiltration [112] and reduced number and impaired function of SC [113].

These changes are the result of the interaction of a constellation of factors involving the aging neuromuscular machinery (reduced fiber muscle perfusion and loss of neurotrophic input secondary to motor neuron loss [114]), dysregulated proteostasis (i.e. balance between muscle protein anabolic and catabolic processes), due to anabolic resistance and downregulation of anabolic hormones (lower testosterone, GH, IGF-I, DHEA levels) and increased catabolism by pro-inflammatory cytokine activity (IL-6, TNFα. CRP) [115], mitochondrial dysfunction-mediated muscle fiber bioenergetics failure [116, 117], all driven by environmental, genetic and behavioral factors not fully unveiled and still under tracing.

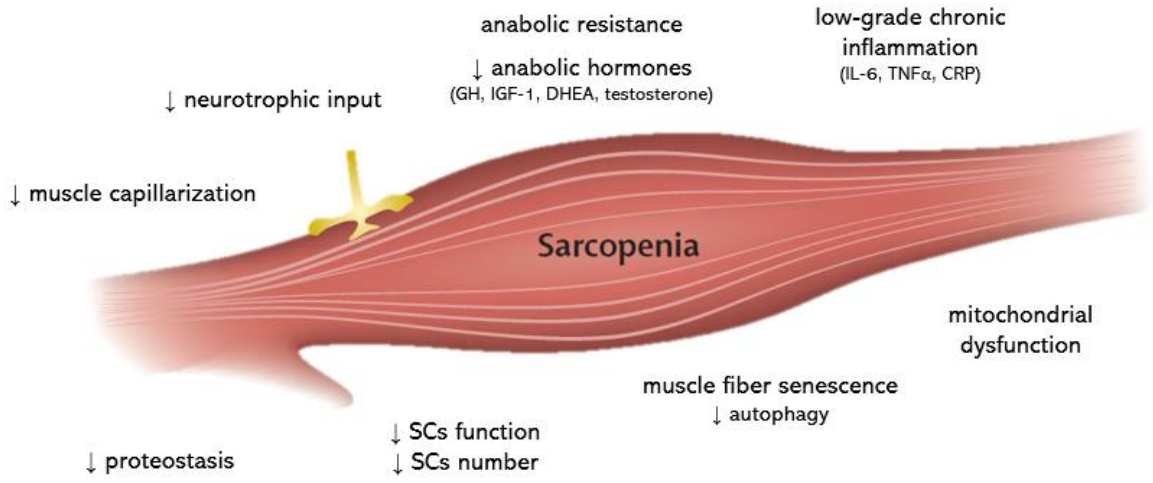


Figure 13. Sarcopenia physiopathology

Adapted from Cruz-Jentoft and Sayer, 2019 [118]; and Kirk et al., 2020 [119].

Important to remark is that, mechanisms underlying age or disease-related impairments in muscle strength or power are not limited to muscle tissue or peripheral nervous system. It has been observed that processes of neuronal atrophy, dysregulation of neurotransmitters activity and reduced neuroplasticity at the central nervous systems are also responsible of diminished muscle function [120], in addition to peripheral processes of muscle mass and function reduction.

4.5 Sarcopenia as a determinant of intrinsic capacity loss

Accelerated MM and function loss might be envisioned as the organ-specific pathophysiological background of the progressive reduction of the physical (or locomotion) domain of intrinsic capacity, thus potentially influencing the ability to reach and maintain the full functional ability of the individual [75].

Notably, the perception of skeletal muscle as pure locomotor unit has progressively shifted. Skeletal muscle represents approximately 40% of the body weight and constitutes the largest protein reservoir in the body. Additionally, muscle is increasingly recognized as an endocrine organ [121], an immune system responses regulator [122], playing a pivotal role in metabolic health, by being the major site of glucose storage and utilization [123].

In turn, age-associated reductions in MM and function imply not only a physical function impairment but the derange of the physiological cross-talk between muscle and other organic systems through reduced and altered myokine-mediated signaling, and might further aggravate chronic conditions including metabolic syndrome [124], T2DM [92], CVDs [125], obesity [126], osteoporosis [127] and cognitive impairment [128, 129], as well as poor immune responses when facing pathogens [122].

4.6 Sarcopenic Obesity and Osteosarcopenia

Two recently coined constructs stand out as examples of the relevance of skeletal muscle mass as an endocrine organ, and specifically in the ageing process. The constructs of sarcopenic obesity and osteosarcopenia have arisen as the combination of age-related low muscle mass and obesity [130] and osteopenia/osteoporosis [131], respectively.

Obesity has rapidly increased worldwide over the last three decades, largely due to combined genetic predisposition and profound lifestyle changes including sedentary

habits and high-calorie dietary intake [132]. Sarcopenia and obesity share common pathophysiological mechanisms including insulin resistance [123], chronic inflammation [126] and oxidative stress that mediate the presence of a dysfunctional adipose tissue [124], increased catabolic activity and blunted anabolic responses at the skeletal muscle level [133].

In the case of osteosarcopenia, both declines in muscle mass and function and bone mass seem to share common pathogenesis, with factors such as certain common genetic polymorphisms, endocrine activity decline-mediated anabolic resistance (low IGF-I, GH, testosterone and estrogens) and reduced physical activity/mechanical load [131].

Interestingly, it has been hypothesized that dysfunctional skeletal muscle and bone tissues and increased ectopic and adipose tissue interact to jointly determine an accelerated bone density and muscle mass loss and function declines [134].

This is explained by the activity of some myokines and adipokines, that are believed to underregulate bone resorption (irisin, follistatin) and formation (myostatin). Conversely, bone (osteocalcin and connexin 43) and adipose tissue-derived cytokines, such as adiponectin and anti- and pro-inflammatory adipokines may have a modulating role on muscle anabolism/catabolism [135], suggesting the existence of bi (tri)-directional relationships between skeletal muscle, adipose, and bone tissues [131, 134] (Figure 14).

The co-occurrence of obesity, sarcopenia and osteopenia/osteoporosis conditions a sharper decline in physical function and exposes older adults to a greater risk of poor health outcomes than the presence of these conditions individually. In the presence of age-related decreases in MM and concurrent increases in fat mass, the BMI-based "obesity paradox" does not operate, and the addition of adiposity to sarcopenia might entails further risk of adverse events among older adults, especially disability [136, 137], whereas the risk of fracture rises notably when low bone density and sarcopenia coexist [138].

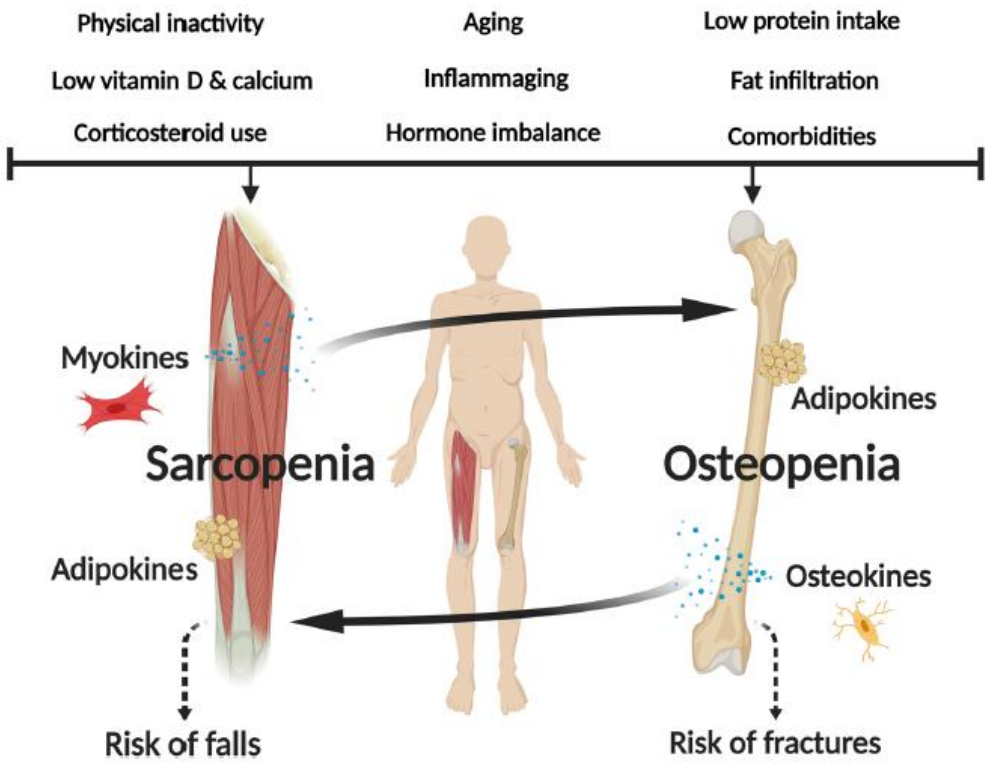


Figure 14. Risk factors, muscle–bone crosstalk (through myokines, osteokines, adipokines), and the pathophysiology of osteosarcopenia.

From Kirk et al., 2020 [131].

4.7 Sarcopenia: Frailty's biological substrate?

Some authors have suggested that sarcopenia could be the biological substrate of physical frailty, a disability-centered frailty conception, close to that of the FP [77, 139].

Nevertheless, there appears to exist little overlapping between sarcopenia and frailty. In a recent work from the TSHA, Davies et al., showed a prevalence of frailty according to FP of 8.2%, and 15.7% among subjects classified as sarcopenic by the EWGSOP and the FNIH definitions, respectively. Moreover, sarcopenia in the form of EWGSOP and FNIH definition was present in 40.7% and 72.2% of frail individuals. These results suggest little overlapping between frailty and sarcopenia, being the presence of the latter a poor marker of the former (sensitivity<10%), but useful for its exclusion when absent (specificity=97%) [140].

Therefore, we can conclude that sarcopenia, besides being an obvious contributor to physical function decline with ageing, by limiting force and power production, also involves alterations in the physiological role of muscle mass in energy balance and as a endocrine organ, constituting a phenomenon with whole-body effects, which explain its associations with a wide range of conditions and adverse events.

Frailty, by its part, is a much broader construct, being musculoskeletal system only one of the constellation of organic systems contributing to the frailty increased vulnerability.

5. Opportunities for healthy ageing promotion

In response to the ageing population, a current major challenge for modern medicine is to find ways for preventing and treating sarcopenia, frailty, and overall intrinsic capacity decline in mid- and late life, in order to avoid disability. To this end, gaining insight into the factors determining healthy and accelerated ageing phenotypes could assist in the development and refinement of public health recommendations and interventions for maintaining functional ability that enables well-being during late life. Furthermore, recognizing that sarcopenia, frailty and intrinsic capacity loss are the result of multi-systemic physiological impairments, the management of older adults should be focused on the prevention of age- and disease-related physiological function loss, fostering whole-body systems functioning as opposed to the diagnosis and treatment of specific diseases [11].

6. Physical Activity: a potential Intrinsic Capacity Booster

6.1 Physical Activity, Sedentary Behaviour, Exercise and Health

PA defined as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level [141] has gain recognition as one of the critical determinants of health across life [142].

Since classical papers emerged in the middle of the 20th century linking labor-related PA and lower CVD mortality [143, 144] a substantial bulk of research has proved the health benefits of greater PA levels on several physiological systems and has pointed to a protective effect of PA for a wide range of chronic diseases [125, 145–148] (Figure 15). These benefits of PA have systematically been traduced into lower mortality and disability rates in both men and women [22, 142, 149, 150].

Physical exercise, "a subcategory of PA that is planned, structured, repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective" [141], has recently been envisioned as a drug [151, 152]. Regular exercise is associated with increased longevity and reduced risks for CVD, stroke, cognitive decline, some cancers, T2DM, osteoporosis, HT, dyslipidemia, obesity, and osteoarthritis in the general population [146, 153].
Furthermore, high quality evidence has shown an important role of both forms of PA in the secondary prevention of non-communicable diseases, such as cancer, T2DM, CVD and HIV, by positively impacting all-cause [154] and disease-specific mortality [154, 155], markers of disease progression [156–160] and disease-related constructs such as physical function [161] and HRQOL [162, 163].

Hence both PA and exercise have been recognized as a cornerstone in the prevention, management, and treatment of numerous chronic conditions.

An important physical behavior impacting health is the lack of PA. Despite SB and inactivity have extensively used interchangeably to refer the accumulation of low-energy consuming activities (usually sitting), they are distinct constructs. Physical inactivity refers to the non-compliance with PA guidelines (lack of MVPA, see below), whereas SB connotes different PA behaviors than non-MVPA, consisting of the

accumulation of time in activities at the low end of the intensity range, eliciting very low energy expenditures in a reclined or sitting position [164].

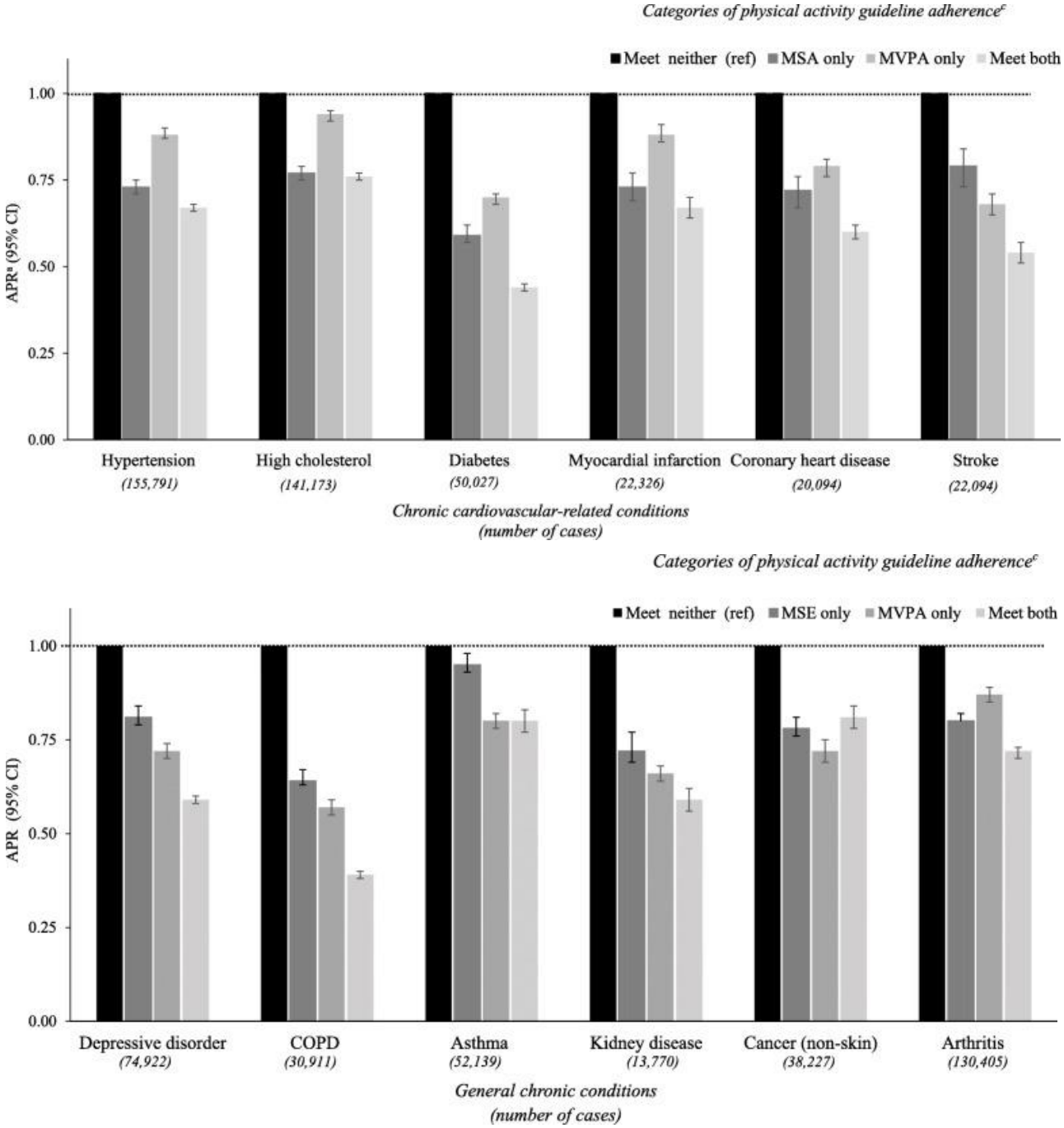


Figure 15. Adjusted prevalence ratios (APR; 95% CI) for chronic conditions by categories of adherence to PA guidelines.

Meet neither=Subjects not adhered neither aerobic nor strength training recommendations. MSE=Subjects uniquely adhering to muscle strength training recommendations. MVPA only= Subjects uniquely adhering to aerobic MVPA recommendations. Meet both= Subjects fulfilling both recommendations.

From Bennie et al., 2019

Then, an individual might be physically active if meeting current PA recommendations but sedentary as for spending large amounts of time in SB. Conversely, a non-physically active individual might accumulate little proportion of the day in SB by engaging in light activities, not accounted in PA recommendations. Taking these insights into a public health research and translational framework, SB may be understood to be a class of behaviors that can coexist with, and potentially compete with PA, with independent health consequences and environmental and social determinants [165, 166].

6.2 Physical Activity parameters as determinants of the response

The effects of both PA and exercise on health rely on certain parameters that determine the features of the homeostatic disruption exerted by PA/exercise and consequently, the adaptative responses activated after muscle contractions.

Intensity refers to the rate at which energy is expended during a muscle contraction. It is usually measured in multiples of the resting metabolic rate (1 MET=3.5 $ml.kg^{-1}.min^{-1}$), and has been generally categorized as: SB (sitting or reclining activities <1.5 METs), LPA (1.5-2.99 METs), MPA (3-5.99 METs) and VPA (≥6 METs) [167–169] in absolute terms. Duration is defined as the amount of time engaged in certain activity or intensity category. The frequency is the times an activity is performed within a specified period, usually expressed as bouts, episodes or sessions per week. Finally, the mode or type of PA refers to the modality of PA: walking, swimming running, etc.…, whereas in the case of exercise a classical distinction between aerobic (i.e. low-intensity repetitive contractions) mainly inducing adaptations that lead to improved oxygen uptake, transportation, and utilization, and resistance (i.e. low frequency and high-resistance demand) exercises, believed to mainly play a role in proteostasis and neuromuscular function [170].

PA/exercise parameters condition different responses at the cellular level in a hormetic fashion: from insufficient stimulus to trigger responses to deleterious if excessive, trough adequate at physiological ranges [171]. These stimuli, if repetitive, induce adaptations according to the principles of overload, specificity and progression [172].

On the other hand, and despite its recent incorporation as an independent health factor, parameters associated with SB accumulation, mean life of sedentary bouts, the number of breaks in SB and even the type of activities while sitting/lying (TV watching vs. reading or mentally demanding tasks) and their correlates (i.e. poor nutrition) have been suggested to modulate the consequences of SB on health [166, 173].

Unfortunately, molecular mechanisms explaining the relationship between PA/exercise and lower SB and benefits in specific disease processes have recently started to be investigated and remain partially understood. In fact, whether the deleterious effects of inactivity and SB are exactly opposite to the positive health benefits of increased physical activity remains widely unresolved [174–176].

6.3 Physical Activity Guidelines for Health

Since in 1995 the US CDCP and the ACSM issued the first evidence-based PA recommendation for public health [177], public PA recommendations have evolved and expanded by different public health institutions (WHO, US DHHS, AHA [178–180]), with the aim to adapt to growing evidence regarding the role of PA as a health factor in different age (children, youth adults, older adults) and health process-specific populations, and the emergence of SB as a crucial health factor.

Currently under-public consultation WHO Physical Activity and SB guidelines for adults [181] recommend *"to accumulate at least 150 minutes to 300 minutes of moderate-intensity aerobic PA, or do at least 75 to 150 minutes of vigorous-intensity aerobic PA or an equivalent combination of moderate- and vigorous-intensity PA throughout the week for substantial health benefits. In addition, adults should also engage in muscle-strengthening activities at a moderate or greater intensity 2 days a week".* Nevertheless, PA associations with health benefits seems to have a curvilinear dose-response shape in terms of volume and intensity, that level-off at the upper limits. Hence, it points that "*further benefits might be acquired by engaging in more than 300 minutes and 150 minutes of moderate- and vigorous-intensity aerobic PA "*. Acknowledging that some adults with functional impairments or conditions might not be able to reach recommended volumes and intensities of PA, the report indicate that such individuals should be as physically active as their conditions allow, and increase their PA in terms of intensity and volume with the aim of achieving PA general goals, with the premise that any PA is better than none.

With regards to SB, the recommendation advise "*to limit the amount of time spent being sedentary and replacing sedentary time with physical activity of any intensity (including light intensity) has health benefits"* and further recommend to those highly sedentary (for example office-based workers) to achieve or exceed the upper levels of PA recommendations in order to minimizing the detrimental effects of sedentariness [182]. No SB maximum volume is advised since evidence remains scarce in this regard.

6.4 Mechanisms underlying benefits of Physical Activity/Exercise on Health

There is increasing consensus envisioning PA as a physiological need, giving that our genetic background was forged in a milieu in which high levels of PA were crucial for survival [183]. Hence, current chronic disease "pandemic", besides of the phenomenon of ageing population, might be the result of the discrepancy between current day human PA levels and that required physiologically [184]

Unfortunately, despite an increasing number of scientific works are deepening in the acute and long-term mechanisms triggered by muscle contraction impacting local and systemic adaptations to exercise, the understanding of the molecular and physiological mechanisms underlying the benefits of PA/exercise on health is in its infancy [185, 186].

Those classically associated to physical fitness improvements through exercise might be also responsible for the widely epidemiologically confirmed health benefits of PA.

Exercise adaptations at the cell and systemic levels

Any PA increase needs the coordinated activity of multiple body physiological systems in order to match the mechanical/metabolic demand of the activity. PA challenges practically every system in the body and start mechanisms to preserve or re-establish homeostasis [186], that include both short-term and long-term processes.

Exercise induces adaptations in several cell types and tissues throughout the body. At the cell level, structural and metabolic adaptations to PA and exercise are tailored at minimizing the homeostatic disruption elicited by a subsequent PA/exercise bout. These changes are mediated by a complex interplay between intracellular signaling pathways activated in response to changes in cellular homeostatic parameters

(metabolic and mechanical stress), which in turn regulate transcription and translation, and exercise-responsive gene expression [170]. At the cellular level, maximization of substrate delivery [187, 188], mitochondrial respiration and improvements in contractile properties of the myocytes are common adaptations to sustained PA/exercise participation [189, 190]. Figure 16 display the mechanisms underlying skeletal muscle fiber adaptations to exercise.

Additionally, substances delivered by muscles are believed to induce systemic adaptations. Despite mechanisms beneath remote effects of exercise still poorly understood, recent research suggest that they might result from the secretory activity by muscle cells of biomolecules that are synthesized and released by contracting muscles in the form of myokines (cytokines or small peptides), growth factors and metabolites [191] and extracellular vesicles implicated in the autocrine regulation of metabolism in the muscle as well as in the paracrine/endocrine regulation of other tissues [121, 192] (Figure 17). Hence, PA and exercise promote a crosstalk between muscle and other tissues/organs including adipose tissue, the liver, bone, myocardium, endothelium, the immune system and the brain [121, 127, 146], absent in non-contracting muscle.

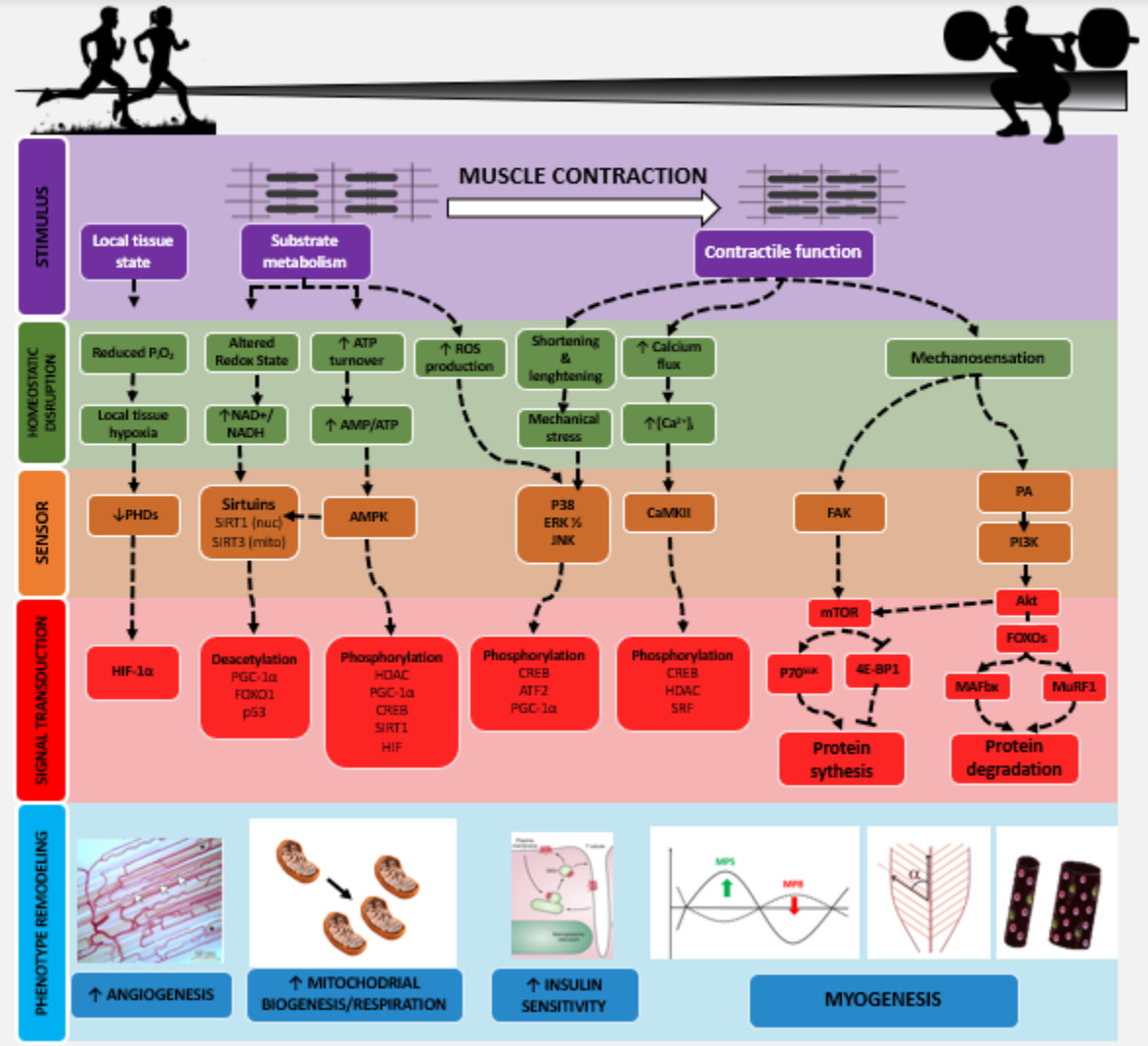


Figure 16. Schematic representation of Excitation-Transcription-Adaptation Coupling in Skeletal Muscle

Muscle contraction derives in biochemical and biophysical stimuli mainly related with mechanical and energy stress. These perturbations in skeletal muscle homeostasis lead the activation of networks of signaling molecules (enzymes) including protein kinases, phosphatases, and deacetylases, which are integrated into physiological processes by downstream targets, including transcription factors and transcriptional coregulators. Importantly, the relative activation, contribution, and magnitude of the described pathways and downstream targets are dependent on the intensity, duration, and mode of the PA/exercise. Linear pathways are depicted, but in fact, these pathways demonstrate some degree of dependence, crosstalk, interference, and redundancy in their regulation.

PiO2=oxygen partial pressure; ATP=adenosine triphosphate; AMP=adenosine mono-phosphate; ROS=reactive oxygen species; NAD+/NADH=oxidized/reduced nicotinamide adenine dinucleotide ratio; [Ca2+]i=ionized calcium concentration; PHDs=prolyl hydroxylase enzymes; CaMKIII=calmodulin-dependent protein kinase; SIRT=sirtuin; AMPK=AMP-activated protein kinase; p38=p38 mitogen-activated protein kinases; ERK1/2= Mitogen-activated protein kinase 3; JNK=c-Jun N-terminal kinases; FAK=focal adhesion kinase; PA=phosphatidic acid; PI3K=phosphatidylinositol 3-kinases; Akt=protein kinase B; mTOR=mammalian target of rapamycin; FOXO=forkhead box protein; HIF1-α=hypoxia inducible factor 1 α; PGC-1=peroxisome proliferator-activated receptor γ co-activator 1 α; HDAC=histone deacetylase; CREB=cAMP response element-binding; ATF2=activating transcription factor 2; SRF=serum response factor; p70s6k=ribosomal protein S6K; 4E-BP1: eukaryotic translation initiation factor 4E (eIF4E) binding protein. MAFbx= MAFbx/atrogin-1 ubiquitin ligase; MuRF1= muscle RING finger 1 ubiquitin ligase. Adapted and updated from Egan and Zierath, 2013 [170].

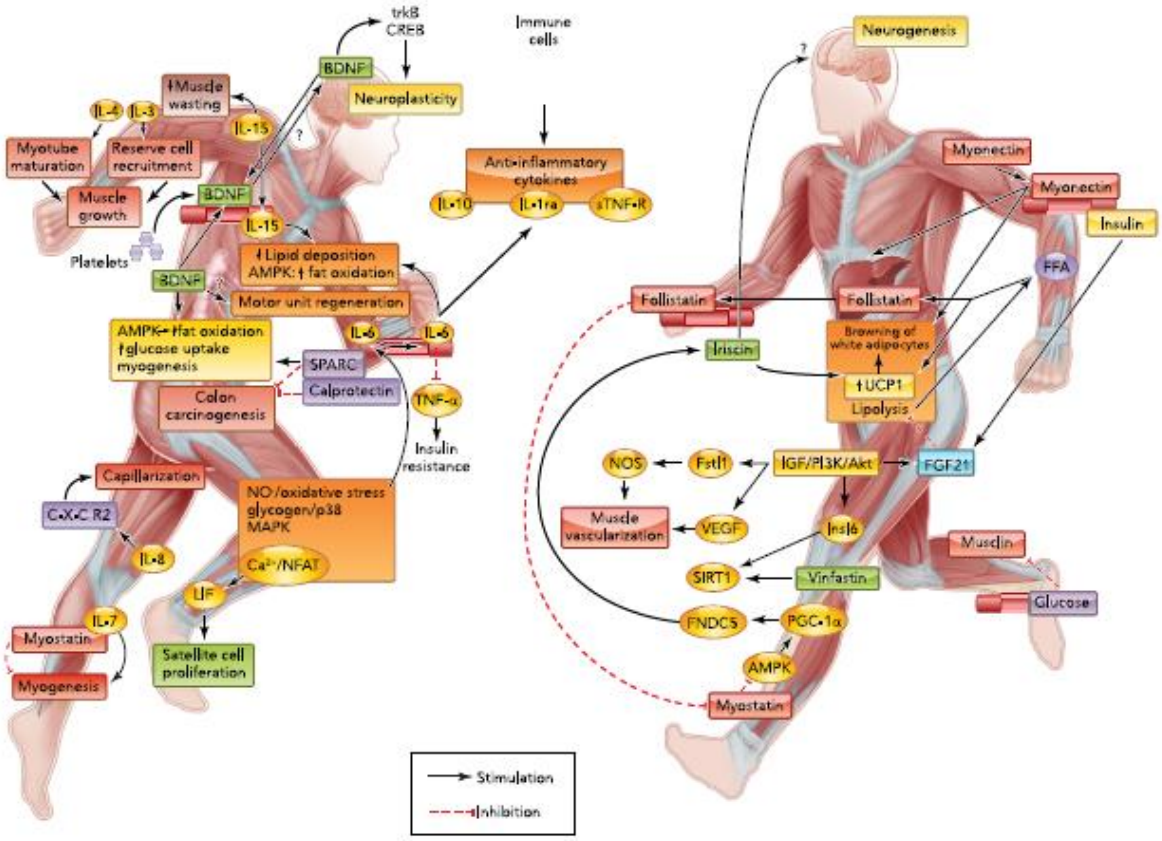


Figure 17. Summary of the main myokines, their putative effects, and the molecular signals/pathways involved.

From Fiuza-Luces, 2013

6.5 Mechanisms underlying PA/SB effects on health

Overall, the benefits of PA on health might arise from increased insulin sensitivity [193], optimized substrate utilization [194], reduction in low-grade chronic inflammatory activity [195], and functional adaptations through increased neurogenesis and neuroplasticity [196], skeletal muscle and myocardial hypertrophy [189], neovascularization [197, 198] and improved endothelial-function [125], which might prevent and positively impact cardio-metabolic diseases, diabetes, cancer, neurodegenerative conditions and depressive disorders [146].

On the other hand, putative mechanisms through which SB might negatively impact health and contribute to chronic disease might be related to the development of risk factors such as hyperglycemia, dyslipidemia, and HT (Figure 18) [175], secondary to reductions in both muscular/metabolic demand and blood flow/shear stress, muscle atrophy, post-meal substrates loading, decreased lipid trafficking/oxidation, and concurrent decrements in muscle/liver insulin sensitivity and vascular function, that mediate processes that at current understanding are opposed to those of PA (lipotoxicity, insulin resistance, excess oxidative stress, and impaired interorgan signaling) [174].

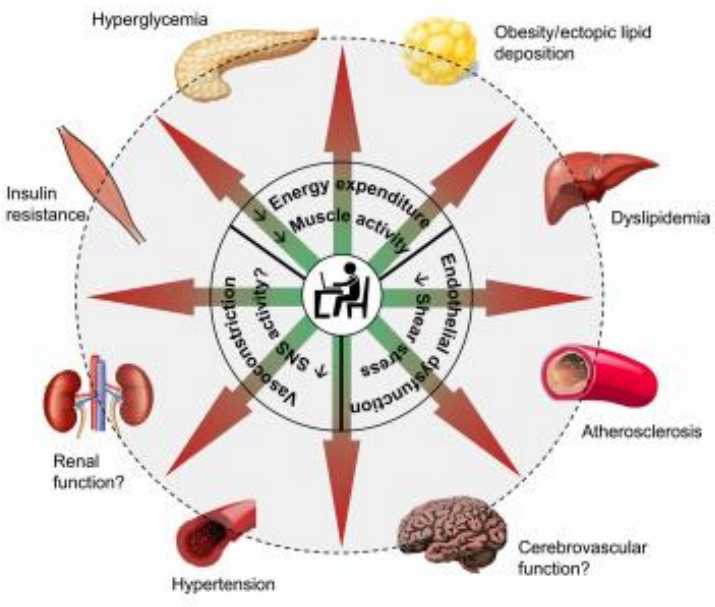


Figure 18. Putative mechanisms linking SB and chronic disease

Lack of muscle contraction involves reductions in metabolic and mechanical demands that induce insulin resistance, mitochondrial dysfunction, inflammation and lipotoxicity.

From Dempsey et al., 2019 [175]

7. Physical Activity and Health in Older Adults

Older adults retain superbly abilities for PA/exercise adaptations. PA/exercise have shown effectiveness for attenuation of age-related declines in physical fitness and neurodegeneration [199]. Tellingly, increased PA has been proved to promote MM and function enhancements [200–202], and to positively impact cardiorespiratory [203, 204], cardiovascular [125], immune [205] and nervous systems [206] function in older adult samples.

From the functional point of view, these adaptations to exercise are translated into improved mobility and physical functioning [207, 208], reductions in the risk of falling [209] and disability in older adult at-risk populations [210]. Importantly, exercise has demonstrated effectiveness for maintenance or improvement of cognitive function [211], and consequently, has proven positive impact on both intrinsic capacity domains (physical and cognitive capacities).

Even in bedridden, hospitalized patients, early mobilization and participation in resistance-based exercises have proven effectiveness for preventing hospitalization-associated functional decline, which illustrates the potential of physical exercise to countermeasure even the most extreme acute and sharp intrinsic capacity declines [212].

7.1 Physical activity/exercise to counteract intrinsic capacity loss of ageing

Due to their potential to attenuate or reverse age- and disease-related whole-body declines in physiological reserve and functions, both PA and exercise are now recognized as outstanding approaches for prevention, postponement or attenuation of physiological reserve deterioration with age [213]. In the absence of pharmaceutical interventions for frailty and sarcopenia, increased PA/exercise constitute unique therapeutic strategies for the prevention and reversal of both syndromes [214–216].

Remarkably, similarly to drug-based therapeutic approaches, the effects of PA rely on the treatment regimen. As mentioned in previous sections, in the case of exercise it is determined by the mode (aerobic vs. resistance exercise), intensity, frequency and volume [170].

In older adults, multicomponent exercise programs (especially those including aerobic and high velocity power-based resistance exercises) [217, 218] appears to yield

the greatest benefit in terms of overall physical fitness and health among older adults, by combining different stimulus that promote positive adaptations at different organic systems [219].

Despite unquestionable evidence regarding the positive effects of exercise on the processes that mediate accelerated ageing [199] and the fact that great efforts are being made to prompt implementation of exercise protocols in the daily practice [220], evidence regarding the appropriate design (mode, frequency, intensity and volume) of an exercise protocol tailored at maximizing its beneficial effects in specific populations is still scarce [221–223], as illustrated by the substantial proportion of non-responders to specific exercise regimens [224–226].

Additionally, the proportion of older adults that take part in structured physical exercise regrettably remains very low [227, 228], due to barriers such as poor perceived health and physical function limitations, presence of pain, lack of motivation, depression and cognitive impairment, fear of falling or injury, lack of accessible facilities, staffing shortages and funding constraints [229, 230].

7.2 Free-Living Physical Behaviors and Healthy Ageing Epidemiology

In this context, since it accounts for the major part of the PA in which older adults partake, the role of non-structured PA behaviors, usually imputable to daily living and leisure activities, might constitute a relevant differential factor determining healthy ageing. Observational evidence might assist to gain insight into the determinants (PA intensity, volume, frequency and mode) that maximize the PA benefits on different older adult phenotypes and thereby inform the design of optimally designed structured exercise programs and public health policies.

Interestingly, several observational studies have shown that higher levels of free-living PA are associated with lower rates of frailty [231], sarcopenia [232, 233], disability [234, 235], mortality [236, 237] and other adverse outcomes in older populations [238, 239], supporting the role of free-living PA behaviors as the determinants of healthy ageing.

PA and SB patterns, frailty and sarcopenia

As described before, lifestyles are considered a fundamental factor for health, function and well-being at older ages. Although multiple modifiable factors might influence physiological reserve trajectories along ageing, physical behaviors may play a paramount role in the modulation of the decline in physiological reserves [231] driving accelerated ageing.

PA and SB levels reduction have been suggested to counteract several of the mechanisms underlying the deranges of multiple physiological systems driving comorbidity (obesity, diabetes, CVD, cancer, etc…), sarcopenia and frailty development such as chronic inflammation, mitochondrial dysfunction, insulin resistance, neuroendocrine dysregulation and endothelial dysfunction [240].

Hence, physical behaviors are considered a milestone in frailty and sarcopenia development. Xue et al. hypothesized that declines in PA, besides a component of frailty syndrome, might trigger the development of the rest of the phenotype and likely exacerbate both frailty-related outcomes and the underlying dysregulation [241].

These assumptions have been confirmed by observational studies which have associated higher PA levels with lower frailty levels both cross-sectionally and longitudinally [242–244].

Fewer studies have explored the associations between SB and frailty, with some mixed results (positive [245–247] and non-significant associations [248]) observed. SB effects on frailty seems to be independent of PA [231], but in a recent study from the TSHA, the detrimental effect of SB on frailty was attenuated or even eliminated with increased in PA in the form of MVPA [249].

In the same way, since mechanisms underlying losses of MM and function induced by conditions such as increased adiposity, T2DM and other diseases are highly dependent on lifestyle behaviors, it is not rare to envision PA and SB together with nutrition habits as relevant determinants of sarcopenia modulation. Several studies have shown clear associations between higher PA levels and MM [233, 250, 251], muscle strength [104] and physical performance [252, 253] and sarcopenia rates in older adults [254]. More scarcely studied have been the associations between SB and musculoskeletal health, with existing research yielding mixed results [255, 256].

7.3 Free-living PA epidemiology pitfalls

Notwithstanding the extensive and consistent evidence linking higher levels of PA and better health in senior populations, there remains pitfalls in late-life PA epidemiology, mainly related to the way PA is assessed and categorized and how it is defined as an exposure.

Subjective vs. Objective PA assessment tools

The majority of previous studies exploring associations between PA and SB levels and health parameters have relied on self-report or questionnaires, which has raised concerns regarding potential bias related to failures in subjective recall of activities eliciting energy expenditure and social desirability, usually leading to free-living PA overreporting and SB underestimation [257] , especially among older adults, probably obscuring the associations between PA behaviors and the outcomes.

Relatively recent availability of wearable accelerometers assists to overcome self-reported or questionnaire-based PA estimation bias by offering the opportunity of objectively measuring PA in population-based studies [258]. Additionally, accelerometry allows for comprehensive characterization of physical behaviors in terms of intensity and duration, previously identified as important determinants of PA effects [259]. Briefly, these devices are attached to body segments and measure

accelerations resulting from motions, usually ambulation-related activities, converting them into activity counts. The amount and intensity of daily SB and PA are then obtained by classifying activity counts accumulated in a specific time interval (epoch) with a set of cut-points, matched to the categories in which PA intensity continuum has been classically split, based on multiples of the RMR (i.e. metabolic equivalents of tasks; METs): SB (<1.5 METs), LPA (1.5-2.99 METs) MPA (3-5.99 METs) and VPA (>6METs) ([167–169]. For practical analytical purposes and given the low engagement in VPA in certain populations such as older adults, MPA and VPA are usually merged in a MVPA intensity category. The amount of time spent in each of the intensity categories can be computed by summing all the minutes within a category, which allows to characterize PA and SB in terms of intensity, duration, frequency and volume.

Rationale beneath the use of age-specific cut-points in PA intensity characterization

Importantly, processing decisions regarding data collection (device placement and sampling frequency) and processing (non-wear time identification, epoch length, minimum duration of bouts within a intensity category, and cut-points for intensity classification) have been shown to have a substantial impact on PA estimation [260]. Among these, cut-point selection has the greatest impact on PA and SB time estimates [261]. These cut-point are usually computed and validated against the so-deemed gold-standard indirect calorimetry. Due to differences in the relative energy cost of activities and RMR, cut-points validated in specific groups might not be extrapolable to other age, sex, fitness, disease or level-of-impairment groups [262]. This is especially appealing among older adults, which present with a lower RMR than young counterparts (RMR=2.8 ml O2. Kg-1. min-1 vs RMR=3.5 $O2.Kg^{-1}.min^{-1}$) [263]. Hence, the relative energy cost associated with a given activity is greater among this age group [264]. For instance, the LPA-MVPA transition in a young adult (3 METs=10.5 ml O2. $Kg^{-1}.min^{-1}$) would imply an exertion of 3.75 METs in an average older adult.

Despite this important fact, most of previous works using accelerometry in older adults have categorize both PA and SB using cut-points validated in healthy, young adults populations [167, 265], leading to substantial misclassification of actual PA levels [266]. Recent research have derived accelerometry cut-points for older adults

[267–270]. Using age-standardized cut-points, Koster et al. demonstrated that the use of young-adults reference cut-points implied an overestimation of time spent in SB by almost 2 hours [267]. PA underestimation has also been shown to be induced using young-adults reference cut-points [271] (Figure 19).

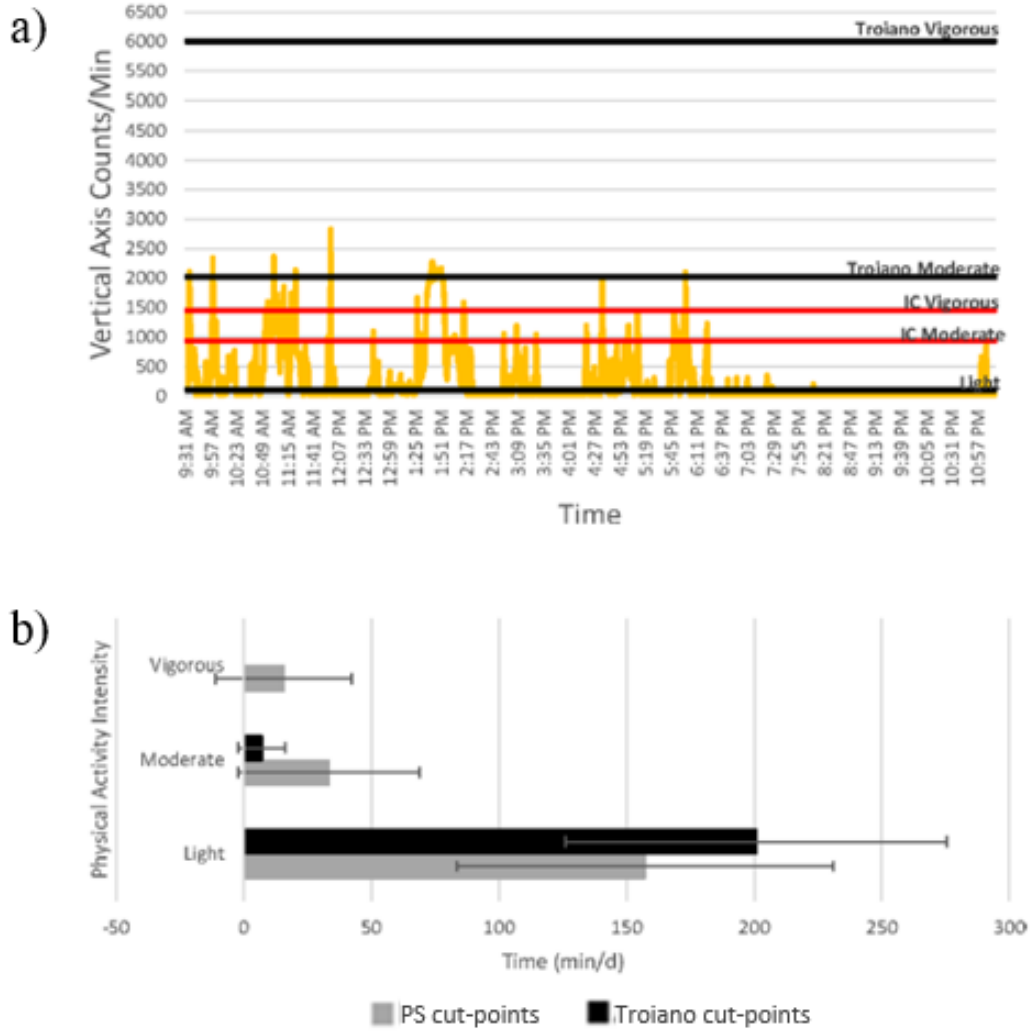


Figure 19. Accelerometer-derived minute by minute (a) and day-long (b) estimates of time in each PA intensity category using healthy young adults reference PA intensity cut-points vs. age- and disease (T2DM)-specific PA intensity cut-points.

PS= Population Specific; min/d= minutes per day.

From Welch et al., 2017 [271].

Altogether, these observations illustrate the necessity of using age-specific accelerometry cut-points when assessing PA in older adults to ensure accuracy in the observations and correct categorization of PA intensity, an outstanding crucial mediator of the effects of PA on health.

Intensity as a relevant determinant of the effect of PA on health

Similarly to exercise responses, free-living PA effects on health are highly dependent on parameters such as volume and intensity [170]. The role of MVPA as a determinant of health has been widely studied. Of special interest is the potential role of LPA in highly inactive older adults, for whom the more strenuous MVPA might be hardly bearable [272, 273]. LPA constitutes a distinct stimulus and is believed to trigger differential responses and adaptations compared to the widely previously explored MVPA [274–276], but unfortunately, there still exist limited evidence of its associations with relevant outcomes in older adults populations, such as frailty or sarcopenia.

Additionally, as stated before, SB has recently been suggested as a relevant health determinant. Despite SB, LPA and MVPA being presumably highly co-dependent, they have been scarcely considered jointly in late-life epidemiology until recently [277].

The described advancements in PA volume and intensity characterization (objective estimation tools and availability of age-specific cut-points) may lead to better understanding of the relationships between distinct types and patterns of PA and SB and health outcomes, which in turn should inform intervention goals, whose effectiveness should be subject of experimental research.

Classical vs. Isotemporal Substitution Regression Models

Second, a relevant issue when exploring the associations between PA and health outcomes arise from the truism fact that the time in which a subject can partake in PA is finite. Given that the effect of different PA behaviors are highly interdependent, the effects of a certain PA intensity (for example, LPA) are highly reliant not only on that specific PA intensity but also on the type of intensity it displaces (SB or MVPA) [278]. Associations between PA and SB and health outcomes in previous research have been explored by means of classical regression models that assess the strength of the

relationships by estimating the effect of increasing an amount of time in one PA behaviour or intensity category on a given outcome, accounting for confounding factors (such as time in other activities and other possible covariates). Nevertheless, these approaches do so by artificially "adding" time to the day, given that the rest of PA behaviors remain constant, overlooking two important facts: a) available hours in a day are fixed, finite, and may differ between subjects, and b) physical behaviors are co-dependent and hence, augments in one of them indispensably occur at expenses of reducing time in others. Accordingly, this approach might lead to unrealistic and distorted associations between PA behaviors and health-related outcomes and have little utility in informing PA public health endpoints.

To account for this limitation, substitution models, developed in the context of isocaloric nutrition epidemiology, have been recently incorporated into the PA epidemiology field [279, 280]. Isotemporal substitution regression models allow for the mathematical simulation of the effects of increasing a given amount of time engaged in certain activity or PA intensity by displacing an equal amount of time in others in the context of a finite period of time (day, week, etc.…) [281], mathematically mirroring real behavioral PA-related changes.

Single time-point estimation vs. Prospective changes in PA as the exposure variable

Most of available evidence exploring associations between PA and health outcomes in older adults use single time-point assessment of PA (primarily baseline PA levels) as the exposure variable [268, 282]. PA is a dynamic behaviour that undergo a steep decline during ageing (Figure 20) [283–285]. In turn, it is plausible that the study of different prospective patterns of change in PA behaviors may influence associations with health parameters compared to cross-sectional estimates [286]. Several studies have accounted for this shortcoming and used PA change as the exposure variable. Nevertheless, most of these works defined PA evolution groups of individuals based on clinical or empirical cut-points (based on percentiles, the adherence to PA recommendations, etc.…), qualitatively classifying subjects into PA-increasing, decreasing or maintaining categories [287].

PA prospective changes might not only differ in their direction, but also in their magnitude and rate of occurrence. In turn, categorical classifications of changes might

result coarse and limited for fully capturing the nature of PA evolution, undermining the possibility of drawing inferences, since they only accounts for qualitative changes.

Group-Based Trajectory Modelling

Novel data-driven methods (such as GBTM) have arisen as informative analytical methods that enable the identification of individuals within a population following similar patterns of change for a variable along follow-up from a similar baseline value [288, 289].

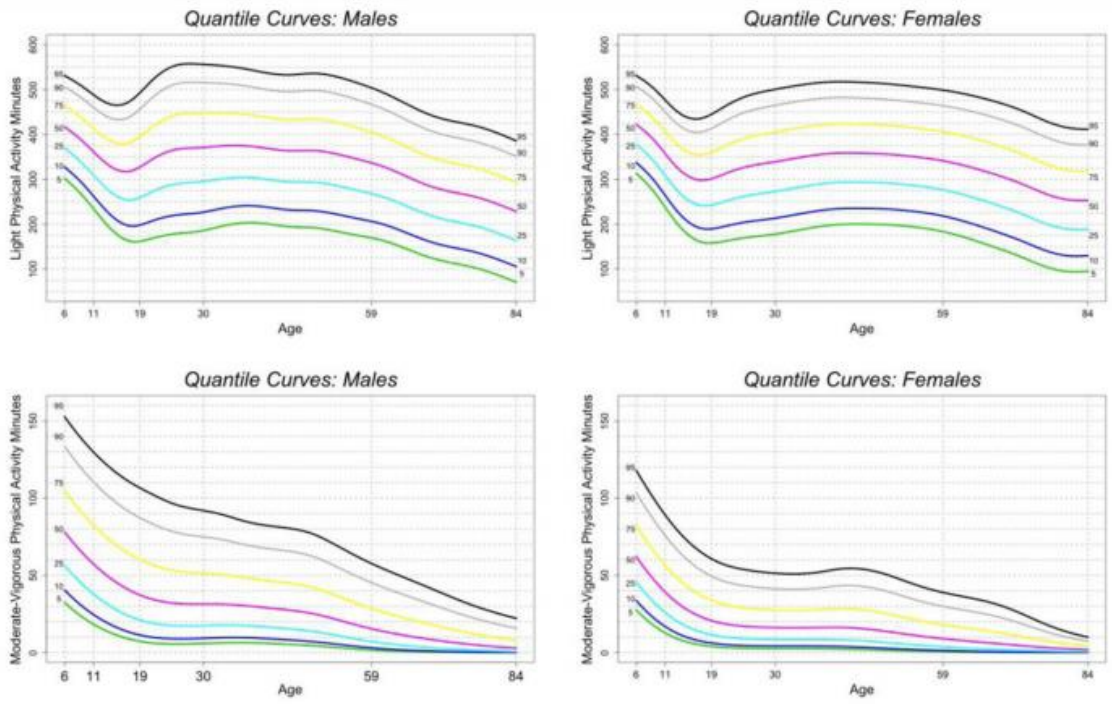


Figure 20. Percentile Curves LPA, and MVPA over the lifespan (6 years old to 84 years old) for males (left) and females (right).

Percentiles of LPA, and MVPA, from 5%-95%, are indicated using different colors (black = 95%, gray = 90%, yellow = 75%, purple = 50%, cyan = 25%, blue = 10%, green = 5%).

From Varma et al., 2018 [284]

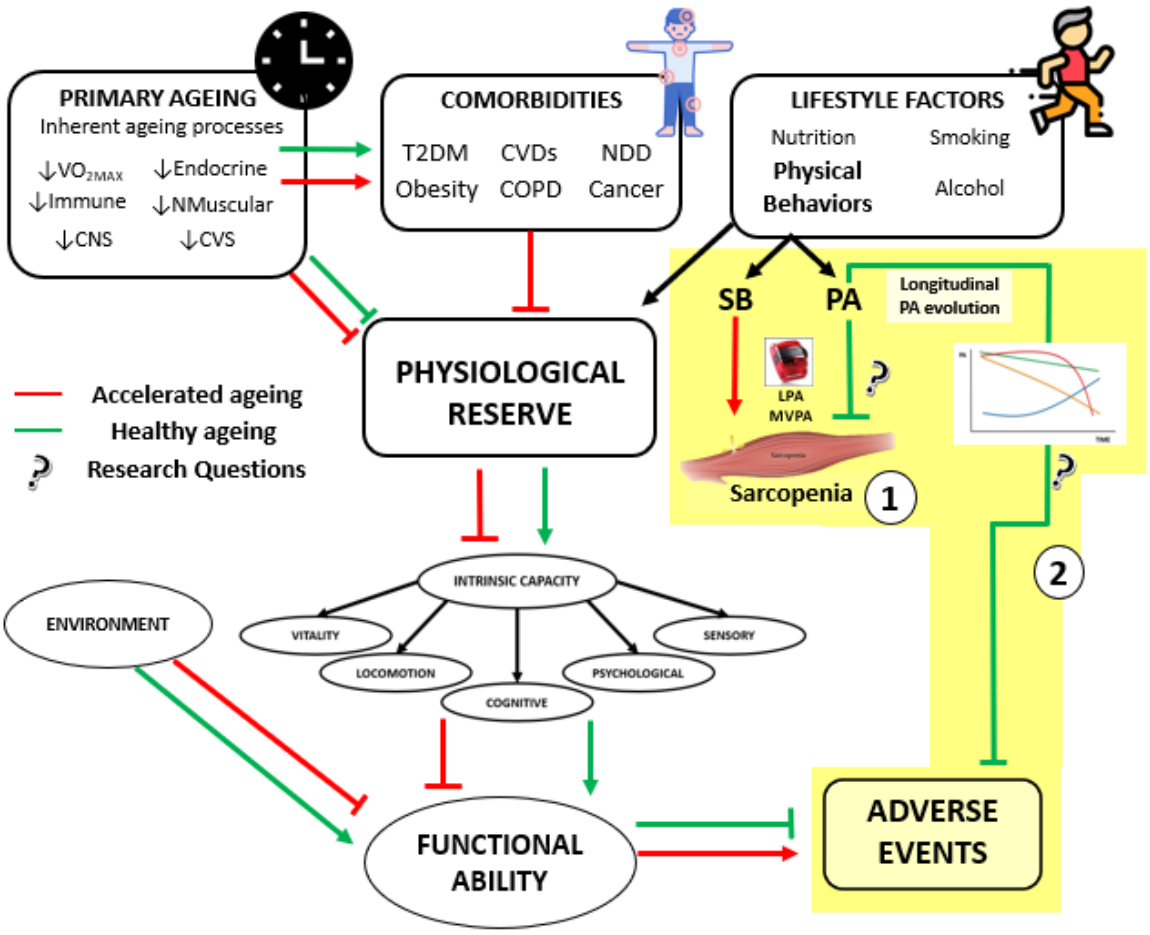
The incorporation of these methods into PA epidemiology contributes to refining the definition of PA evolution as an independent variable, overcoming the limitations of categorial definitions. Due to the recent incorporation of data-driven methods into PA epidemiology and the need for several PA estimations along time to identify PA trajectories within a study, there is a scarcity of evidence linking PA patterns of evolution and relevant outcomes at older ages [290].

Novel advancements in PA characterization (age-specific accelerometry cut-points, isotemporal substitution models, GBTM) allow to partly address and overcome some of previous late life PA epidemiology evidence limitations. In addition to the reshaping of outcome definitions (frailty, sarcopenia) [80, 291–293] and availability of data related to previously scarcely researched outcomes (intrinsic capacity, adverse events), altogether, they have opened new research questions amenable to be addressed in relation to PA, one of the most promising healthy ageing determinants.

8. Toledo Study of Healthy Ageing

To give response to some of these questions, data from the TSHA was used in the studies included in this thesis dissertation. TSHA is an ongoing population-based study primarily designed for gaining insight into frailty determinants in a Spanish older adult population. 2488 subjects <65 years were recruited through a two-stage random sampling of Toledo province census. The whole sample was comprised of two different cohorts: the survivors of a previous study (the Toledo Study), that were older than 77 years [294] and individuals recruited on purpose ranging 65-76 years of age. Baseline data collection (wave 1) took place between 2006 and 2009 and subsequent assessments (waves 2 and 3) were carried out between 2011-2013 and 2015-2017, respectively.

This thesis is intended to contribute to the evidence exploring the role of physical behaviors as healthy ageing determinants, overcoming some limitations of previous research (Figure 21).



1 Sedentary behaviour, physical activity, and sarcopenia among older adults in the TSHA: isotemporal substitution model

2 Physical activity trajectories, mortality, hospitalization and disability in the Toledo study of healthy aging

Figure 21. Conceptual map of research questions addressed by this thesis, within the healthy vs accelerated ageing scope.

SB=Sedentary Behavior; LPA=Light PA; MVPA: Moderate-to-vigorous PA; T2DM=Type 2 Diabetes Mellitus; COPD=Chronic Obstructive Pulmonary Disease; CNS=Central Nervous System; NMuscular= Neuromuscular; CVS=Cardiovascular System; CVDs=Cardiovascular Diseases; VO_{2MAX}=Maximum oxygen uptake. NDD= Neurodegenerative Diseases;

General Background References

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Aims and layouts of the thesis

Chapter 1

Study 1

Title:

Sedentary behaviour, physical activity, and sarcopenia among older adults in the TSHA: isotemporal substitution model

Research aim:

To explore the associations between reallocations of time engaged in different PA intensities and SB and sarcopenia and its determinants in an older adult cohort.

Hypothesis:

Increasing time spent in SB is inversely associated with MM, gait speed, and handgrip strength and with a higher sarcopenia prevalence whereas greater time spent in LPA and MVPA are associated with higher MM and handgrip strength, faster gait speed, and a lower sarcopenia prevalence. Furthermore, we hypothesize differential effects of increasing time spent in a specific intensity category depending on the intensity nature of the time displaced in the isotemporal substitution models.

Chapter 2

Study 2

Title:

Physical activity trajectories, mortality, hospitalization, and disability in the Toledo Study of Healthy Aging

Research aim:

To investigate the existence of different PA trajectories within the Toledo Study of Healthy Aging (TSHA) sample, a Spanish longitudinal population-based study, and to evaluate their associations with adverse outcomes (mortality, disability onset and worsening, and hospitalization).

Hypothesis:

Chronically active older adults and those maintaining PA over time will have a lower likelihood of experiencing adverse outcomes compared with consistently inactive

subjects or those reducing PA levels during follow-up and that increasing PA even at older ages promotes healthy aging, as characterized by reduced mortality, disability onset/worsening, and hospitalization rates.

Chapter 1:

Sedentary behaviour, physical activity, and sarcopenia among older adults in the TSHA: isotemporal substitution model

Published in the Journal of Cachexia, Sarcopenia and Muscle

Introduction

Sarcopenia is an age-associated syndrome which comprises loss of muscle mass plus a loss of muscle function (strength and power) and/or physical performance [1]. Sarcopenia is a core contributor to frailty, physical limitations and disability at advanced ages [2]. Although primary ageing contributes to sarcopenia, the rate of muscle mass and function loss appears to be modifiable relying upon lifestyle habits, mainly diet and physical activity (PA) [3]. Structured physical exercise, specifically strength training, has shown to be effective in sarcopenia prevention and reversal [3–5]. However, the associations between walking-related daily PA and sarcopenia remains to be elucidated. Moreover, the majority of the studies have assessed PA and SB by either self-report or using questionnaires, raising potential biases related to failures in subjective recall of past events associated with activities eliciting energy expenditure and social desirability, yielding daily-living PA overreporting and/or SB underestimation [6,7]. The use of accelerometers has allowed the objective daily living-related-PA estimation, trough motions derived from ambulation. Studies that aimed to improve the insight into the preventive role of objectively measured PA and health-related conditions at older ages have applied thresholds validated in healthy young adults for PA intensity categorization [8,9]. This could have led to inaccuracy and misclassification of actual PA behaviors, generating an overestimation of SB [10] and underestimation of actual PA [11], due to differences in energy cost of a given activity in older adults, when compared to younger cohorts [12]. It has already been demonstrated that using classical younger-adults cut-points when exploring older adults PA patterns can artificially decrease PA adherence rates among older adults [12,13], and that PA estimates vary notably depending upon the cut-points used [14]. Recently, isotemporal substitution models were introduced to the analysis of PA data. They take account for the finiteness of the time in which a subject can partake in activities in the different intensity categories of PA. Engaging in activities in a specific level of intensity, necessarily involves reducing time in another. Although previous research suggests a beneficial effect of PA on sarcopenia, the analytic methods overlooked the possibility of different effects elicited by the reallocation of time in a given intensity, relying upon the nature of the intensity it displaces. For example, an increase of time in LPA is likely to induce different effect on sarcopenia and its determinants whether it displaces SB or MVPA [15].

The aim of the current study is to assess the associations between objectively-measured PA levels and different sarcopenia-related variables (muscle mass (MM), gait speed (GS), and handgrip strength (HS)) and sarcopenia prevalence, by using accelerometers that can objectively assess ambulation-related PA and SB [16], and classifying the intensity of activities using age-specific cut-off points for older adults in order to classify time into different PA intensity bands and SB. Our hypothesis is that increasing time spent in SB is inversely associated with MM, GS, and HS, and with a higher sarcopenia prevalence whereas greater time spent in LPA and MVPA are associated with higher MM, HS and faster GS and a lower sarcopenia prevalence. Furthermore, we hypothesize differential effects of increasing time spent in a specific intensity category depending on the intensity nature of the time displaced in the isotemporal substitution model.

Methods

This work describes a cross-sectional analysis of the data from the Toledo Study of Healthy Ageing (TSHA), a Spanish longitudinal population-based study, designed for evaluating frailty determinants in individuals older than 65 years of age [17]. The study protocol was approved by the Clinical Research Ethics Committee of the Toledo Hospital, Spain. Participants signed informed consent forms prior to their inclusion in the cohort.

Measurements

Identification of sarcopenia

MM was measured using Dual X-ray Absorptiometry scan (DEXA) (Hologic, Serie Discovery QDR, Bedford, USA). All DEXA scan tests were analysed using the software Physician's Viewer, APEX System Software Version 3.1.2. (Bedford, USA). Whole-body scans were made in a supine position, in which the participants were scanned wearing light clothing with no metal and no shoes or jewellery. Body Mass Index-adjusted Appendicular Lean Mass (ALM/BMI) was used as marker. Low muscle strength in kilograms was assessed with HG measurement using a JAMAR hydraulic hand dynamometer (J. A. Preston Corporation, Clifton, NJ, USA); three attempts were performed in the dominant hand with the elbow extended while sitting and the best record was registered. Low physical performance was defined as a low

GS, computed by measuring the time (seconds) needed to cover a 3-meters path at a usual gait speed. The best of two measurements was recorded. Sarcopenia was identified using the FNIH diagnosis algorithm. According to this algorithm, sarcopenia is present in older adults with a gait speed <0.8 m/s in both genders [18] plus clinically relevant low MM and weakness. As stated by FNIH report, cut points for low MM and HG were an ALM/BMI below 0.789 in men and 0.512 in women, a HS lower than 26 kg for men and lower than 16 kg.

Physical Activity Assessment

Physical activity and SB were estimated using an ActiTrainer accelerometer (ActiGraph, LLC, Fort Walton Beach, FL, USA). All participants were asked to wear a device on the left hip during waking hours for 7 consecutive days and remove them during any bathing or swimming activities. The delivery and reception, as well as the explanation of use, were made in person by trained staff [19]. Data were processed using standard methods; Raw ActiTrainer data were converted to counts per minute (CPM), which reflects the acceleration and hence the intensity of PA. The higher the CPM, the higher intensity of movement measured. Data collected from movement were integrated into 60 s increment periods (epochs).

PA intensity is typically categorized based on metabolic equivalents (METs), being the unit of the resting metabolic rate (RMR). Each valid wearing-time minute was classified using CPM-based thresholds matched to the classical MET-based transitions between intensity categories: SB (<1.5 METs in lying or sitting position), LPA (1.5–2.99 METs), and MVPA (≥3 METs). In this study, cut-off points specific to the older adult population were applied to classify minutes per day spent in each intensity band based on the conversion of accelerometer vector magnitude (that integrates the three axes of movement) CPM to MET [10,20] (Table S1). Moderate intensity and vigorous intensity were merged together in an MVPA category.

Non-wear time was defined as periods of at least 60 consecutive minutes of zero counts, with allowance for 2 min of counts from the accelerometer-vertical axis between 0 and 100 [21] . The study included the results from participants with at least four valid days recorded. A valid day was defined as at least 480 min (8 h) of wearing without excessive counts (>20 000 vertical-axis counts). Minutes spent in each of these activity intensity bands were computed and used as the number of 1 hr intervals per

day in the analysis. Also, total activity counts (TAC) was taken as a composite measure of PA, independent of intensity, frequency, and patterns.

Statistical Analysis

All analyses were adjusted for age residuals obtained from the linear regression of chronological age on the three levels of PA [23]. T-Student test was used for between-groups comparison. Three different linear regression models were used for the associations between PA and SB and sarcopenia determinants: a) single PA-parameter model, b) a partition model and c) an isotemporal substitution. For the analysis of the association between PAL levels and sarcopenia we used logistic regression. All models adjusted for age residuals, sex, the presence of comorbidities (Charlson Index) and functional ability (Katz and Lawton Indexes). Statistical significance was set at $p<0.05$. All analyses were done in R 3.4.1 (R Core Team, Vienna, Austria).

Results

512 subjects with DEXA and valid accelerometer measures available were included in this analysis. Among them, 497 subjects had available data for sarcopenia diagnosis and 116 (23.3%) were classified as sarcopenic according to FNIH criteria. Mean age of the whole sample was 78.08 (5.71) years and 54.3% of subjects were women. Mean MM, GS and HS were 0.72 (0.1) kg/(kg. h^{-2}), 0.77 (0.26) m/s, 28.01 (7.65) kg for men and 0.51 (0.07), 0.69 (0.25) and 17.53 (5.02) for women, respectively. Participants spent 53.6% of the wearing time in SB, 38.6% in LPA and 7.8% in MVPA.

In the bivariate comparisons, subjects classified as sarcopenic showed differences with regard to those classified as non-sarcopenic in the variables related to sarcopenia and in those related to PA: longer time in SB ($p<0.01$) and shorter time in both LPA ($p<0.01$) and MVPA ($p<0.001$) (Table 1.1).

In the single PA-parameter model (Table 1.2, model A) each 1-hour/day increase in MVPA showed a significant association with greater values in MM, GS and HS, whereas each 1-hour/day increase in LPA did so with a higher HS; 1SD increase in TAC was significantly associated with MM, GS, HS. In the partition model (Table 1.2, model B), adding 1-hour/day of MVPA to the actual PA and SB patterns was associated with greater MM and GS, whereas adding 1-hour/day of LPA was associated with a reduction in GS (β=-0.022; 95% CI=-0.040, -0.004; p=0.017).

Table 1.1 Demographic characteristics stratified by the sarcopenia status according to FNIH

	Whole sample (n=512¥)	Non-Sarcopenic (n=381)	Sarcopenic (n=116)
Demographic data			
Age (mean/SD)	78.08 (5.71)	77.4 (5.83)	**80.21 (4.8)** ***
Women (n, %)	278 (54.3%)	218 (57.2%)	54 (46.6%)
Accelerometer-related data			
Total Wearing Time (h, mean/SD)	84.39 (16.03)	85.15 (15.86)	82.66 (15.82)
SB h/day, (mean/SD)	6.98 (1.62)	6.82 (1.57)	**7.53 (1.63)** ***
LPA h/day, (mean/SD)	5.01 (1.5)	5.15 (1.47)	**4.63 (1.53)** **
MVPA h/day, (mean/SD)	1.02 (0.78)	1.09 (0.79)	**0.76 (0.69)** ***
TAC/day (mean/SD)	409365.62 (180677.01)	428558.64 (179575.42)	**343391.76 (167575.43)** ***
Sarcopenia-related measures			
ALM/BMI (mean/SD)	0.6 (0.13)	0.62 (0.14)	**0.56 (0.12)** ***
Gait Speed (m/s, mean/SD)	0.73 (0.26)	0.79 (0.25)	**0.52 (0.14)** ***
Handgrip Strength (kg, mean/SD)	22.26 (8.21)	24.1 (8.04)	**16.45 (5.2)** ***
Conditions			
Type 2 Diabetes Mellitus (n, %)	117 (22.9%)	79 (20.7%)	**33 (28.4%)** *
Hypertension (n, %)	335 (65.4%)	242 (63.5%)	82 (70.7%)
Myocardial Infarction (n, %)	23 (4.5%)	18 (4.7%)	5 (4.3%)
Heart Failure (n, %)	11 (2.1%)	8 (2.1%)	3 (2.6%)
Charlson Index Score (mean, SD)	1.97 (1.75)	1.77 (1.54)	**2.64 (2.21)** ***
Functional Ability Measures			
ADL Dependency, Katz Index (n, %)	96 (18.8%)	64 (16.8%)	29 (25%)
IADL Dependency, Lawton Index (n, %)	278 (54.3%)	187 (49.1%)	**81 (69.8%)** ***

¥ =Missing data for at least one FNIH sarcopenia determinant in 15 subjects (2.9%). Statistically significant between group differences in boldface, when P-value <0.05: *p<0.05; **p<0.01; ***p<0.001; SD=Standard Deviation. SB=Sedentary Behaviour; LPA=Light Physical Activity; MVPA=Moderate-to-Vigorous Physical Activity; TAC=Total Activity Counts; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living

Table 1.2. Regression coefficients expressing associations between time engaged in different PA intensity bands and sarcopenia determinants

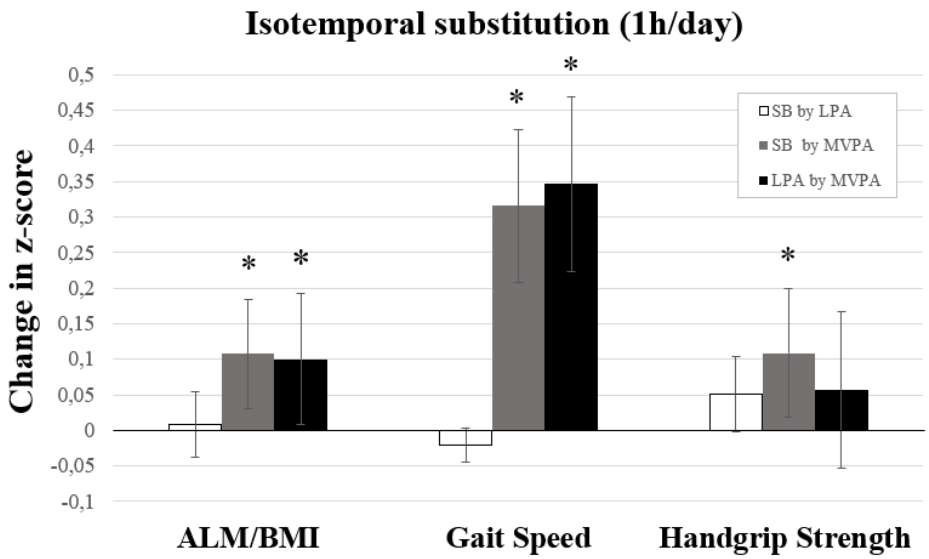
		Muscle Mass (ALM/BMI) β (95% CI)		**Gait Speed (m/s)** β (95% CI)		**Handgrip Strength (Kg)** β (95% CI)	
A) Single Parameter Model							
Each 1-hour increase (independent of the rest of PA categories)	**SB**	-0.003 (-0.007, 0.001)		-0.010 (-0.024, 0.003)		-0.467 (-0.807, -0.128)	
	LPA	0.003 (-0.002, 0.008)		-0.006 (-0.021, 0.009)		0.428* (0.051, 0.805)	
	MVPA	0.015** (0.005, 0.024)		0.070*** (0.043, 0.097)		0.933** (0.246, 1.620)	
B) Partition Model							
Adding 1 hour/day of	**SB**	0.001 (-0.005, 0.007)		-0.007 (-0.024, 0.011)		-0.243 (-0.687, 0.202)	
	LPA	0.001 (-0.005, 0.008)		-0.022* (-0.040, -0.004)		0.179 (-0.289, 0.647)	
	MVPA	0.0147** (0.004, 0.025)		0.076*** (0.046, 0.105)		0.645 (-0.108, 1.399)	
C) Isotemporal Substitution Model							
Replacing 1 hour/day of		**With LPA**	**With MVPA**	**With LPA**	**With MVPA**	**With LPA**	**With MVPA**
	SB	0.001 (-0.005, 0.007)	0.014** (0.004, 0.024)	-0.015 (-0.031, 0.001)	0.082*** (0.054, 0.11)	0.422 (-0.014, 0.857)	0.888* (0.145, 1.631)
	LPA		0.013* (0.001, 0.025)		0.090*** (0.057, 0.122)		0.466 (-0.437, 1.370)

A) Single PA-parameter model. examining the association of each intensity category (SB, LPA, and MVPA) individually (one regression model for each one) with the values of sarcopenia determinants. **B) Partition model**, displaying the association of a 1-hour increase in each activity, adjusted by time engaged in the rest of activity categories, with the values of sarcopenia determinants. **C) Isotemporal substitution model**, considering a finite timeframe, examining the effect replacing 1-hour engagement in each activity with 1 hour in a distinct intensity band on sarcopenia determinant values. All models are adjusted by age, sex, the presence of comorbidities (Charlson Index) and Functional Ability (Katz and Lawton Indexes). *P<0.05. **P<0.01; ***P<0.001. 95% CI = 95% confidence interval; β = beta coefficient. SB = Sedentary Behaviour; LPA = Light Physical Activity; MVPA = Moderate-to-Vigorous Physical Activity;

Isotemporal substitution showed that reallocating 1- hour/day of SB by MVPA was significantly associated with greater values in MM, GS and HS. When this volume of MVPA substituted the same volume of LPA, we found significant associations with greater MM and GS, but not with HS (p=0.312) (Table 1.2, model C and Figure 1.1).

In the partition model, we found deviations from linearity when including the second polynomial of time spent in MVPA for GS and HS. Figure 1.2 illustrate the associations between MVPA and GS and HS for an average study participant and suggest a saturation of the beneficial effect of increasing MVPA beyond 1.5 hours per day.

Figure 1.1. Isotemporal substitution of SB (1h min/day) LPA and MVPA on standardized sarcopenia determinant values.

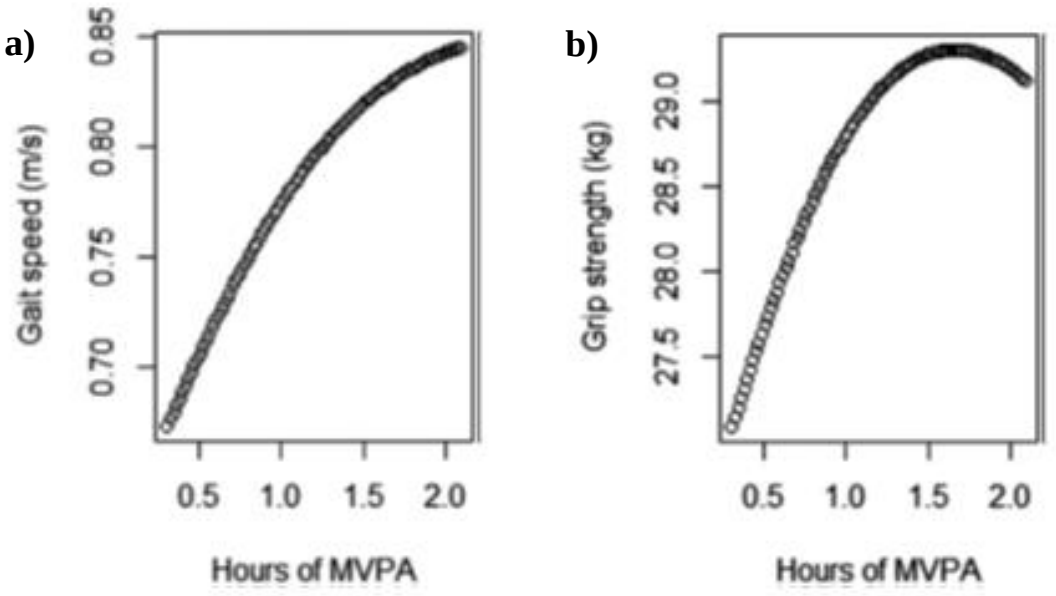


Values shown are β coefficient (95% CI). These represent the change in sarcopenia determinants (z-scores) when substituting 1h per day of SB with either LPA and MVPA and LPA with MVPA, mirroring increases in PAL. Created with Microsoft Excel 2019 (Redmond, Washington, USA). *p<0,05. SB = Sedentary Behaviour; LPA = Light Physical Activity; MVPA = Moderate-to-Vigorous Physical Activity.

Regarding the relationship between PA, SB and sarcopenia prevalence when we used the single parameter model (Table 1.3, model A) a 1-hour/day increase of SB showed an association with higher sarcopenia prevalence and 1-hour/day increase of MVPA with lower sarcopenia prevalence, respectively. Additionally, an increase of 1SD in TAC was significantly associated with lower rate of sarcopenia. In the partition model (Table 1.3,

model B), the inclusion of the time spent in other intensity categories suppressed the association between SB and higher sarcopenia risk, whereas MVPA-sarcopenia rate association remained significant (OR=0.555; 95% CI = 0.376, 0.799; p=0.002). In the isotemporal substitution model, the reallocation of SB only yielded a significant lower sarcopenia risk when it was substituted with MVPA (OR = 0.520; 95%CI = 0.361, 0.750; p<0.001). Likewise, a significant risk reduction was observed when displacing LPA with MVPA (OR = 0.557; 95% CI = 0.356, 0.871; p = 0.01). The effect of reducing SB at expenses of increasing LPA on sarcopenia risk pointed into the expected direction but did not reach statistical significance (OR=0.935; 95% CI = 0.766. 1.141; p=0.507).

Figure 1.2. Predicted values for gait speed (a) and handgrip strength (b) for an average male participant obtained from fitting a natural cubic spline with 5 degrees of freedom.



Created with R 3.4.1 (R Core Team, Vienna, Austria). MVPA, moderate-to-vigorous physical activity.

As behavioral changes entailing a 1 hour-increments in MVPA are rather unattainable in our population [24], we calculated the effects from the isotemporal substitution model of shorter periods of time at different PA intensities, emulating more feasible modifications in PAL patterns (Table 1.4).

Table 1.3. Associations between time engaged in different PA intensity bands and sarcopenia prevalence

A)	**Single Parameter Model; OR (95% CI)**			
Each 1-hour increase (independent of the rest of PA categories)	**SB**	**1.206 (1.039, 1.404) ***		
	LPA	0.872 (0.736, 1.030)		
	MVPA	**0.522 (0.367, 0.726) *****		
B)	**Partition Model; OR (95% CI)**			
Adding 1 hour of	**SB**	1.067 (0.879, 1.298)		
	LPA	0.998 (0.812, 1.224)		
	MVPA	**0.555 (0.376, 0.799) ****		
C)	**Isotemporal Substitution Model; OR (95% CI)**			
		With SB	**With LPA**	**With MVPA**
Replacing 1 hour of	**SB**		0.935 (0.766, 1.141)	**0.520 (0.361, 0.750) *****
	LPA	1.070 (0.876, 1.306)		**0.557 (0.356, 0.871) ***
	MVPA	**1.922 (1.333, 2.771) *****	**1.797 (1.149, 2.811) ***	

A) Single PA-parameter model. examining the association of each intensity category (SB, LPA, and MVPA) individually (one regression model for each one) with the values of sarcopenia. **B) Partition model**, displaying the association of a 1-hour increase in each activity, adjusted by time engaged in the rest of activity categories, with the values of sarcopenia. **C) Isotemporal substitution model**, considering a finite timeframe, examining the effect replacing 1-hour engagement in each activity with 1 hour in a distinct intensity band on sarcopenia. All models are adjusted by age, sex, the presence of comorbidities (Charlson Index) and Functional Ability (Katz and Lawton Indexes). *P<0.05. **P<0.01; ***P<0.001. 95% CI = 95% confidence interval; OR=odds ratio. SB=Sedentary Behaviour; LPA=Light Physical Activity; MVPA=Moderate-to-Vigorous Physical Activity;

Table 1.4. OR of the isotemporal substitution of different volumes of SB and LPA with MVPA.

		With MVPA
Replacing 15 min/day of	**SB**	0.85 (0.78, 0.93)
	LPA	0.86 (0.77, 0.97)
Replacing 30 min/day of	**SB**	0.72 (0.60, 0.87)
	LPA	0.75 (0.60, 0.93)
Replacing 45 min/day of	**SB**	0.61 (0.47, 0.81)
	LPA	0.64 (0.46, 0.90)
Replacing 1 hour/day of	**SB**	0.52 (0.36, 0.75)
	LPA	0.56 (0.36, 0.87)

All models are adjusted by age, sex, the presence of comorbidities (Charlson Index) and Functional Ability (Katz and Lawton Indexes). *P<0.05. **P<0.01; ***P<0.001. 95% CI = 95% confidence interval; OR=odds ratio. SB=Sedentary Behaviour; LPA=Light Physical Activity; MVPA=Moderate-to-Vigorous Physical Activity;

Discussion

This analysis of data from a community-based cohort of older people revealed that more time engaged in PA is congruently positively associated with better performance of sarcopenia-related measures (MM, GS and HS) and with a lower prevalence of sarcopenia, independent of the analytic method and adjustment for age, sex, the presence of comorbidities and the functional ability. Being engaged in MVPA accounts for the major part of this benefit, while engagement in LPA only shows a marginal effect on some of the components related to sarcopenia, without any significant effect on the sarcopenia prevalence.

These observations suggest the presence of an intensity threshold under which little benefit is obtained. In this regard, it must be underscored that even little increases in the levels of MVPA could be enough to significantly reduce the prevalence of sarcopenia, either replacing SB or LPA. Although our main analysis is focused in the substitution of 1-hour MVPA, of note is the reduction in sarcopenia prevalence associated with only a 15-minute/day increase in MVPA at expenses of reducing either SB or LPA (15% and

14%, respectively) (Table 4). This suggests that even little changes in PA patterns, embracing intensity and volume, might have positive effects on sarcopenia. Focusing on sarcopenia determinants, it appears to be that higher PA engagement improves performance across all sarcopenia determinants.

In accordance with our results, previous literature supports the positive association of greater PA levels and MM at old ages [23,25–29], but there have been some contradictory findings in this regard [30–32]. With respect to the relationship between PA and performance measures (GS and HS), existing evidence points towards a positive effect of greater levels of PA on performance and maintenance of physical function [26,30,33,34]. Our study reinforces these observations. Of note is the trajectory of the association between the amount of PA and HS and GS with increasing MVPA, displaying a probable ceiling effect with values greater than 1,5 hours/day of MVPA eliciting modest improvements in HS and GS (Figures 1 and 2). The partition model showed an absence of association between MVPA and HG in our sample. This might be due to the activity registered by the accelerometer (mainly ambulation) having little effect on upper limbs strength. In this sense, it could be interesting to study the relationship between accelerometer-derived PA and lower limb strength. Although SB was not significantly associated with any sarcopenia determinants, the direction of the effect was in the expected direction of SB in producing worse performance across all of them (MM [35], HS [23,30], and GS [25]).

Our results support the accumulating evidence of an inverse association between PA and sarcopenia prevalence, reinforcing the unique role of MVPA on sarcopenia reduction. LPA seems to be insufficient to reduce sarcopenia rates. Mijnarends et al. [26] and Tyrovolas et al. [31] showed a protective effect of greater accumulation of self-reported PA on sarcopenia. In contrast, in the study by Hai et al. in community-dwelling Chinese people aged 60 years and older (mean age 68 years old) no association was found using questionnaires-based PA assessment [36].

Controversy might be caused by differential PA assessment tools and sarcopenia definitions. In fact, the three studies previously cited used self-reported activity, showing striking differences both in the amount and intensity of PA and their association to sarcopenia. They also used different sarcopenia definitions (European Working Group on Sarcopenia in Older People definition, a body weight-adjusted ASM of -2SD with respect to a healthy-young cohort in body weight-adjusted ASM, Asian

Working Group for Sarcopenia criteria). But even if a definition of sarcopenia can be agreed up, different sarcopenia assessment tools for MM (DEXA, BIA analysis, anthropometry-based measures), strength (HS, lower extremity strength) and gait performance (GS, up and go test), and the absence of population-specific cut-points may lead to discrepancies in the conclusions. Importantly, it should be recognized that the sarcopenia criteria employed may arguably condition the associations. Recent research suggests the need for MM, GS and HS cut-points harmonization following the characteristics of the population [37–39].

The role of LPA for MM and function preservation remains controversial. Some previous work has showed an association between light activity (assessed objectively) and HS in men but not women [33]. The link between LPA and HS might be explained by the effects of myokines released by the muscle after muscle contraction [40,41], among other potential explanations [42]. In our study, such LPA-HS association was only significant in the single parameter approach and faded both in the partition and isotemporal substitution models.

Parameters such as mode, intensity, duration and volume of and the type of muscle contraction (i.e. aerobic, resistance, concentric, eccentric…) determine the induced homeostasis disruption PA generates, and consequently the adaptations obtained through muscle activation. Aerobic and resistance exercise represent extremes on a continuum and elicit markedly different metabolic and structural responses. Whereas aerobic PA (i.e. low-intensity repetitive contractions) mainly induces adaptations that lead to improved oxygen uptake, transportation and utilization, resistance exercise (i.e. low frequency, high resistance demand) is believed to play a role in proteostasis and neuromuscular function [43]. The beneficial effect of high intensity, explosive resistance training on muscle mass and output, and physical function, maintenance at older ages is clear [44–46]. The LPA captured in our study might be classified as aerobic, having little effect on these outcomes. Conversely, we suggest that activities classified as MVPA (energy expenditure ≥ 3 MET) according to the Compendium of Physical Activities by Ainsworth and colleagues [47] and correcting MET values to the mean age of our populations [48], constitute a sufficient stimulus to trigger responses that stimulates MM, strength and physical function. Walking for pleasure (4.375 MET), Tai Chi (5 MET) and recreational swimming (6 MET) are among that type of activities.

Considering sarcopenia as one of the biologic substrates of frailty, our group showed similar results when exploring the associations between PA, SB and frailty status in the same cohort [49].

Strengths and limitations

The present study has several strengths. Consequently, objective measures are assumed to solve limitations of self-reported estimation. However, there are important issues to consider when classifying PA behaviors through accelerometry. As stated in the methods section, Actigraph monitors typically categorize activities intensity classifying each valid wearing-time minute into one of the classical intensity bands using count-based (CPM) thresholds, usually those defined in calibration studies among healthy young cohorts [9,52]. With a lower RMR, the relative energy expenditure (MET value) associated with these CPM thresholds, would be greater in older adults in relation to younger counterparts. For instance, the LPA-MVPA transition (3 METs) in a young person (= 10.5 ml O2. Kg^{-1} . Min^{-1} , assuming a RMR of 3.5 ml O2. Kg^{-1} . Min^{-1}) would imply an exertion of 3.75 METs in an older adult (with a RMR = 2.8 ml O2. Kg^{-1}) [53,54]. Despite this limitation, most previous studies objectively measuring PA and SB patterns considered thresholds validated in healthy young adults, systematically assuming similar energy costs across different age-groups. In an attempt to solve these problems, Koster et al., calculated a threshold for the SB-LPA transition against a measure deemed a gold-standard (ActivPAL accelerometers) among elders. Additionally, they demonstrated an overestimation of time spent in SB by almost 2 hours per day among older adults when using the classical cut-points in the The Aging Research Evaluating Accelerometry (AREA) study [10]. Similarly, Barnett et al., determined an age-specific LPA-MVPA transition threshold in a population of older adults (mean age 70.2), in a calibration study against indirect calorimetry [20]. The use of these age-specific thresholds in our study, partially overcomes the previously described shortcomings. Nevertheless, and very importantly, we acknowledge there could still be bias because of variability in several factors that might influence energy cost, such as sex, fitness, body weight, disability, movement impairment and illnesses [55]. In addition, subjects in our study wore a triaxial accelerometer (ActiTrainer). Triaxial accelerometer data capture motions in all three axes resulting from more complex movements [56,57] and has shown

better performance in terms of intensity prediction in laboratory-based validation studies in relation to uniaxial accelerometry [55].

Second, as the time in a day in which a person can partake in PA is finite, engaging in one intensity category inevitably means reducing the time engaged in another. The benefits of different PA intensities depend not only on the specific PA intensity but also on the type of intensity it displaces. This fact has been systematically overlooked in previous research using different statistical models. For example, the single PA-parameter model separately examines the associations between an amount of time in each intensity category and its effect on a dependent variable, disregarding the amounts of time spent in other intensities. The partition model accounts for the role of the amount of time in distinct intensity categories but analyses the effect of adding time in the intended PA intensity category to the actual distribution of time in all the intensity bands, instead of accounting for the limited time available. Thus, it is not a realistic approach. Conversely, the use isotemporal substitution might mirror feasible changes in PA patterns by accounting for the finiteness of the time in which a subject can engage in different-intensity activities in a given period and captures disparate effects of lifestyle changes in one dominion that affects other behaviors [15]. This fact reinforces the external validity of our observations and its suitability for formulating public health recommendations.

Finally, in contrast to the majority of the studies published to date assessing the relationships between PA and sarcopenia, we have used DEXA scans to assess MM, a more reliable and accurate method than the estimations of MM derived from anthropometric measures or bioelectrical impedance analysis [58] Moreover, we used an internationally recognized sarcopenia definition based on MM, HS and GS (FNIH criteria).

Nevertheless, our work presents some limitations. The cross-sectional nature of this study hampers exploration of directionality between PA and SB and sarcopenia and its determinants and reverse causality could not be ascertained: Although we hypothesized that higher PA and lower SB would lead to lower sarcopenia prevalence; lower MM, HS, and GS might also diminish PA and increase SB. In addition, although ActiGraph accelerometers can accurately estimate PA derived from walking, the most popular activity among older people [14], they are unable to capture non-ambulatory PA like resistance training swimming or cycling; activities that have shown a strong association

with muscle mass and function [59,60]. In any case, this kind of activities are rather unusual in our population. Furthermore, we could not capture vigorous intensity (corresponding to energy expenditures over 6 METs) because of the absence of cut-points for this the transition between moderate and vigorous PA intensity categories. Notwithstanding, a very low proportion of older adults regularly reaches vigorous intensities.

Current PA-recommendations suggest a minimum MVPA bout-duration of 10 minutes to gain health benefits [61], but acknowledge the inconclusively nature of previous evidence [62] and the possibility that shorter periods might be valid in sedentary individuals, as those in our cohort [63]. Taking this into account, in our analysis the SB, LPA and MVPA variables were computed summing all the minutes within each category, irrespective of the duration of the bout in which they were contained. Hence, we could not evaluate how differences in PA-bout length contribute to overall PA effect on sarcopenia and its determinants. Considering our observations (as few as 15-miutes/day of MVPA is good enough to produce some benefit on sarcopenia), this finding does not look to support the need of bouts of a minimum of 10 minutes to get benefits in terms of MM and muscle function.

Finally, we recognize that although isotemporal substitution might be a more realistic approach, it is not more than a mathematical method for replacing time in one intensity with another and in no case could substitute experimental evidence. Research is guaranteed to explore the potential effects of reducing SB and increasing LPA and MVPA on MM and function through properly designed randomized clinical trials.

To our knowledge, this is the first study in exploring the associations of sarcopenia and objectively estimated PA classified using age-specific thresholds. In addition, we explored the associations through different analytic methods, among which the isotemporal substitution, that yields more directly interpretable and meaningful results to public health evidence. In conclusion, our findings, stemming from a study with an accurate assessment of both PA and the presence of sarcopenia, strongly support the hypothesis of the association between higher PA levels, in the form of increments in MVPA and SB reduction, lower sarcopenia rates and better performance across sarcopenia determinants in older people. LPA appears to have marginal effects on sarcopenia determinants and but any on the risk since the substitution of SB by LPA is not significantly associated.

Considering the growing older population in Western countries and the functional and economic burden of sarcopenia [64], improving insight into its aetiology, contributing factors and possible interventions should be a priority for researchers. Appropriately designed longitudinal studies assessing the causal relationships and which of the components of the PA are involved in that association with sarcopenia are needed to design targeted interventions in the older population at risk or suffering sarcopenia.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical issues

The study protocol was approved by the Clinical Research Ethics Committee of the Toledo Hospital, Spain. This work was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments. Participants signed informed consent forms prior to their inclusion in the cohort. The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle [65].

Supporting Information

Table 1.S1. Older adults-specific cut-off points for classifying PA behaviour.

Intensity Category	MET equivalence	VM output cut-points (CPM)
SB	MET < 1.5 (sitting or lying)	CPM <174
LPA	1.5 ≤ MET< 3	174 ≤ CPM < 1924
MVPA	MET ≥ 3	CPM ≥ 1924

SB = Sedentary Behaviour; LPA = Light Physical Activity; MVPA = Moderate-to-Vigorous Physical Activity; MET = Metabolic Equivalent; VM = Vector Magnitude; CPM = Counts per minute.
1 MET= 3.5 $mlO_2.Kg^{-1}.min^{-1}$.

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Chapter 2:

Physical activity trajectories, mortality, hospitalization and disability in the Toledo study of healthy aging

Published in the Journal of Cachexia, Sarcopenia and Muscle

Introduction

Lifelong physical activity (PA) promotes a wide range of health benefits and has long been recognized as an important protective factor for chronic diseases [1–6]. These beneficial effects consistently translate into lower mortality rates in both men and women [7–12]

The salutary effects of PA might extend to late life, as it is known to delay the onset of disability [13,14], and to increase lifespan [7,8,15,16]. Furthermore, PA might be negatively associated with other adverse outcomes such as hospitalization, thereby reducing healthcare expenditure [17,18]. Remarkably, at advanced ages, PA levels might surpass other cardiovascular or sociodemographic risk factors that are classically associated with adverse outcomes in younger cohorts [19,20].

The World Health Organization (WHO) defines "Healthy Aging" as the process of developing and maintaining the functional ability that enables wellbeing in older age [21]. Accordingly, PA is suggested to be an important contributor to healthy aging through the maintenance and enhancement of intrinsic capacity – mental and especially physical capacities [22]. A common methodological limitation in exploring the association between PA and adverse outcomes in older populations is the use of a single time-point assessment of PA (primarily the baseline PA levels) as the exposure variable [23–29], which does not account for the dynamic nature of PA behaviors [30]. It is plausible that prospective trajectories (patterns) of PA levels along time in late life may influence adverse outcomes distinctly as compared with cross-sectional estimates [31,32], a hypothesis that remains untested to our knowledge.

Some studies have recently addressed this shortcoming and used prospective PA level evolution as the exposure variable. Most of these studies employed categorical analyses with clinical or empirical cut-points for identifying groups with different PA progression patterns [9,33–35].

Data-driven approaches such as Group-Based Trajectory Modelling (GBTM) have emerged as an informative and interesting analytical method that allows grouping of subjects presenting with similar baseline values and longitudinal patterns of change, in terms of their direction and magnitude, along follow-up for a given variable within a population [36,37]. Using this methodology, some studies have shown the existence of

different PA level trajectories in older adult cohorts [30,38], and one study explored their associations with mortality in a sample of older men [39].

The main aim of this study is to investigate the existence of different PA trajectories within the Toledo Study of Healthy Aging (TSHA) sample, a Spanish longitudinal population-based study, and to evaluate their associations with adverse outcomes (mortality, disability onset and worsening, and hospitalization). Our hypothesis is that chronically active subjects and those maintaining PA over time will have a lower likelihood of experiencing adverse outcomes compared with consistently inactive subjects or those reducing PA levels during follow-up, and that increasing PA even at older ages promotes healthy aging, as characterized by reduced mortality, disability onset/worsening and hospitalization rates.

Methods

Study Design and Participants

Data were taken from the TSHA study, the details of which have been reported elsewhere [40]. Briefly, this is a population-based prospective cohort study examining the determinants and consequences of frailty in institutionalized and community-dwelling individuals older than 65 years living in the province of Toledo (Spain). For the present analysis, we used data from those subjects with non-missing PA scores from the first (2006–2009) and second (2011–2013) TSHA waves, and available mortality and hospitalization information at the censoring time and functional ability from the third wave (2015–2017).

The Clinical Research Ethics Committee of Toledo Hospital, Spain, approved the study protocol and participants signed an informed consent prior to their inclusion in the study.

Measures

Physical Activity Scale for the Elderly

PA levels were estimated using the Physical Activity Scale for the Elderly (PASE). This questionnaire was designed to assess PA in epidemiologic studies of older people over a 1-week period. It ascertains the duration, intensity and frequency of several activities and consists of 10 items that focus on three domains: leisure (5 components), household (4), and work (1) activities. Participation in leisurely activities is recorded by frequency

(e.g., never, seldom, sometimes, and often) and duration (e.g., less than an hour, 2–4 hours, or >4 hours); paid or unpaid work is recorded by total hours of work per week; and household activities and care for others are recorded with yes or no answers. Total PASE score is calculated by multiplying activity participation (yes/no) or the amount of time spent on each activity (hours/week) by empirically derived item weights, which are summed [41]. In the present study, PASE was administered by interview, because this modality has proven superior reliability than self-administration [42]. We used PASE scores from wave 1 and wave 2 to construct the trajectories.

Mortality

Vital status was ascertained through the information provided by the Spanish National Death Index (Ministry of Health and Social Services). Participants were followed-up to death or June 2018, whichever came first. The average follow-up for mortality was 5.92 years (range 0.01–7.5 years).

Hospitalization

Hospitalization was ascertained by review of the Toledo Hospital Complex records and was defined as the occurrence of a first admission to the hospital during follow-up, up to December 2016. Median follow-up for hospitalization was 4.08 years (range 0.01–5.24 years).

Disability and worsening disability

The Katz Index was used to assess the functional ability in basic activities of daily living (BADL) [43]. Incident disability was defined as the transition from a score of 6 to 5 or less in the Katz Index at follow-up. Worsening disability at follow-up was defined as the advent of a new difficulty in the Katz Index at follow-up in those participants with a prevalent disability at baseline. Median follow-up for disability onset/worsening was 2.99 years (range 2–5.4 years).

Covariates

We selected covariates based on the literature and the biological plausibility for confounding the main associations of interest. Age, sex, education (non-educated, non-finished primary education, finished primary education/superior) and smoking status (yes/past/never) were registered during study visits. Presence of comorbidities was ascertained by self-report and by checking the medical history to compute the Charlson Index score [44]. Body mass index (BMI) was computed using the standard formula

(body mass × height^{-2}). Cognitive status was assessed by using the Mini-Mental State Examination (MMSE) [45]. The number of prescription and non-prescription drugs within the Anatomical Therapeutic Chemical Classification System taken by the participant was calculated. Polypharmacy was defined as the intake of ≥5 drugs/day [46]. All covariates were measured at wave 2 assessment.

Statistical Analysis

Descriptive analysis

All analyses were performed using the R statistical environment for Windows. Mean (standard deviation) and frequency (percentage) are provided for continuous and categorical variables, respectively. Descriptive variables were compared between included and excluded subjects and between trajectories with an independent Student´s t-test or analysis of variance for continuous variables, and the Chi-square test for categorical variables.

Trajectory modelling

We used a GBTM approach to identify PA trajectories within our population. This type of finite mixture model provides an empirical means of identifying clusters of individuals defined by their developmental courses for a variable over time (trajectories) within a population. Briefly, this method assumes that the general population is composed of literally distinct subpopulations that are not identifiable based on measured characteristics ex-ante. In GBTM, each group is conceptually thought of a collection of individuals who follow approximately the same developmental trajectory, where population variability is captured by differences across groups in the shape and direction of their trajectories [37]. First, the best model among those with different number of classes (trajectories) were identified by using Bayesian Information Criterion (BIC). BIC is an index used in Bayesian statistics to choose between two or more alternative models, given the data. In our study, two-times the change in the BIC between model greater than 10 was used as indicative of better fit in order to compare more complex – with a greater number of trajectories – versus more parsimonious – with a lower number of trajectories – models [47]. Each subject was assigned to a trajectory depending upon his individual values (baseline PASE score and progression patterns). Secondly, average posterior probabilities of membership were computed for each group to estimate the reliability of the classification. Individual posterior probability of

membership for a subject represents his probability of belonging to the group he is assigned to by previous grouping based on his individual features. Trajectory average posterior probability of membership represents its internal consistency, with higher values indicating better classification quality [37]. We finally checked the number of subjects within each trajectory to ensure adequate sample size for assessing the subsequent risk of adverse outcomes.

Associations between PA trajectories and adverse events

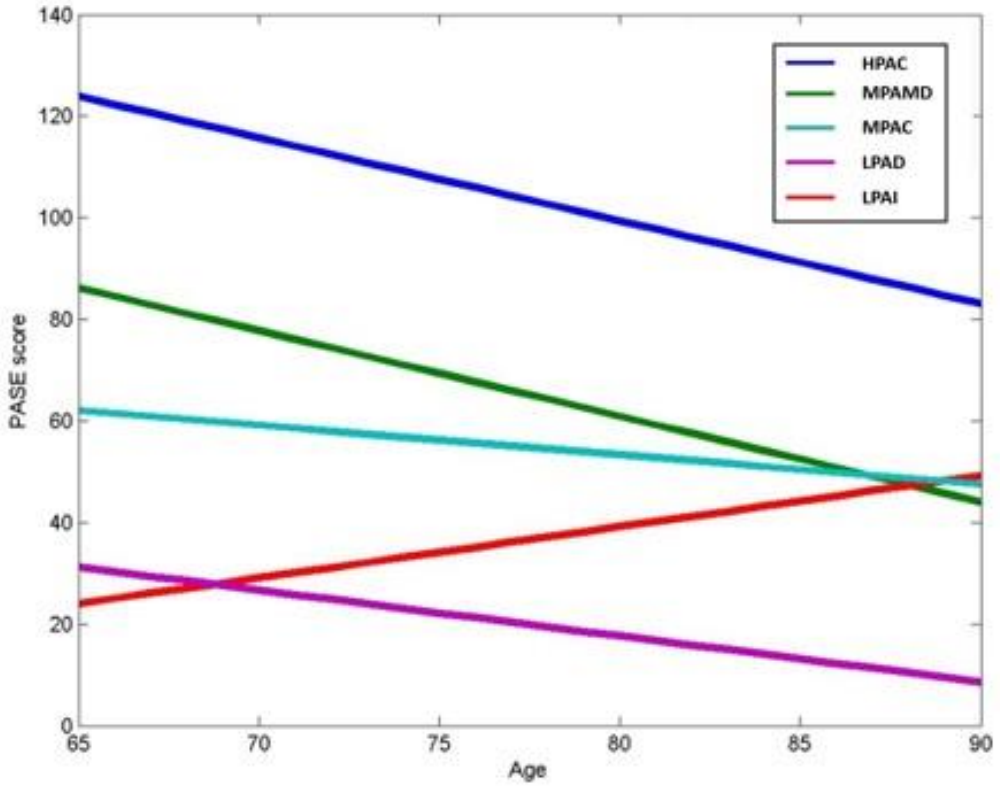
Cox proportional hazards regression was used to investigate the associations between the GBTM-derived PA trajectories and the adverse outcomes for which we had the date of occurrence (mortality and hospitalization). Logistic regression analysis was used for disability onset and disability worsening (that were registered during study visits). Multivariate trajectory models were adjusted for age and sex (Model 1), plus Charlson Index (Model 2), and additionally for baseline Katz Index, level of education, polypharmacy, cognitive status (MMSE) and smoking status (Model 3).

Results

Baseline characteristics of the subjects within each trajectory are presented in Table 2.1. 1679 subjects (67.48% of TSHA whole sample; mean age = 74.26 ± 5.32; 41% men) had data available for the purpose of this analysis. Not-included subjects were significantly older, had lower scores for the MMSE, Charlson Index, and Katz Index (Supplementary Table 1).

GBTM yielded 5 PA trajectories as the best model: 1) High PA-Consistent (n=566; 33.7%), 2) Moderate PA-Mildly Decreasing (n=392; 23.3%), 3) Low PA-Increasing (n=237; 14.1%), 4) Moderate PA-Consistent (n=191; 11.7%), 5) and Low PA-Decreasing (n=293, 17.5%) (Figure 2.1). The mean posterior probability of membership, an index of quality classification used in GBTM like ours, was 0.79 ± 0.65, indicating an acceptable classification of the subjects within each PA trajectory.

Figure 2.1. PA Trajectories by age. N = 1679; PA groups based on self-reported PA via PASE scores



HPAC= High Physical Activity-Consistent; MPAMD: Moderate Physical Activity-Mildly Decreasing; MPAC: Moderate Physical Activity-Consistent; LPAD: Low Physical Activity-Decreasing; LPAI: Low Physical Activity-Increasing; PASE: Physical Activity Scale for the Elderly.

Table 2.1. Baseline Characteristics of the Sample

	HPAC n=566; 33.7%	**MPAD n=392; 23.3 %**	**LPAI n=191; 11.7%**	**MPAC n=293, 17.5%**	**LPAD n=237; 14.1%**	**Whole sample n=1679**	**Between groups differences (p-value)**
Age, mean (SD)	72.37 (4.41)	73.76 (4.83)	74.94 (5.06)	72.42 (4.41)	78.9 (5.56)	74.94 (5.06)	<0.001
Men, No. (%)	287 (50.71)	156 (39.79)	107 (56.02)	57 (19.45)	94 (39.66)	701 (41.74)	<0.001
BMI, mean (SD), $kg.m^{-2}$	28.9 (4.1)	29.3 (4.5)	30.1 (5.6)	29.5 (5.1)	29.9 (5.2)	29.4 (4.7)	<0.05
Current smoker, No. (%)	181 (31.98)	109 (27.81)	77 (40.31)	45 (15.36)	60 (25.32)	472 (28.11)	<0.001
BADL disability, No. (%)	37 (6.54)	45 (11.48)	49 (26.06)	42 (14.33)	94 (39.66)	267 (15.9)	<0.001
MMSE score, mean (SD)	25.47 (3.8)	24.02 (4.37)	22.56 (5.91)	23.5 (3.96)	20.34 (7.14)	23.8 (5.07)	<0.001
Charlson Index, mean (SD)	0.82 (1.33)	1.02 (1.45)	1.37 (1.71)	1.02 (1.56)	1.45 (1.9)	1.05 (1.55)	<0.001
Depression (GDS ≥ 5), No. (%)	48 (9.76)	45 (12.71)	47 (27.01)	52 (19.11)	59 (29.21)	251 (16.8)	<0.001
PASE score, mean (SD)	115.61 (49.15)	80.65 (11.32)	21.53 (11.88)	53.27 (3.82)	28.74 (20.81)	73.6 (46.85)	<0.001
Δ in PASE, mean (SD)	-3.26 (18.24)	-5.64 (7.22)	5.92 (6.27)	0.87 (5.97)	-4.69 (3.74)	-2.25 (12.24)	<0.001

Data are presented as mean (SD) or No. (%). Significant differences between men and women group were analyzed by Student's t-test or Chi^2 test.
HPAC: High PA-Consistent; MPAMD: Moderate PA-Mildly Decreasing; MPAC: Moderate PA-Consistent; LPAD: Low PA-Decreasing; LPAI: Low-PA Increasing; BMI: Body Mass Index; BADL: Basic Activities of Daily Living; MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale; PASE: Physical Activity Scale for the Elderly. Δ: Change.

In the Cox regression model, subjects in Low PA-Decreasing trajectory group had a higher mortality risk than peers in the reference group (High PA-Consistent) across all models (hazard ratio [HR] = 1.68; 95% confidence interval [CI] = 1.21–2.31 in the fully-adjusted model [model 3] ; Table 2.2, Figure 2.2).

Subjects in the Low PA-Increasing (HR = 1.24; 95%CI = 1.004–1.54, [model 3]) and Low PA-Decreasing (HR = 1.25; 95%CI = 1.01–1.55, [model 3]) trajectory groups showed a significant increase in the likelihood of hospitalization when compared to subjects in the High PA-Consistent group, across all models (Table 2.2, Figure 2.2).

In the "raw" model, logistic regression analysis showed a greater risk of progressing into incident disability across all the trajectories as compared with the reference High PA-Consistent group. These associations weakened as covariates were included in the models but remained significant for Low PA-Decreasing trajectory group (OR = 3.14; 95%CI = 1.59–6.19, model 3).

Low-PA Decreasing trajectory group showed significant increased risk of worsening disability when compared with subjects classified into the High PA-Consistent group (OR = 2.16; 95%CI = 1.35–3.45, model 3; Table 2.2, Figure 2.2).

We additionally sought to compare groups with similar baseline PA (similar starting risk) but divergent PA trends along time (Low PA-Increasing vs. Low PA-Decreasing trajectory groups). Subjects in the Low PA-Decreasing trajectory group were more likely to be women (56 vs. 39%; p=0.001), older (78.9 vs. 74.4 years; p<0.0001), and to have difficulties in one or more BADLs at baseline (39.7% vs. 25.6%; p=0.0032) (Data not shown).

Taking the Low PA-Decreasing as the reference, subjects in the Low PA-Increasing trajectory showed a significantly lower risk for disability onset (OR = 0.39; 95%CI = 0.19–0.82; Figure 2.3) in the fully adjusted model. We failed to find differences between these two trajectories in terms of mortality, hospitalization or worsening disability risks.

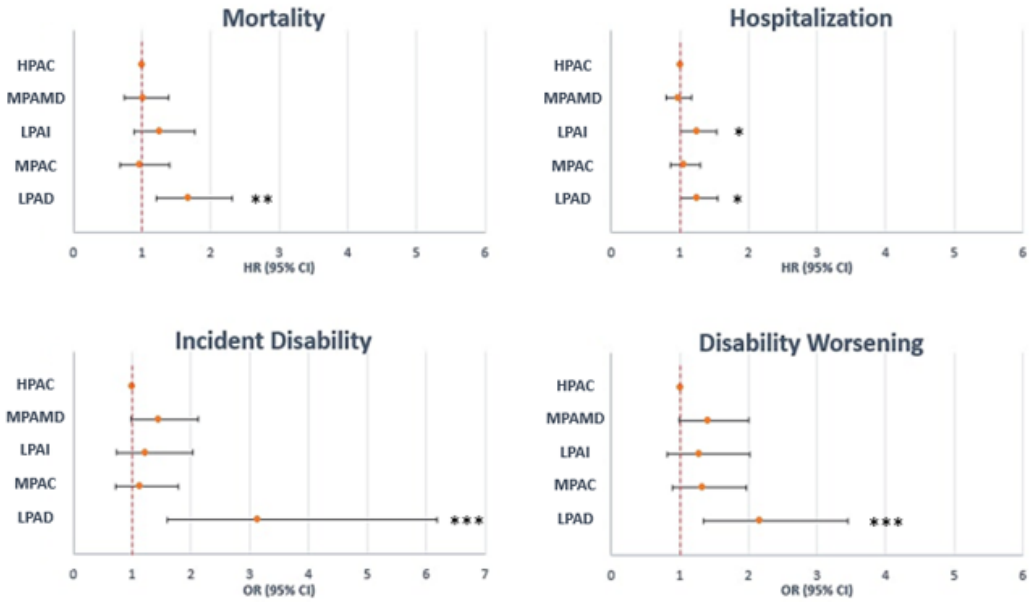
Sensitivity analyses excluding subjects with posterior probabilities <0.5 (n=65; 3.87% of the sample) for the group they were classified into did not meaningfully change the associations [30].

Table 2.2. Multivariate Associations between PA Trajectories and Adverse Outcomes

	HPAC n=566; 33.7%	**MPAMD** n=392; 23.3 %	**LPAI** n=237; 14.1%	**MPAC** n=191; 11.7%	**LPAD** n=293. 17.5%
Mortality (HR; 95% CI)					
Raw	*Reference*	**1.41 (1.04-1.91)***	**2.26 (1.62-3.14)*****	1.27 (0.9-1.79)	**5.15 (3.92-6.77)*****
Model 1		1.19 (0.88-1.63)	**1.56 (1.12-2.19)****	1.15 (0.8-1.64)	**2.53 (1.86-3.44)*****
Model 2		1.13 (0.83-1.54)	1.4 (0.99-1.97)	1.08 (0.76-1.55)	**2.21 (1.62-3.03)*****
Model 3		1.01 (0.74-1.39)	1.26 (0.89-1.78)	0.97 (0.68-1.4)	**1.68 (1.21-2.31)****
Hospitalization (HR; 95 CI)					
Raw	*Reference*	1.1 (0.92-1.32)	**1.68 (1.37-2.05)*****	1.19 (0.98-1.45)	**2.22 (1.85-2.66)*****
Model 1		1.04 (0.86-1.25)	**1.43 (1.16-1.77)*****	1.2 (0.98-1.47)	**1.68 (1.37-2.07)*****
Model 2		1.01 (0.84-1.21)	**1.33 (1.08-1.64)****	1.15 (0.93-1.4)	**1.48 (1.2-1.83)*****
Model 3		0.97 (0.8-1.17)	**1.24 (1.00-1.54)***	1.05 (0.86-1.3)	**1.25 (1.01-1.55)***
Incident Disability (OR; 95% CI)					
Raw	*Reference*	**1.84 (1.27-2.66) ****	**1.93 (1.21-3.09)****	**1.66 (1.1-2.51)***	**4.93 (2.62-9.28)*****
Model 1		**1.5 (1.02-2.2) ***	1.5 (0.92-2.46)	1.23 (0.79-1.91)	**3.39 (1.74-6.59)*****
Model 2		**1.51 (1.03-2.21) ***	1.41 (0.86-2.32)	1.24 (0.8-1.94)	**3.31 (1.7-6.48)*****
Model 3		1.44 (0.97-2.13)	1.22 (0.73-2.04)	1.13 (0.72-1.78)	**3.14 (1.59-6.19)*****
Disability Worsening (OR; 95% CI)					
Raw	*Reference*	**1.71 (1.22-2.38)****	**1.99 (1.31-3.02)****	**1.75 (1.21-2.52)****	**3.33 (2.23-4.98)*****
Model 1		**1.46 (1.04-2.06)***	**1.61 (1.05-2.49)***	**1.48 (1.01-2.18)***	**2.05 (1.3-3.18)****
Model 2		**1.45 (1.03-2.04)***	1.52 (0.99-2.36)	**1.47 (1.002-2.17)***	**1.86 (1.19-2.91)****
Model 3		1.41 (0.99-2.01)	1.28 (0.81-2.02)	1.32 (0.89-1.97)	**2.16 (1.35-3.45)****

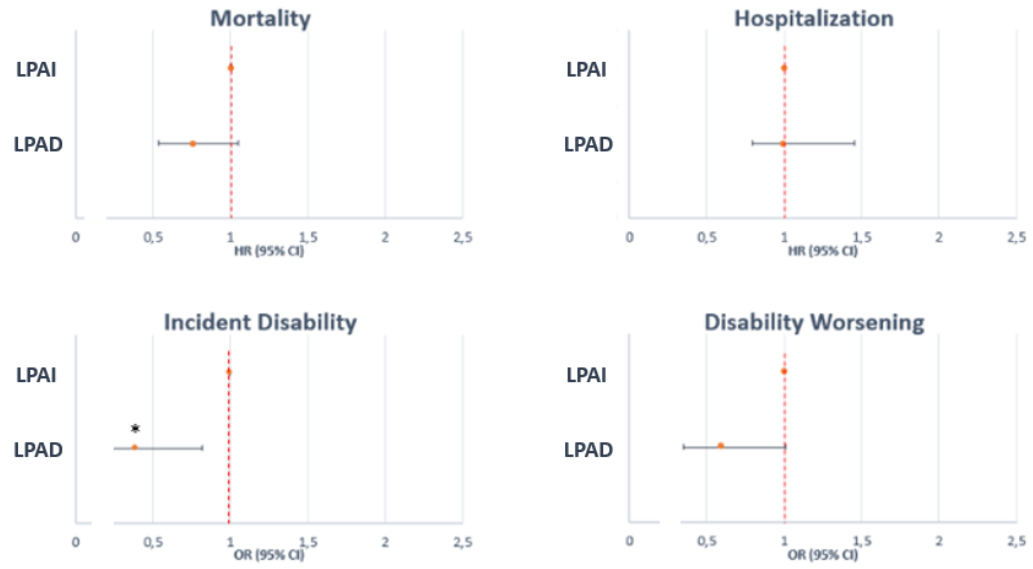
*P<0.05 **P<0.01 ***P<0.001. Model 1 (Age and Gender); Model 2 (Age, Gender, Charlson Index); Model 3 (Age, gender, Charlson Index, MMSE, educational level, smoking status, Katz Index and polypharmacy).HPAC: High PA-Consistent; MPAMD: Moderate PA-Mildly Decreasing; MPAC: Moderate PA-Consistent; LPAD: Low PA-Decreasing; LPAI: Low-PA Increasing.

Figure 2.2. Forest plots of the risk of the different adverse outcomes in the different PA trajectory groups



HPAC= High Physical Activity-Consistent; MPAMD: Moderate Physical Activity-Mildly Decreasing; MPAC: Moderate Physical Activity-Consistent; LPAD: Low Physical Activity-Decreasing; LPAI: Low Physical Activity-Increasing; OR=Odds Ratio; HR: Hazard Ratio; 95% CI: 95% Confidence Interval.

Figure 2.3. Forests plot of the differences in the risk of adverse outcomes between Low Physic Activity-Increasing and Low Physical Activity Decreasing trajectory groups.



LPAD: Low Physical Activity-Decreasing; LPAI: Low Physical Activity-Increasing; OR=Odds Ratio; HR: Hazard Ratio; 95% CI: 95% Confidence Interval

Discussion

The present study aimed at identifying PA trajectories in the TSHA and exploring their association with adverse outcomes. Overall, our study shows that in this large representative cohort of older adults, prospectively maintaining higher baseline PA levels at older ages is associated with a lower risk of relevant adverse outcomes (mortality, disability onset and worsening, and hospitalization), independently of important confounding factors. Subjects showing higher PA levels at baseline and sustaining them along time (High PA-Consistent trajectory) had lower odds of all adverse outcomes compared with those presenting with low baseline PA levels and an important decline along time (Low PA-Decreasing trajectory), and lower risk for hospitalization than those with a low initial PASE score even when PA increased over time (Low PA-Increasing trajectory). These findings support the need to promote effective intervention strategies aiming to maintain or increase PA among older adults, as a key factor for healthy aging.

We identified five longitudinal trajectories within our population. Of these, four showed a prospective reduction in PA at old age, which agrees with previous observations of a majority of older adults reducing PA along time [48]. Of special note is the presence of one PA-increasing trajectory (Low PA-Increasing), suggesting the existence of qualitatively distinct trajectories in our population of interest, as previously described in other works [49–54], and extending the findings of classical studies describing heterogeneous patterns of free-living PA at older ages [55].

Regarding the GBTM algorithm classification quality, the identified trajectory groups showed mean posterior probabilities of membership that were close to 0.8. As values of 0.7–0.8 are deemed indicative of an aggrupation that sufficiently discriminates between individuals with dissimilar patterns of change in a behaviour over time [56], we conclude that our classification is reliable.

In relation to the association of prospective PA changes and mortality, our results showing an increased risk for Low PA-Decreasing in relation to High PA-Consistent trajectory groups are consistent with the general notion that increased levels of PA lead to greater longevity in both men and women. These findings were also observed when using cross-sectional PA estimates [9,20,23,23–25,27–29], prospective categorical changes in PA [9,33,57] and, more recently, finite mixture-modelling approaches for PA trajectories identification as the exposure variable [39], irrespective of the PA-estimation

tool (self-reported vs. objective measures) [58]. While it is known that even a low level of participation in PA reduces mortality rates in comparison with inactive behaviour [8,27,28], the benefits increase in a dose-response manner at older ages in both men and women, with a saturation effect in the upper limit of both intensity and volume of PA [23]. Interestingly, the magnitude of PA effect on mortality might be contingent upon the intensity of the displaced activity, which underscores the importance of this parameter as a determinant of PA effects on health [59].

Importantly, the mortality-sparing benefits of late-life PA might only be slightly affected by pre-cohort PA behaviour [60], meaning that at advanced age even subjects that have never engaged in PA might gain similar benefits to those that used to be active. Additionally, PA seems to attenuate the excess risk of mortality associated with other classical predictors such as frailty [61], cognitive impairment [62] and poor mental, social and physical health among elders [63].

Because PA is a powerful countermeasure against the development and progression of chronic conditions, it is assumed to constitute a means to reduce healthcare system utilization [71]. In this context, our results point to an important reduction in the likelihood of hospitalization among those remaining active along time (High PA-Consistent trajectory) versus those showing low PA baseline levels (Low PA-Increasing and Low PA-Decreasing trajectories). The little research that is available has demonstrated that PA is related to fewer and shorter hospital admissions [72, 73].

With regards to the association between PA and disability onset, our results support previous work reporting an inverse association [14,67], with greater PA levels (measured heterogeneously) associated with lower likelihood of functional disability captured as mobility [67,68], clusters of BADL [69,70], instrumental ADL (IADL) [69,70], or both [69–71]. The inverse PA-disability association seems to be graded, since slight increases in terms of volume [71] and intensity [72] are associated with significantly better functionality

Yu et al. sought to explore associations between PA-trajectories and functionality in a Taiwanese older-adult cohort of 3186 subjects (mean age 63.89 ± 8.17 years; 50% women) using a growth mixture model along 11 years follow-up [73]. Notwithstanding the differences in methodology between their study and ours, the results were similar. Importantly, and analogous to our findings, their PA-increasing trajectory group

benefitted from protection against disability to a similar extent as those who remained highly active along follow-up, despite their low baseline PA levels [73].

Regarding the associations between PA levels and disability worsening, the limited evidence points to a negative association between higher activity levels (measured in diverse ways) and the odds of showing lower functionality at follow-up. In this line, Tak et al. performed a meta-analysis of 4 studies that reported associations between PA and BADL disability progression [14]. These findings are also compatible with our data. Given the paucity of studies, further research is needed to study the complex relationships between PA and other determinants of disability.

The Low PA-Increasing trajectory group showed an increased risk of hospitalization, but not disability, when compared with the High PA-Consistent group. We hypothesize that the strong association between increasing-activity and functionality during late life might arise as the result of actual improvements in the physical domain of intrinsic capacity resulting from PA. Tellingly, associations between PA and functionality tend to be stronger in the case of motor ADL [54, 66], whereas the associations with performance on more cognitive demanding tasks might be more modest [69,74]. On the other hand, the absence of significant reductions in hospitalization in the Low PA-Increasing trajectory group observed here might suggest a limited potential of late-life increases in PA to avoid outcomes that lead to hospitalization in senior populations – mainly cardiovascular events, pulmonary disease exacerbations and fractures resulting from lifelong development of prevalent conditions in the presence of low PA levels. Accordingly, members of more active trajectories are more likely to have been active during mild-life, and thus their odds of developing these conditions and subsequently being admitted to the hospital might be lower.

Our study has several strengths including the large sample size, excellent ascertainment of adverse outcomes and the inclusion of relevant variables that could confound the associations. The TSHA is a representative population of community-dwelling and institutionalized men and women with a wide range of ages. Furthermore, we used the novel GBTM, a powerful statistical tool to group subjects into qualitatively distinct developmental progressions that differ not only at baseline, but also in the direction and magnitude of the change and that are not readily identifiable using ad hoc, ex ante classification rules. By doing so, we accounted for the factual dynamic nature of PA, overcoming bias of previous research. Although GBTM might remain unfamiliar for

most of clinical focused researchers, it presents some compelling features that might be quite useful to study longitudinal data. The characterization of groups of subjects following different evolutions for a variable has commonly relied on subjective categorization based on clinical or empirical thresholds (cut-points derived in other cohorts, tertiles, etc…). Although reasonable, these assignment rules present with some pitfalls. First, the existence of different groups is assumed a priori, and this point cannot be tested objectively. Second, they do not allow for assessing the precision of individual classifications to the various groups and hence, uncertainty about individual group membership might emerge. In our case, an important strength of GBTM is that it allows for a data-based in-depth study of the features of potential healthy aging-phenotypes (PA-maintainers/increasers), which in turn could help clinicians to identify strategies for maintaining PA engagement among senior. To estimate PA levels, we used a well-validated tool specific for older adults, whose advantages include its brevity, easy scoring process, the inclusion of activities other than exercise, and the inclusion of activities common to older ensuring a comprehensive assessment of overall PA. While objective PA measures are more reliable and overcome PA questionnaires' limitations, they might be impractical in large cohorts, as in ours. This work is one of the first to our knowledge trying to explore the presence of different PA trajectories within a cohort of older adults and their associations with important adverse outcomes in an older adult cohort.

Our study, nevertheless, has important limitations. First, self-reported PA tools are poorly correlated with objectively measured PA and their use is subject to the inclusion of recall errors and social desirability leading to bias, especially among older adults. Additionally, over-reporting of PA levels, if present, would lead to an underestimation of the actual effect of PA on adverse outcomes [7,32]. Secondly, PASE cannot be translated into actual PA levels or the metabolic equivalent of task or time performing exercise. Thus, it fails at directly accounting for important modulators of the effect of PA on health, mainly intensity and volume. This makes our results challenging to interpret in relationship with other studies or PA recommendations. Thirdly, hospitalization was only ascertained by checking Toledo's Hospital Complex records. Although this centre is the reference hospital for the Toledo's province, where the whole sample dwelled at baseline, it is possible that some subjects have travelled or moved during follow-up and some events could have gone unreported.

Although GBTM is increasingly been used for identifying trajectories both for exposures and outcomes in observational and experimental research, it is inherently limited in capturing individual variability and may lead to over-grouping [36]. Furthermore, we could only construct linear trajectories since we could only evaluate two time-points prior to follow-up.

Reverse causality cannot be excluded in our study, due to its observational nature. PA participation might be conditioned by health status and vice versa. Nevertheless, the associations remained significant after adjustment for important risk factors, comorbidities and functional status.

We acknowledge the potential absence of unrecognized or uncontrolled covariates that could affect our observations. Of note is the absence of a measure of sedentary behaviour as a competing exposure. Sedentary behaviour has recently been postulated as a key health factor, independent of PA patterns, and is associated with mortality [75,76], disability [69,77] and increased healthcare expenditure [78]. Furthermore, as we did not have information about PA before the study entry time, we are not able to assess whether the benefit from PA observed in this study could respond to a life-long acquired benefit rather than to a recently gained PA beneficial effect. Direct comparison of our study with others is not possible due to the unique distribution of trajectories that GBTM yields within individual populations. Finally, our sample is restricted to a specific area of Spain with unique features. Although this fact may limit the generalizability of our results, it offers the advantage of reduced potential confounding by race, education, social economic class and access to healthcare.

Our study contributes to expand the notion of PA as a powerful modifiable factor that promotes healthy aging by means of preventing important adverse outcomes including mortality, disability, and hospitalization. It does so from a new perspective, by using a novel approach that allows to empirically identify different PA-related aging phenotypes, that as our results suggest, are associated with relevant outcomes for older people. The prevention of BADL disability is especially relevant, since it is associated with receiving home-care services, and an increased risk of long-term nursing home admission and healthcare costs [14]. In the context of a global aging population, our findings have important clinical and economic implications. Given that the association between PA and healthy aging seems to be valid and physiologically plausible, especially if the PA is in the form of structured exercise, the goal should be to enhance

exercise participation among older people living in the community. Unfortunately, PA levels fall dramatically in the last years of life [20]. If, as the evidence indicates, any activity above sedentarism in terms of volume [8,27–29,35] and intensity [23,32,59], and longitudinally maintaining PA levels, are associated with better health outcomes in older adults [27,29,79], clinicians, relatives and caregivers should encourage them to be as active as possible, both during planned exercise sessions and in everyday life activities. Policymakers, for their part, should increase social awareness and promote accessible, popular and everyday activities such as walking and active commuting among older populations. Hopefully, efforts are being made to increase late-life PA participation [80].

In summary, we confirmed our hypotheses in our older adult cohort that consistent high PA levels provide protection against important adverse outcomes when compared with low PA baseline levels and decreasing PA. Importantly, increasing PA levels during late life might entail a lower risk of disability in comparison with prospectively reducing activity.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical issues

The study protocol was approved by the Clinical Research Ethics Committee of the Toledo Hospital, Spain. This work was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments. Participants signed informed consent forms prior to their inclusion in the cohort. The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle [81].

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Chapter 3:
General discussion

General Discussion

In the following sections I discuss the implications of the results of the present thesis and I debate surrounding their possible applications.

Physical Behaviors as modulators of healthy ageing

The ongoing demographic and epidemiologic transitions worldwide, have contributed to growing interest in the physiology of the ageing process [1]. The superimposition of chronic diseases to the "physiological" primary ageing conditions an accelerated loss of physiological reserve at whole-body systems [2] and drives reductions in intrinsic capacity, which in turns conditions premature disability, poor health outcomes and compromise health-related quality of life. Importantly, neither the development of chronic disease or disability are irremediable consequences ageing, since "healthy ageing" models do exist [3, 4].

Therefore, the understanding of the processes underlying healthy *versus* accelerated ageing and the factors associated with different intrinsic capacity trajectories have attracted the interest of healthcare professionals and researchers in the field of ageing.

Among the myriad of known and unknown factors potentially determining biological age, special interest has been posed on modifiable lifestyle factors (physical behaviors, nutrition, toxic habits…). Of those, physical activity, physical inactivity and sedentary behavior, have widely been identified as decisive determinants of health [5].

Part of this doctoral thesis focused on the role of physical behaviors as determinants of healthy ageing, focusing on a crucial organ-specific age-related process (i.e. sarcopenia) and the association between temporal evolution of physical activity and adverse outcomes.

Associations between PA and SB and sarcopenia and its determinants (Chapter 1)

Among the constellation of physiological function losses in body systems along the ageing process, that affecting the musculoskeletal system, sarcopenia, stands out as one of the most critical given its relatively high prevalence [6], direct implications (association with development and aggravation of chronic diseases) [7–9], falls and fractures [10], disability [11], mortality [12, 13] and increased healthcare expenditure [14]). In fact, some experts consider sarcopenia to be at the forefront of health issues associated with ageing and to constitute a public health concern [15].

Consequently, it seems mandatory to increase the awareness about the need of the maintenance of muscle mass and function levels across the lifetime and to prompt initiatives aimed at attenuating sharp decreases in muscle mass and function in late life [16].

Focusing on the role of free-living physical activity, available evidence remains scarce (mainly in relation to physical activity parameters such as intensity and volume) and presents with several limitations that could be overcome given the recent advances in late-life physical behaviors epidemiology (use of accelerometers [17], isotemporal substitution models [18]) and recent reshaping of sarcopenia definition [19–21].

The study presented in Chapter 1 [22] aimed at exploring the cross-sectional associations between objectively assessed physical behaviors and sarcopenia and its determinants in a Spanish older adults' population. Our results suggest that greater levels of moderate-to vigorous physical activity are associated with lower sarcopenia rates and greater muscle mass and gait speed, independently of light physical activity or sedentary behavior, whereas the association with handgrip strength seems to be confounded by sedentary behavior and light physical activity. Additionally, the isotemporal substitution model showed that replacing both sedentary behavior and light physical activity with moderate-to-vigorous physical activity is associated to a reduction in the odds of presenting with sarcopenia and is positively related to muscle mass and gait speed, whereas in the case of handgrip strength, only the substitution of sedentary behavior with moderate-to-vigorous physical activity resulted significant.

To this day, several observational studies have explored the association between leisure-time, total physical activity and lower sedentary behavior accumulation and sarcopenia

rates, obtaining mixed results. A recent meta-analysis of cross-sectional observational studies showed that physical activity was associated with a 45% (OR=45; 95% CI=0,37-0,55) lower probability of presenting with sarcopenia [23], including both muscle mass-based and multi-domains sarcopenia definitions.

Using physical activity questionnaires, studies such as those of Tyrovolas et al. (2016) [24] and Rosique-Esteban et al., (2018) [25] showed cross-sectional associations between higher levels of physical activity and lower sarcopenia rates; whereas Volpato et al., (2014) (using a non-validated physical activity questionnaire) [26] and Hai et al., (2017) [27], did not find such association. Longitudinally, Mijarends et al. (2016) [28] found a protective role of high levels of physical activity on sarcopenia incidence. Regarding self-reported sedentary behavior, evidence points towards a positive association [29, 30].

Recent advancements in actimetry have allowed to better characterize physical activity in terms of intensity and volume, overcoming limitations of self-reported questionnaires. Hence the poorly understood association between sedentary behavior and different physical activity intensities (probably triggering different response at the cellular, organ and systemic levels) with sarcopenia and its determinants is now possible. In this regard, sarcopenia has consistently been negatively associated with accumulation of time in the higher end of the intensity continuum (moderate-to-vigorous physical activity) [31–33], with only one study showing associations between light physical activity (termed non-sedentary activity) and lower sarcopenia rates [34]. The role of sedentary behavior by its part has been less investigated, with two accelerometer-based studies showing no association with greater sarcopenia rates [31, 33, 35].

Concurrent to the evolution of sarcopenia envisioned as a condition not only comprising age-related reductions in muscle mass but also in physical performance and muscle strength, studies started to explore the association between physical behaviors and individual sarcopenia determinants. Overall, observed associations tended to be graded, greater at higher levels of physical activity in terms of volume and intensity and stronger in the case of muscle strength [31, 33, 36–38] and physical performance [31, 33, 34, 39], over those with muscle mass [32, 33, 36]. Sedentary behavior by its part was poorly associated with sarcopenia determinants as an independent factor with some significant associations observed with muscle mass [36] and gait speed [31, 40].

Among the available studies employing the presumable more valid accelerometer-based physical behaviors estimation, the results were unanimous pointing towards a unique and independent association between moderate-to-vigorous physical activity and sarcopenia [31–33] and its determinants [31, 33, 36, 38, 39], which is compatible with our results, with the exception of handgrip strength. With regards to sedentary behavior, previous research has pointed to the absence of an independent association between total time in sedentary behavior [31, 33, 35] and sarcopenia, congruently with our results. Findings might be expanded to muscle mass [31, 33, 35, 38] and handgrip strength [33, 35–38, 40], whereas the associations between sedentary behavior and gait speed have been mixed [11, 13, 19, 20], with significant [31, 39, 40], and non-significant associations encountered [33, 35, 38].

Physical Activity Intensity and Sarcopenia and its Determinants

Altogether, available evidence suggests that in order to gain benefits in terms of muscle mass, strength and physical performance, the breaching of a physical activity intensity threshold might be required, with little or none benefit obtained at physical activity lower intensities. In fact, light physical activity benefits observed in single-parameter models tend to fade when accounting for time spent at moderate-to-vigorous physical activity, which reinforces the independent effects of different physical activity intensities and the role of intensity as a crucial determinant of physical activity benefits on health.

These findings have recently been reinforced by emerging experimental research, proving that moderate-intensity walking-based aerobic exercise programs have the potential to contribute to musculoskeletal health. Brightwell et al., showed that a 24-weeks aerobic exercise training (3 times a week, 45 minutes per session, at an intensity of 70%of the heart rate reserve) was associated with increases in muscle capillarization, muscle proteostasis, and lower-limb muscle strength in a sample of sedentary older adults [41]. They failed at reporting gains in muscle cross-sectional area, confirming the expected little potential of aerobic exercise for muscle hypertrophy [42]

Anyhow, the increases in muscle function (strength) observed after aerobic training have relevant implications since this parameter is a better predictor of functional ability than muscle mass [43, 44] among older adults.

Notwithstanding, long-lasting aerobic exercise training participation might contribute to muscle mass maintenance by means of preserving a healthier muscle fiber phenotype,

extending survival and hence preventing inactivity and age-related muscle atrophy [45, 46], which is consistent with findings of some observational studies showing associations between ambulatory "aerobic" moderate-to-vigorous physical activity and muscle mass [28, 32, 36, 36]. Unfortunately, experimental research is scarce and optimal aerobic exercise parameters for prevention of late-life sarcopenia attenuation remain to be elucidated.

Importantly, similar to observational studies, available clinical trials point to the intensity reliance of adaptations to aerobic exercise training, with low intensity exerting insufficient stimulus such as to promote adaptations in terms of muscle protein synthesis [47, 48].

Contrary to this hypothesis, some observational studies showed associations between light physical activity and some sarcopenia determinants: muscle mass [33, 36], handgrip strength [37], and physical performance [33, 34, 36, 49].

Two potential explanations for these incompatible observations regarding light physical activity exist. First, in mentioned studies, time in each physical activity intensity category was determined using accelerometry cut-points validated in healthy young reference populations [50–52], which could have leaded to labelling as light of minutes actually corresponding to moderate-to-vigorous physical activity, explaining the positive associations between light physical activity and some sarcopenia determinants. In our study, we employed age-specific intensity cut-points [53, 54]. Thus, the minutes identified as light physical activity in our study correspond to much lower intensities, with a substantial lesser potential for disrupting homeostasis and hence triggering responses than actual moderate-to-vigorous physical activity minutes misclassified as light physical activity in previous studies.

The striking differences in estimates of sedentary behavior, light physical activity and moderate-to-vigorous physical activity by using young-reference or older adult thresholds are illustrative of the importance of using age-specific cut-points for activity classification by accelerometers. The use of Freedson et al. cut-points [50] in the same Toledo Study of Healthy Ageing population as ours yielded greater sedentary behavior (540 minutes/day), and underestimated light physical activity (by 73 minutes) and moderate-to-vigorous physical activity (by 41 minutes) in comparison with the use of age-specific cut-points in our work [55]. This fact exemplifies the degree of distortion

arising from the use of standard reference cut-points for intensity categorization, and the imperative need of the use of population-specific cut-points to allow for correct inference [17, 56]

Second, another potential explanation for the recurrent association between light physical activity and better gait speed (observed in most of previous studies) might result from the reliance of the latter on body functions besides those involved in pure strength production [57–59], resulting from the integrative function of organic systems that might be positively impacted by light physical activity, such as cardiovascular [60] and central nervous systems [61] .

Moreover, light physical activity might exert some beneficial effects on muscle mass and function indirectly through its potential effects on visceral adiposity [62] and obesity [63] and its consequences (low-grade inflammation) and lipotoxicity, known core processes of sarcopenia pathophysiology [64], especially in sarcopenic obese subjects [31, 65], but this might be confirmed by further research.

Sedentary Behaviour and Sarcopenia and its determinants

Whereas evidence is consensual regarding the cross-sectional associations of greater levels of physical activity in terms of intensity and volume with lower sarcopenia rates, evidence regarding the role of sedentary behaviors is ambiguous.

Congruent with our results, accelerometer-based works found no association between sedentary behavior and sarcopenia when taking into account light physical activity and moderate-to-vigorous physical activity [31–33, 35]. Nevertheless, two studies by Gianoudis et al. [30] and Smith et al. [29] found a significant increased risk of sarcopenia with self-reported sedentary behavior. Disparity in findings could be due to measurement error or recall bias in self-reports (for which there is evidence particularly among older adults) [66]. Additionally, sedentary behavior is usually associated heterogeneously to a range of specific activities in self-reported instruments (television viewing, labor-related activities or screen time), potentially overlooking a proportion of sedentary behavior corresponding to activities non-included in questionnaires. Furthermore, sedentary activities include different chores, whose effects on health might be differential upon the presence of different correlates, for example associated behaviors including poor nutritional habits, and their nature (mentally-demanding activities vs. mentally-inactive sedentary behaviour) [30].

Regarding the association between sedentary behaviors and sarcopenia determinants, evidence suggest that physical performance (in the form of gait speed) might be the only sarcopenia-related parameter affected by sedentary behavior [31, 33, 35, 40]. Again, in the absence of associations between sedentary behavior and muscle mass or muscle strength, the link between higher sitting or reclining activities with gait speed might respond to the same rationale than the proposed reduced light physical activity-mediated impairment of other systems involved in gait performance. In fact, time engaged in light physical activity has been seen to correlate with sedentary behaviour breaks and (negatively) with total sedentary time [63], which suggest that both physical behaviors might be complementary and so their effects on health.

The SB/LPA Sarcopenic Obesity association

Similarly to our results, Aggio et al. found a significant elevated risk (OR=1.19; 95% CI=1.06-1.35) of sarcopenia with increasing time in sedentary behavior in raw models [31]. Nevertheless, such an association faded when moderate-to-vigorous physical activity levels were accounted for in both studies. Interestingly, in the same British Regional Study cohort, excess and lower risks associated with sedentary behavior and light physical activity, respectively, remained marginally significant after controlling for time in moderate-to-vigorous physical activity in the case of sarcopenic obesity [31]. Taken together, the uniqueness of moderate-to-vigorous physical activity as a sarcopenia protective physical behaviour factor and the independence of sedentary behavior and light physical activity for sarcopenic obesity risk might be justified by the existence of two sarcopenia phenotypes resulting from different physical behavior patterns. On one hand, a model of sarcopenia resulting from lack of higher intensity physical activity stimulus and on the other, sarcopenic obesity, in which muscle wasting is further aggravated by the additive detrimental consequences associated to increased adiposity (low-grade inflammation, insulin resistance, etc.…) [67], for what light physical activity might be protective by means of reducing time in sedentary behavior [68].

Isotemporal substitution

An exclusive novelty of our work is the use of isotemporal substitution models to explore the associations of reallocating different physical behaviors and sarcopenia, mimicking behavioral changes or interventions from a mathematical approach. This type of analyses considers the finiteness of the time in which a subject can partake in physical

activity. Thus, spending time in one behavior (i.e. sedentary behavior) results in less time being spent in another (i.e. moderate-to-vigorous physical activity) [18], further understanding that daily behaviors (sedentary behavior and physical activity) are co-dependent [69]. Hence, the use of isotemporal substitution might pave the way for the development and refinement of effective lifestyle-based interventions in older adults.

To our knowledge, Study 1 is unique in the use of isotemporal substitution to explore associations between different physical behaviors and sarcopenia. Our findings support the existence of an intensity threshold below which no benefit is achieved in terms of sarcopenia risk and/or muscle health parameters, as observed in studies using classical linear regression models. In the Study 1 both the replacement of either sedentary behavior or light physical activity with moderate-to-vigorous physical activity were associated with lower sarcopenia rates and better values in its determinants, except for handgrip strength, for which only the substitution of sedentary behavior by moderate-to-vigorous physical activity yielded a significant association. The latter might be explained by the little involvement of upper limbs in ambulatory activities captured by accelerometers.

Several studies have used isotemporal substitution approaches to disentangle the effects of time reallocation between intensities on older adult's health outcomes.

Overall, associations with better physical function outcomes (such as gait speed [39, 70] and self-reported physical function [71]) were restricted to moderate-to-vigorous increases, which is compatible with our observations. In fact, the evident health benefits of light physical activity increase and reductions in sedentary behavior may be restricted to cardio-metabolic health in older adults. The reduction of sedentary behavior at expenses of increasing light physical activity has been associated with reductions in body mass index, waist circumference [62], total fat, visceral adipose tissue, markers of glucose metabolism dysfunction (fasting glucose and HbAC1) and triglycerides, with concomitant increases in muscle mass and HDL-cholesterol [62], which might explain observed reductions in cardiovascular disease risk factors such as heightened resting heart rate, endothelial dysfunction and increased inflammatory activity (fibrinogen levels) [72].

Isotemporal substitution models have also showed theoretical positive effects of both light and moderate-to-vigorous physical activity increases on depressive symptoms [73],

whereas improvements in executive function were restricted to sedentary behavior-moderate-to-vigorous physical activity substitutions [74] among elders.

Special attention deserves the sarcopenia-related frailty syndrome, for which four studies using isotemporal substitutions are available. All of them showed associations between increasing moderate-to-vigorous physical activity reducing sedentary behavior with lower frailty levels using four distinct definitions (Frailty Phenotype [75], Frailty Trait Scale-12 [76], Frailty Index [77] and a continuous modified version of the Frailty Phenotype [71]). Nagai et al. [75], and Godin et al [77], found significant beneficial effects of the sedentary behavior-light physical activity reallocation on frailty, whereas Mañas et al. [76], did so only among older adults with comorbidities. Finally, no associations of increases in light physical activity and frailty were found in the isotemporal substitution in Higueras-Fresnillo et al. [71]. These contradictory findings might result from the use of different frailty operationalizations, with light physical activity positively impacting more comprehensive definitions (i.e. Frailty Trait Scale-12 and Frailty Index), and no effect on oligo-dimensional (physical dominion) frailty conceptualizations (such as Frailty Phenotype).

Mechanisms underlying PA and SB associations with sarcopenia

Mechanistic research deepening in the physiological processes underlying the association of free-living moderate-to-vigorous physical activity and musculoskeletal health is scarce. However, we hypothesize that putative mechanisms linked to exercise responses and adaptations in basic and experimental research [78, 79] might be valid to explain beneficial effects of free-living physical activity on muscle mass, strength and physical performance. First, the bioenergetics/mechanical homeostatic disruption caused by physical activity (absent during sedentary behavior) at the muscle tissue might trigger responses that start molecular signaling pathways leading to expression of genes involved in the improvement of fiber bioenergetics [80], upregulation of anti-oxidant defenses [81, 82] and contractile properties (protein synthesis [83] and satellite cell differentiation [84]), attenuating or preventing age-related fiber atrophy and apoptosis and consequently, the loss of muscle mass, strength and physical performance [79]. Furthermore, it is possible that both increases in moderate-to-vigorous and light physical activity (the latter probably implying sedentary behavior reductions) might promote a healthier muscle fiber and adipocyte secretomes, putatively exerting local and

remote (nervous, cardiovascular and skeletal systems) beneficial effects in an auto, para, endocrine fashion, prompting whole body health [85–87].

Nevertheless, these hypotheses are mere assumptions, that might be confirmed by future research.

In summary, the results of Study 1 support available evidence of the association between higher intensities of physical activity and sarcopenia and its determinants, although the presence of some mixed findings in previous studies should be acknowledged. These inconsistencies might be the result of specific features of individual populations, the use of different methods to estimate physical behaviors (self-reporting vs objective instruments) and sarcopenia definitions (only muscle mass-based vs. more comprehensive sarcopenia definitions including muscle mass and performance) and cut-points and instruments (reference, population-specific) for muscle mass (bioimpedance, dual-X-ray absorptiometry scan, anthropometric measures, height and weight derived equations), physical performance (usual gait speed, fast gait speed, Up and go Test, Short Physical Performance Battery) and strength measurement (handgrip strength, leg strength, 30-seconds Chair Stand Test…) [23].

Late-life PA trajectories and healthy ageing (Chapter 2)

The sub-clinical physiological changes occurring during ageing together with the accumulation of chronic conditions manifest in the form of functional decline and increased risk and premature advent of the so-called age-related adverse outcomes (mortality, hospitalization, disability, and institutionalization).

Physical activity promotes ample health benefits and has long been recognized as an important determinant of survival [88–91].

The salutary effects of greater levels of physical activity on body physiological systems have been traduced increased life- and healthspan [88, 92]. These observations might be explained from the fact that lifelong physical behaviors are key factors in the development of chronic diseases and determine the pace of derange of physiological systems along ageing. Hence physical activity and sedentary behavior might be key factors of intrinsic capacity at older ages and therefore, of healthy ageing [93, 94].

Previous research tended to use a single-point estimation of physical activity as exposure. Nevertheless, physical activity behaviors are strikingly volatile, especially among older adults [95–97], and therefore, the study of physical activity evolution as a predictor of healthy ageing might be of high interest. Physical activity intensity and volume have been seen to be maintained from mild life into old adulthood, where both suffer a sharp decline around the age of 70 [98]. Despite mean population values point to these generalized decreases in physical activity, inter-individual variability might exist within populations [99], and different rates of decline and even late life physical activity-increasing trajectories might condition different physiological ageing, and hence, the occurrence of adverse events.

The Chapter 2 of this thesis dissertation presents the results of Study 2 [100], whose aim was to explore the presence of different late-life physical activity evolution patterns in the Toledo Study of Healthy Ageing and their associations with relevant adverse outcomes in the older populations (mortality, disability, and hospitalization). Briefly, our study demonstrates the presence of different physical activity trajectories within the Toledo Study of Healthy Ageing sample, differing both in the baseline levels and evolution; and the association between maintenance of high physical activity levels and healthy ageing, characterized by lower rate of adverse events. Furthermore, it suggests that increases in physical activity might exert benefits in the disability dominion,

irrespective of baseline levels, but fail at reducing death or hospitalization rates, which reinforces the potential of physical activity benefits even in the most inactive older adults.

Late-life physical activity and mortality

Our results contribute to previous evidence linking single-time point physical activity estimates and survival in older adult cohorts [101–103]. The protective role of physical activity seems to follow a dose-response pattern, with the maximum reductions in the likelihood of early-mortality at higher intensity and volume, showing some saturation in the upper limits [89, 90] but pointing to overt benefits gained from the lowest physical activity participation, compared to no engagement [101, 104–109]. Recent research incorporating objectively assessed physical activity corroborated such findings [92, 106, 110]. Interestingly, physical activity might outpace or attenuate classical mortality risk factors at advanced ages, such as the presence of multiple diseases [110, 111], disability [112] or cardiovascular disease [113]. In fact, physical activity-associated reductions in mortality seems to be greater at older ages [89, 114]

With regards to studies exploring late-life physical activity evolution using a crude physical activity categorical classification, Stessman et al. showed that both prospectively keeping up high physical activity levels and becoming active from sedentary was associated with reduced mortality at follow-up, whereas reducing physical activity or remaining sedentary conferred an increased risk [115]. Wannamethee et al. found similar results in the British Regional Heart Study [109].

Recent works have incorporated data-driven methods in order to identify trajectories of physical activity over the life course. Overall, these studies point to a beneficial effect of maintaining baseline physical activity levels, compared to reducing or showing persistently low physical activity on all-cause and cause-specific mortality. Interestingly, prospectively increasing physical activity seems to contribute to survival, with these physical activity prospective patterns reaching risk reductions similar to those maintain physical activity levels, irrespective of baseline values [114, 116]. However, these works focused on physical activity evolution from early adulthood to mild-life and followed individuals up until early late-life.

To our knowledge, only two studies have restricted the study of the evolution of physical activity to late-life using data-driven methods.

Using latent class analysis, Xue et al., found the presence of four 12-year physical activity trajectories within the Women Health and Aging Study (n=443 women; mean age 73,9 ± 2,8 years of age) and found a stepwise association between physical activity trajectories and mortality, with an increased risk in those in the persistent low physical activity level trajectory (HR=3,34; 95%CI=1,2-4,59) and those in the "fast declining" trajectory (HR=2,34; 95%CI=1,72-6,47). Interestingly, those maintaining moderate physical activity levels did not show an excess risk of mortality when compared to those "always active" [117]. More recently, Laddu et al. identified three physical activity-decreasing trajectories in a sample of older men (mean age=79,24 ± 5,2) that differed mainly in baseline levels. Belonging to the trajectories with higher baseline physical activity engagement was associated with reductions in the odds of dying during the average 7-year follow-up in a dose response fashion (HR=0,78;95%CI=0,7-0,88 and HR=0,69; 95%CI=0,57-0,83 for the moderate- and high-physical activity levels at baseline-trajectories, respectively), compared to the baseline low-physical activity trajectory [99].

The results in Study 2 are consistent with these observations pointing to a positive association between physical activity maintenance/increase along follow-up and survival, given that in our study, only the group that showed reductions in physical activity from low levels showed an increased risk for mortality in multivariate models, compared to those belonging to trajectories of physical activity increase and maintenance.

Late-life physical activity and hospitalizations

The accumulation of comorbidities and sub-clinical processes mediated by physiological reserves exhaustion associated with ageing conditions an increased risk of hospital admission and longer stays, which drives an increased hospitalization-associated healthcare cost [118, 119]. A current key public health issue is the increased stress that a growing ageing population poses on public healthcare systems. But besides the economic burden of this adverse event, hospitalizations have been associated with sharp functional declines and increased risk for nosocomial disability among older adults [120], resulting from forced inactivity [121], which produces sharp reductions in different body systems functioning [122].

Therefore, the identification of strategies for avoiding the development of conditions or paroxysmal events (such as falls or fractures) leading to hospital admission acquires special relevance. As described before, physical activity attenuates age-related

physiological declines and is protective against chronic conditions development and aggravation [123] and the occurrence of falls [124, 125] and might therefore reduce rates of hospital admission.

Our results are in line with scant previous research pointing to a protective role of physical activity for hospitalizations [126, 127]. Some studies also suggested an association between physical activity and shorter hospital admissions [128, 129], which might further reduce hospitalization-related healthcare costs and diminish the potential exposition to nosocomial disability and infections.

Nevertheless, none of previous studies exploring physical activity-healthcare utilization associations included physical activity evolution as the exposure variable.

Late-life physical activity and disability

In the context of ageing populations, and with the premise of the need of promoting a free-of-disability ageing, the exploration of age-related functional decline-related factors is of paramount importance, in order to develop preventive strategies [130]. The World Health Organization defines disability as "an umbrella term for impairments, activity limitations and participation restrictions" [131]. Disability has often be captured as the difficulty for performing activities of daily living, that represent severe limitations, threatening the ability of an individual to live independently, and being associated with early mortality and burden on public health and social services [132].

In the development of disability, several intrinsic and extrinsic and modifiable and non-modifiable factors are believed to intervene [133]. Among them, physical activity has outstanded as a critical protective factor against functional decline in epidemiological studies [134–136], often captured as ability for activities of daily living [134].

Likewise in the case of mortality, virtually all studies exploring physical activity-disability associations at older ages used single-time physical activity estimations as the exposure variable [137]. In these studies, physical activity was associated with better functional status captured as ability to perform basic activities of daily living [137–142], instrumental activities of daily living [137, 139, 141, 142] or mobility performance [141–143].

Recent studies incorporating accelerometers for physical activity estimation point to a positive association between moderate-to-vigorous physical activity and lower rates of

disability, in a volume linear dose-response manner [137, 144–146]. In the case of light physical activity mixed results point to a protective effect when it is accumulated <10 minutes but not in longer bouts, which can be a reflection of the observed effect of breaking sedentary behaviour [147] rather than the direct effects of light physical activity [144], given the existing correlation between short light physical activity bouts and sedentary breaks [63].

Until today, only one study approached associations between physical activity and disability using data-driven methods to identify different trajectories. Yu et al., identified four 11-year leisure activity trajectories (consistent-high, decreasers, increasers and consistent-low) by using a growth mixture modelling approach in a cohort of older adults (aged >60). Their consistent-high and increasers trajectory groups showed significantly better function, whereas decreasers experienced a greater functional decline than the consistent low leisure activities at follow-up [148]. In their study, functional ability was captured through a cluster of 12-item scale (including 6 basic activities of daily living and 6 instrumental activities of daily living), whereas leisure activities corresponded to a cluster of 8 daily living chores including sedentary and strenuous physical activities, which might poorly capture actual physical behaviors or energy expenditure. Interestingly, in addition to the high-consistent leisure activities, those in the increased activity trajectory group showed better functional ability than those in the low-consistent or decreasing longitudinal patterns, which is compatible with our results showing the potential of increasing physical activity for disability onset prevention, irrespective of baseline levels.

Recent research by Laddu et al., using data from two cohort of older men (Osteoporotic fractures in men) [149] and women (Women's Health Initiative) [150] found a lower rate of decline in physical performance measures (gait, speed, grip strength and the chair-stand test) in subjects belonging to late-life trajectories of high physical activity (measured with the Physical Activity Scale for the Elderly) along time. The observed preservation of physical function by sustained physical activity is compatible with the attenuation of the physiological losses that concurrently mediate the progression from functional decline to overt disability, hypothetically, by preserving muscle strength, balance, and mobility [151, 152]. Therefore, the results by Laddu et al. might be complementary to our observations, pointing to an association between higher physical activity maintenance along ageing on the preservation of the physical domain of intrinsic

capacity, that together with mental capacities, also positively influenced by higher physical activity continuance [153], determines a retention of functional ability.

From the clinical point of view, the reduction in the progression of functional decline might acquire special relevance. It is well known that prodromic phases are much more reversable than more advanced stages of functional decline [154, 155]. Hence, the reduction in the pace of disability progression might expand the opportunities for functional gain through interventions. Our study contributes to the scarce previous evidence showing associations between higher physical activity levels (both in the form of moderate-to-vigorous and light intensities) and lower odds of presenting greater levels of disability at follow-up [134, 145].

Notwithstanding the fact that the link between physical activity and functional ability arise from well-designed and at times very large prospective cohort studies and are pathophysiologically plausible, experimental research is lacking. Unfortunately, randomizing populations to be physically active over longer periods of time and comparing them to others that were instructed to remain inactive is infeasible.

Recently, well-powered randomized clinical trials have been designed to evaluate the effectiveness of sustained participation in physical activity (usually based on current physical activity recommendations) and disability development in older adults at risk of disability. [156, 157]. In particular, the LIFE study (clinicaltrials.gov identifier: NCT01072500), which recruited 1635 American older adults (mean age=78,9 ± 5,2) at risk of mobility disability (Short Physical Performance Battery ≤ 9), showed that those randomized to the intervention program (multicomponent exercise comprising aerobic, lower limb-strengthening, balance and flexibility domains) experienced significantly less mobility disability that those in the control group during 2,6 years of follow-up. Mobility disability is a crucial determinant of functional independence [158] and hence its prevention might directly relate to the ability to carry activities of daily living. A post-hoc analysis showed a dose-response effect of increase in physical activity and reduced mobility disability, which is consistent with our findings pointing to the beneficial effect of late-life increases in physical activity on disability [159]. Song et al., also found functional improvements after 2-year physical activity increases among previously inactive older adults with osteoarthritis, even when not reaching the public health recommended levels [157].

Late-life sedentary behaviour and adverse events

A relevant pitfall of our study using the Physical Scale for the Elderly for physical behavior characterization is the inability of this instrument for capturing sedentary behaviors and its limited potential for distinct intensities of physical activity.

As mentioned in previous sections, activities eliciting very low energy expenditure in a reclining or sitting position might play a fundamental and independent role in the development of chronic conditions and the rate of functional decline [160, 161], especially among older adults, that are the highest sedentary age-group (65-80% of waking hours) [162, 163].

Epidemiological evidence has pointed to an association of greater amounts of sedentary behaviour and adverse outcomes in cohorts of older adults [164, 165].

Previous research exploring possible links between sedentary behavior and survival in older adults has yielded mixed results, probably due to the use of different instruments for assessing sedentary behaviors [166]. A recent systematic review and meta-regression of accelerometer-based studies showed a dose-response effect in the association between sedentary behavior and mortality [167], but acknowledged that, as observed in studies controlling for time in moderate-to-vigorous physical activity, the excess risk might be eliminated by increases in the latter, as previously described in younger cohorts [88], since the inclusion of moderate-to-vigorous physical activity as a covariate tends to attenuate the associations [106, 168]. Nevertheless, in some studies such attenuation did not appear and sedentary behavior stood as an independent risk factor [92, 169]. These inconsistencies might mainly result from the misclassification of substantial proportion of time in sedentary behavior/moderate-to-vigorous physical activity estimations due to the use of several cut-points when using accelerometry [165]. Irrespective of the true existence of a buffering effect of physical activity for sedentary behavior deleterious influence on survival, it has been suggested that the combination of low levels of moderate-to-vigorous physical activity and high levels of sedentariness might confer the highest mortality risk among older adults [161, 170].

Likewise, physical activity, sedentary behavior patterns are believed to change along late-life [96]. Very few studies have accounted for this fact by cross-classifying sedentary categories over two time-points. Results pointed to decreased mortality risk for those remaining lowly sedentary [171–173], with one study also showing benefit from

longitudinally reducing sitting time [173], compared to those increasing time in sedentary time or remaining highly sedentary, independently of leisure-time physical activity.

With regards to the associations between sedentary behavior and functional ability, some recent studies showed an association of greater volume of sitting or reclining positions and increased odds of presenting with difficulties in activities of daily living, irrespective of moderate-to-vigorous physical activity levels [145, 146, 174, 175]. These findings suggest that total sedentary time might play a crucial role in the development of disability at advanced ages. Interestingly, not only the volume of sedentary behaviors but the pattern of accumulation might influence disability development. Chen et al., showed that breaking sedentary behavior up was associated with lower odds of presenting difficulties for instrumental activities of daily living. Afterwards, Sardinha et al. confirmed such findings and expanded evidence to basic, and advanced activities of daily living independent of moderate-to-vigorous physical activity levels [147, 174].

These observations support the role of sedentary behavior as an independent contributor to functional decline and therefore, the need of shifting sedentary behavior patterns towards a reduction of long periods besides increasing moderate-to-vigorous physical activity levels.

In summary, the results of Study 2 support available evidence linking late-life physical activity levels maintenance and healthy ageing, characterized by a reduction in the incidence of adverse outcomes. Unfortunately, given the scarcity of studies including late-life prospective changes in physical activity and the novel incorporation of data-driven methods, comparability of our results is limited.

Implications for clinical practice and public health

In the context of globally ageing populations, the prevention of conditions and physiological changes driving intrinsic capacity decline and leading to burdensome adverse events such as falls, fractures, hospitalization and disability constitutes a priority of current medicine. Fortunately, such conditions are partially due to modifiable lifestyle behaviors and hence, there is a possibility for the modulation of the rate of physiological reserve and functional decline with ageing.

The findings of the research included in this thesis dissertation contribute to the unequivocal evidence supporting the role of physical behaviors as critical determinants of the functional trajectories of ageing. Its implications stretch to clinical practice, public health and policymaking.

From a clinical perspective the recognition of physical behaviors as key risk factors in the development of a relevant syndrome with important multiple associated adverse outcomes (sarcopenia) and the occurrence of relevant late-life adverse events constitutes a call for the need of accounting for physical behaviors in the processes of anamnesis, evaluation and management of older populations in routine clinical practice. Since physical behaviors might be more predictive than classical risk factors at older age, the assessment of physical behaviors in the clinical scenario might be highly advisable given that it could assist risk profiling, care planning and tailoring of interventions. Moreover, physical activity has been suggested as a biological age marker, and hence, a sharp reduction observed in opportunistic assessments in consecutive medical visits could constitute a red flag for subsequent exploration of the causes driving such changes.

Given that physical activity increases and sedentary behavior reductions have been shown to positively impact sub-clinical health processes and prevent the development of non-communicable conditions, efforts should be made by both healthcare professionals managing older adults and the relatives to keep older adults as active as possible and to reduce time spent sitting in daily living and leisure-time activities [94]. Of relevance are the prevention of functional ability decline resulting from increases in physical activity participation even in those previously inactive, as our results indicate.

Furthermore, physical activity, (preferably in the form of exercise), has recently gain recognition as a therapeutic agent for a wide range of conditions [176]. Physical activity-based interventions might act synergistically to or even supersede pharmacological

approaches for the management of chronic diseases, that are more costly and entail potential adverse side-effects. In a usually multi-morbid older adult population, polypharmacy, the harmful use of multiple drugs [177], might be reduced by the adoption of effective and safe non-pharmacological approaches with whole-body potential, such as exercise [178].

Besides the fragmented individual disease management, current focus of medicine has shifted to the preservation of function along ageing [179, 180]. Strategies for the attenuation or elimination of age-related functional decline should target the multi-systemic physiological deranges that underly body functions impairment and might ultimately compromise intrinsic capacity. Therefore, physical activity and exercise, given their whole-body effects have been envisioned as unique and critical candidate strategies for functional decline prevention [5, 181] .

With regards to free-living physical activity, benefits on older adult's health seems to follow a dose-response pattern both in terms of intensity and volume, starting from slight increases and expanding thereafter. Hence, older adults should be advised to reach the higher zones of the intensity continuum whenever possible, but the potential of lesser intensities must be remarked [182]. In addition, encouragement should emphasize the reductions of prolonged sedentary periods [160, 163].

Out of the scope of this thesis dissertation is the role of exercise-based interventions on older adult health. Nevertheless, epidemiological and experimental evidence is unequivocal in the potential of structured physical exercise for healthy ageing promotion. Individually tailored multicomponent exercise programs, involving different stimulus (mainly endurance, resistance and balance) have been suggested as the most effective strategies for healthy ageing [183–185]. Despite the fact that optimal features of exercise programs for the older adults remain to be elucidated, in general terms, benefits widely exceed the harms [185]. Therefore, exercise participation should be counselled and considered as a potential intervention in different sub-populations of older adults [186].

Possibly, the combination of resistance exercise training [176], embedded in a multicomponent exercise program (including aerobic exercise and balance training) [183, 187], increases in free-living moderate to vigorous physical activity, and breaking-up of sedentary behaviour with light physical activity might be the best option for

healthy ageing, given their synergistic effects [84, 188]. Recently, high-velocity resistance exercise training (low-moderate loads with high velocity of execution) has gained recognition as the optimal approach to avoid physical function decline, given the tight link between muscle power output and the capacity to perform activities of daily living in older populations and so, might be an interesting and well-tolerated alternative approach [183, 189].

From our perspective, the current physical activities recommendations that advise moderate-to-vigorous physical activity [190, 191] are valid in that they generate a frame for public health messaging. Nevertheless, currently upcoming updates should emphasize the potential of high-velocity resistance training and the reduction of long-lasting sedentary activities by means of light physical activity, along with the establishment of minimum cut-points of volumes of higher intensities activities.

From the economical perspective, the adoption of more active lifestyles leading to reduced rates of sarcopenia, disability and lower healthcare utilization might have relevant implications in the sustainability of jeopardized healthcare and social welfare systems in the context of a growing aged population and reduced support ratios [192].

Therefore, in the sphere of healthcare management and planning, accumulating evidence linking physical behaviors and health in older populations should be translated into the real scenario and incentive the setting-up of policies aimed at increasing physical activity and exercise participation in this population. Providing healthcare providers specific training, easing of access to exercise facilities and skilled personnel, barriers elimination for non-structured physical activity participation, and public awareness increase of the potential of physical activities to promote health may be keystones in the development of such strategies [193].

Physical activity for sarcopenia management

In the absence of pharmacological interventions for sarcopenia prevention and management [16, 194, 195] non-pharmacological approaches have arisen as current unique therapeutic options [16].

In this regard, resistance exercise, has been suggested as the first-line therapy to reverse muscle mass and function loss, given that it has demonstrated to induce increases in muscle strength and power, and physical performance improvements in older populations [196]. Nevertheless, studies exploring the effectiveness of this mode of

exercise in sarcopenic populations in scant and the assumption that resistance exercise is effective for sarcopenia arises from the generalization of observations in healthy older adults [197]. Emerging research is restricting the samples to sarcopenic individuals and recent meta-analyses have shown positive effects of resistance exercise in strength and physical performance also in older adults with sarcopenia [198–200].
Unfortunately, given the methodological heterogeneity among published studies, the subsequent application in the clinical setting is limited by uncertainty regarding the optimal type, volume and intensity of resistance exercise required to optimize the response [200]. Interestingly, despite the wide variability in exercise response in heterogenous older populations, there seems to be no non-responders to resistance exercise, which reinforces the potential of this exercise modality for sarcopenia management [201].

In any case, before clinical guidelines for the treatment of sarcopenia with exercise can be established, further research providing more precision with regards to programs features in populations with diagnosed sarcopenia are needed [101].

In addition, although resistance exercise participation should be advised for both healthy and at-risk older adults, owing to its well-known benefits besides sarcopenia, several barriers limit its correct implementation in clinical scenarios and contributes to the very low adherence in this age-group [202]. Furthermore, older adults' acceptance of structured resistance exercise programs might be restricted to scenarios in which physical function impairments are already present (secondary prevention) [16].

In this context, the potential of free-living physical activity (usually corresponding to walking activities, the type of physical activity in which older adults engage the most) as an intervention for sarcopenia prevention/reversal has recently attracted attention [41]

As reviewed in previous sections, currently available evidence derived from observational and experimental research indicate that free-living activities such as walking may play a crucial role as modifiable factors in the modulation of muscle mass, strength and physical performance losses associated with ageing [24, 28, 31–33, 41, 49, 203].

Consequently, until proper prescription, generalized access to facilities and adherence to resistance exercise is achieved, effective sarcopenia prevention strategies should

include increased participation in free-living activities in the higher intensity continuum zone whenever possible, corresponding to moderate-to-vigorous intensity range. Examples of this activities include fast walking, cycling or swimming [204]. In addition, lighter physical activities as a means of sedentary activities (sedentary breaks) reduction might also benefit musculoskeletal health through indirect influences on mechanisms involved in the pathogenesis of sarcopenia such as increased adiposity, insulin resistance and low-grade non-functional inflammation [37, 182]. Additionally, the incorporation of protein supplementation to the physical activity/exercise intervention plan might have a synergistic effect, especially for those with nutritional deficits [16, 205, 206].

In view of the lack of guidelines for sarcopenia prevention and management through exercise, the World Health Organization physical activity recommendations for older adults together with the fulfillment of current protein intake recommendations (1.0-1.2 g protein/kg body weight/day)* might be useful as temporary approaches for sarcopenia prevention [101, 190].

*An exception concerns older people with severe kidney disease (eGFR<30 mL/min/1.73m^2) and not in dialysis treatment should limit protein intake

Future research

Although robust emerging evidence seems to support the pivotal role of physical behaviors as healthy ageing determinants, there are still several easily identifiable gaps in knowledge amenable to be addressed by coming research.

There is substantial uncertainty regarding the mutual exclusivity of sedentary behaviors and physical activity, or in other words, if increased levels of physical activity might offset high volumes of sedentary behavior. Some previous research has shown that moderate-to-vigorous physical activity might attenuate, but not fully eliminate the negative effect of sedentary behaviors on health [88, 161, 207], but further research is needed for exploring causal links.

Moreover, the potential of different physical behaviors accumulation patterns besides total volume in different physical behaviors is gaining recognition as a modulator of the effects of physical behaviors on health. Whether physical activity or sedentary behavior health effects depend on the duration of the periods in these intensity bands or not remains a matter of discussion. Whereas physical activity public health recommendations emphasize the need of 10-minute minimum bout duration of moderate-to-vigorous physical activity to gain health benefits, such statement lacks a robust evidence basis. In fact, recent research has pointed to similar mortality risk reductions and cardiometabolic benefits obtained from shorter sustained intensity bouts [63, 106]. Moreover, it has been suggested that accumulation of sedentary behavior in longer time intervals might be more harmful than same total amounts scattered in shorter periods along the day. To address these advancements in the understanding of physical behaviors and health associations, new physical behavior metrics have recently been operationalized (i.e., the number of sedentary breaks, mean life duration of sedentary behavior bouts), but its incorporation as exposure variables remains scarce [96, 147, 208].

Despite accelerometers are increasingly being incorporated into large population-based studies, the validity of the observations substantially relies on the data-handling processes. One of the most relevant issues is the use of one-size-fits-all cut-points for intensity categorization, which might inevitably distort estimates and associations with health-outcomes. Physical behaviors studies using accelerometers should incorporate age- or disease-group specific intensity cut-points to minimize the inherent inaccuracy

when using reference cut-points to individual physical behaviors estimation, given to different in energy cost of activities between subjects.

In addition, the use of physical activity and sedentary behaviors evolution as the exposure variable has been residual in populations of older adults. Given the dynamic nature of these behaviors among older adults, researchers should try to address this fact and include physical behaviors evolution as independent variable. Although data-driven methods do assist in trajectories identification and might be more informative than crude prospective categorical changes, they have been barely incorporated to physical behaviors epidemiology, which limits comparability between studies. A recently designed evolution of group-based trajectory modelling (Group-Based Multi-Trajectory Modelling) might be highly promising, given that it allows to identify subjects following similar trajectories in two or more variables, hypothetically allowing for the joint study of physical activity (i.e. moderate-to-vigorous physical activity) and sedentary behavior [209].

Sarcopenia research field has been ubiquitously hampered by the absence of a consensus definition, that has leaded to substantial heterogeneity in sarcopenia operationalizations among studies. Therefore, between-studies inferences comparability is limited due to potential differences in the phenotypes captured by different definitions. Current efforts are being made to generate sarcopenia definition that maximize adverse outcome risk-profiling [210]. Consequently, future research should attempt to adhere to the use of a valid and contrasted consensual sarcopenia definition (preferably using standardized population-specific determinant values), with the aim of eliminating current heterogeneity and allow for more robust and uniform inferences derived from the studies.

With regards to the epidemiological association between physical behaviors and sarcopenia, the deepening in the association between patterns of sedentary behavior accumulation and musculoskeletal health might be specially appealing, given that long-lasting sitting periods avoidance in such a sedentary population might have promising effects, but has not be confirmed by well-powered research [30, 35].

Lastly, of interest are also the associations between physical behaviors and sarcopenic obesity, a more burdensome condition that pool detrimental consequences of sarcopenia

and obesity, two overlapping conditions that might specially benefit from physical activity enhancements.

In the pursuit of expanding insights into the features of exercise programs (intensity of physical activity, duration, frequency and volume) tailored at influencing specific health processes in older adults with particular features (age, comorbidities, functional status, medications…), faster and cheaper epidemiological evidence might pave the way and assist in the generation of experimental research hypothesis [211].

However, laboratory-based and clinical experimental research is needed to contrast hypothesis generated through observational studies, with the aim of providing healthcare policymakers, professionals and users with contrasted therapeutic options. Although resistance exercise training has shown promising results for sarcopenia management given its effects on its individual components in healthy older adults, little is known regarding the optimal features of programs or its potential combination with other exercise types or diet/supplement-based nutritional interventions on functional outcomes in at-risk older adults [196, 198, 200, 205, 212].

Importantly, there is a lack of studies with long intervention times (>12 weeks) in older adults with sarcopenia, which in turn precludes the ascertainment of the effectiveness of such interventions for sarcopenia-related adverse outcomes prevention. Given that such events (falls, fractures and disability onset) require long periods to occur [124, 125], randomized clinical trials with long-lasting interventions and follow-up times are needed, in order to clarify the effectiveness of continued exercise on sarcopenia secondary prevention. Currently the effectiveness of exercise is assumed from the translation of results of studies investigating the effects of long-lasting resistance and multicomponent exercise [213] programs in cohorts of older adults without a sarcopenia diagnosis [214, 215]. Despite biological plausibility-and practically common sense-may allow for translation of these changes to reduced number of falls and functional decline avoidance in older adults with prevalent sarcopenia, future research should confirm such assumptions [156, 216].

Home-based exercise programs have been postulated as possible solutions to overcome one of the barriers to exercise adherence among older adults, the need to commute to the exercise facilities. Currently, some options exist [217, 218], but the effectiveness of these programs should be ascertained in sarcopenic populations by experimental research.

In addition, although biologically plausible, described molecular mechanisms underlying increasing physical activity and sedentary behavior reductions benefits on health remain obscure and should be subject of further investigation [160]. Since the understanding of intracellular/extracellular processes underlying sarcopenia development and adaptations to exercise is poor, research incorporating recent genomic, metabolomic, transcriptomics, and proteomics technologies would be of high interest in order to identify potential novel molecular targets of interventions aimed at promoting healthy ageing [219, 220].

General Discussion References

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Conclusions-Conclusiones

Conclusions

The conclusions that can be drawn from this thesis are listed below.

- Moderate-to-vigorous physical activity levels are associated with sarcopenia rates and better performance in its determinants in an older adult population
- Intensity might be a relevant modulator of the association between physical activity and health
- Sedentary behavior and light physical activity might not be associated independently with sarcopenia or its determinants
- Prospectively maintaining physical activity during late life might be protective against important adverse events
- Increasing physical activity from very low baseline levels might be protective against functional decline, indicating benefits from physical activity even in the less active older adults
- Increased spontaneous free-living physical activity might be a powerful strategy for age-related intrinsic capacity loss attenuation given low adherence to the well-recognized structured physical exercise
- The prevention and attenuation of functional decline through physical activity might have broad clinical, economic, public health implications in the context of a burgeoning older adult population worldwide.

Conclusiones

De la presente tesis doctoral se extraen las siguientes conclusiones:

- Los niveles de actividad física espontánea de intensidad de moderada a vigorosa se asocian negativamente con la probabilidad de presentar sarcopenia y con mejores valores en sus determinantes en una muestra de adultos mayores
- La intensidad de la actividad física espontánea aparece como un determinante crucial en la asociación entre ésta y la salud
- Los niveles de sedentarismo y la actividad física espontánea de intensidad ligera podrían no asociarse independientemente con la sarcopenia y sus determinantes.
- El mantenimiento de los niveles de la actividad física a edades avanzadas podría conferir protección frente a eventos adversos
- El aumento de la actividad física desde los niveles más bajos a edades avanzadas podría ser un factor protector contra el declive funcional, lo que podría indicar la obtención de beneficios a partir de la actividad física incluso en los adultos mayores más inactivos
- Dada la baja adherencia y el limitado acceso a programas de ejercicio físico estructurado entre los adultos mayores, el mantenimiento o aumento de los niveles de actividad física espontánea, en forma de volumen e intensidad, podría constituir una potente estrategia en la prevención/atenuación de la pérdida de capacidad intrínseca durante el envejecimiento.
- La prevención del declive funcional a través de la actividad física en el adulto mayor podría tener importantes implicaciones en las esferas clínica, económica y de salud pública, en el contexto del envejecimiento de la población a nivel global.

Publications-Publicaciones