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Advancements in the assessment of physical function in older persons: methodologies, devices, and metrics

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A Matilde,

con l'augurio che nella sua vita
le domande siano sempre più numerose delle risposte

Riassunto della tesi in italiano

Le transizioni demografiche ed epidemiologiche avvenute nell'ultimo secolo pongono nuove sfide cliniche, di ricerca e di sanità pubblica. In particolare, l'aumento della popolazione anziana e la rilevanza assunta dalla disabilità, dalla fragilità e dall'accumulo di patologie croniche, impongono la personalizzazione dei percorsi diagnostico-terapeutici e la precoce identificazione delle persone ad elevato rischio di morte o di altri eventi negativi (ospedalizzazioni, istituzionalizzazioni, riacutizzazioni di malattie croniche). Lo studio della funzione fisica riveste un ruolo fondamentale nella valutazione globale della salute della persona anziana ed è indispensabile per l'impostazione di un modello di cura focalizzato sulla persona ed il superamento del modello centrato sulla cura di singole patologie acute.

Gli sviluppi tecnologici degli ultimi decenni hanno reso facilmente disponibili numerosi dispositivi utili alla valutazione strumentale della funzione fisica. L'utilizzo di questi strumenti permette di analizzare la funzione fisica delle persone anziane al domicilio o nel proprio ambiente, senza la necessità di ricorrere a valutazioni anamnestiche o basate su test ambulatoriali. I nuovi sensori, inoltre, permettono di limitare la variabilità inter- ed intra-operatore che caratterizza l'attuale valutazione clinica della funzione. Da ultimo, questi strumenti consentono una stima quantitativa di aspetti della funzione che spesso vengono solo qualitativamente descritti (come la variabilità del passo durante il cammino, la simmetria dell'andatura o i disturbi dell'equilibrio). Al fine di ottenere un'implementazione clinica su larga scala della valutazione strumentale della funzione fisica, però, è necessario superare le sfide tecniche e metodologiche poste da questi dispositivi.

Questa tesi di dottorato è composta da tre studi. Il primo consiste in una revisione sistematica della letteratura volta ad indagare l'attuale utilizzo di tecnologie per la valutazione strumentale della funzione fisica in persone affette da broncopneumopatia cronica ostruttiva. Lo studio mostra come, nel campo della ricerca, siano già utilizzati numerosi dispositivi per la valutazione strumentale della funzione fisica. Inoltre, sottolinea come l'eterogeneità dei protocolli di valutazione della funzione, delle caratteristiche tecniche dei dispositivi e dei parametri analizzati rendano difficile la generalizzazione dei risultati e l'implementazione su larga scala di questi dispositivi. Il secondo studio ha lo scopo di investigare l'associazione tra misure obiettive di attività fisica, ottenute tramite un accelerometro triassiale, e la fragilità, valutata tramite un frailty index validato, in un grande studio di popolazione svedese. Inoltre, viene proposto (ed internamente validato) un modello volto all'identificazione delle persone affette da fragilità sfruttando esclusivamente misure accelerometriche. Il frailty index si è mostrato linearmente associato a numerose misure di volume, intensità e frammentazione dell'attività fisica. Queste misure, quando utilizzate in un modello di regressione logistica penalizzata "ridge", permettono di identificare le persone affette da fragilità con una buona capacità discriminativa. L'ultimo studio esplora le differenze in termini di "fluidità del movimento" ("movement smoothness"), analizzata tramite una misura validata ("Spectral Arc Length"), in diversi momenti del cammino, tra persone ad alto e a basso rischio di caduta. I partecipanti a questo studio caso-controllo sono stati sottoposti ad un turn-test (composto da un percorso rettilineo e da una curva di 180°) mentre indossavano un dispositivo di misura inerziale. Lo studio, per quanto fortemente limitato dalla numerosità campionaria, suggerisce che l'andatura delle persone ad elevato rischio di caduta sia meno fluida rispetto a quella dei controlli, in particolare durante la modifica della direzione ("turn phase").

Una profonda collaborazione tra professionisti sanitari e ingegneri sarà probabilmente uno degli elementi più importanti per promuovere la valutazione strumentale della funzione fisica e la diffusione del modello di cura centrato sulla persona nel prossimo futuro.

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Introduction

Aging population: the demographic and epidemiological transitions

Worldwide population considerably increased between 1960 and 2020 (from 3.0 to 7.75 billion)[1]. In the same period, the share of older persons worldwide grew from 5.0% to 8.9%[2–4], expanding the absolute number of people older than 65 years old by more than half a billion. In Europe and North America, the number of older persons is expected to increase by more than the 45% between 2019 and 2050 (from 200 to 296 million). The same figure is projected to be over 200% for Northern Africa and Western Asia[5]. Furthermore, it has been estimated that the number of persons 80+ will be over 400 million worldwide by 2050.

This demographic shift is the result of a combination of lower fertility rates and advancements in biomedical knowledge, prevention, education, and public health. However, such conditions not only modified the demographical asset of the world, but radically changed the epidemiological one. Indeed, acute, infective diseases have given way to non-communicable diseases (NCDs) as primary causes of death and morbidity[6]. Although NCDs are generally controlled by available treatments, they are seldom curable. For this reason, diseases tend to become chronic and to accumulate, leading to a condition known as multimorbidity[7,8]. Furthermore, the physiological and pathological (due to the accumulation of diseases and life-long exposure to risk factors) aging processes impair the functional reserve of several organs and systems[9]. This impairment might hamper the adaptability of the whole organism to changes in the external or internal environment. Such condition results in an increased vulnerability to stressors (acute diseases, trauma, modifications in the medication regimes, widowhood, and so on) and in an augmented risk of developing poor health-related outcomes, configuring a state named frailty[10,11]. Frailty has been operationalized with different methodology in the last decades: the "frailty phenotype" and the "deficit accumulation" models gained the highest success. Shortly, the frailty phenotype is based on the identification of 5 features that has been shown to be associated with poor health-related outcomes (namely, low walking speed, low grip strength, unintentional weight loss, exhaustion, and reduced physical activity)[12]. The deficit accumulation model is based on the idea that health issues ("deficits") tend to accumulate with age: by summing all deficits (chronic conditions, physical and cognitive impairments, pathological results from bioumoral or instrumental tests, and so on) exhibited by a person, is possible to estimate frailty[13]. Lastly, once global or system-specific impairments exceed a certain threshold, the ability to perform specific functions can be strongly weakened and a condition of functional decline and disability might arise[9,14,15].

Multimorbidity, frailty, and disability contribute (together with the life-long exposure to environmental, social, and psychological factors) to the vast heterogeneity in terms of health that can be observed among older persons[16–18]. Individuals with the same chronological age might exhibit different risks of developing poor outcomes, therapeutic and care needs, cognitive and physical functions, and prognosis. The personalization of the diagnostic- and therapeutic-plan for older persons is therefore pivotal to offer the most effective care in the most efficient way. In the last decades, it has been proposed to shift from a "disease-centred" model to a "patient-centred" one[19]. Indeed, the application of specific-disease guidelines and protocols is complex in "biologically" older persons, due to the high number of health conditions and the high probability of overdiagnosis and overtreatment. Several studies, in addition, showed that the application of disease-specific guidelines to persons affected by multimorbidity expose patients to significant drug-drug and drug-disease interactions[20,21]. Furthermore, older persons affected by multimorbidity, frailty, or disability are often excluded from the randomized clinical trials upon which current guidelines are typically based on, hampering their generalizability to this stratum of the population[22].

Understanding health in older adults: function as a key component

To seize the health of older persons using a sum of single-disease models is complicated and potentially harmful. To inform clinical decisions and public health policies, a multidimensional approach to the

health of older persons is needed[18,19,23]. This latter approach offers two main advantages. First, by measuring health across different dimensions (physical, psychological, cognitive, and social, for example) potential harms and benefits of any given diagnostic approach, therapy, or policy can be realistically evaluated and possible issues can be addressed. For example, a person affected by mild cognitive impairment and living alone may not be able to follow a complex therapeutic regimen based on several drugs; by minimizing the drug therapy (for example, taking into account the needs, the expectations, and the risks of developing poor outcomes), by suggesting assistive devices (i.e.: weekly dispensers), and by informing the patient about possible formal care programs, it is possible to provide a more tailored care that is likely to be more effective and efficient. In second place, information other from single-disease severity may offer summary metrics of health that can be used to guide both care pathways and public health policies development. Mobility, the ability to freely move around, assessed by the evaluation of walking speed has been proven to be a reliable and affordable tool able to accurately predict the development of poor health-related outcomes[24]. Walking speed has also been shown to correctly stratify mortality risk among persons affected by multimorbidity or by specific clusters of chronic conditions (such as neuropsychiatric or cardiovascular diseases)[25]. The predictive capacity based on mobility evaluation (and physical function in general) is well established, although the causes of such strong association with poor health outcomes are still debated. To be able to freely move, a sophisticated integration of multiple organ-systems is required: central and peripheral nervous, osteo-muscular, cardiovascular, and respiratory systems are all involved in the generation of walking patterns. However, mobility (as other physical functions) is also often characterized by redundancy[26]; in fact, the ability to move is preserved even when one or more of the involved systems are impaired. For example, persons affected by severe monolateral knee osteo-arthritis are able to walk, even though the resulting gait pattern is less efficient from a biomechanical and energetic point of view. The measurement of the performance in the execution of a function is likely to bring quantitative information about the impairments of the system(s), although the identification of the deficient system(s) requires further evaluations. Additionally, mobility has been graded as one of most valuable resources by older persons themselves, thus the evaluation of function may also help to assess the self-perceived quality of life[27].

New technologies: opportunities and challenges in clinical practice, public health, and research

Novel advancements in technology during the last decades made devices suitable for instrumental assessment of mobility increasingly available. Marker-less motion capture systems, wearable inertial measurement units embedding accelerometers and gyroscopes, instrumented mats or insoles, and force plates are among some of the devices that can be used for the assessment of physical function; all these instruments are fairly affordable from an economical point view, could be classified as medical devices for their use in clinical practice, and are non-invasive, i.e., they can be used maintaining the ecology of the context. Instrumental evaluation of physical function indeed offers some advantages in comparison with the clinical one. Firstly, using wearable non-invasive instruments, health professionals and researchers gain access to objective measurements of real-life physical functioning of older persons[28]. Indeed, the contemporary evaluation of physical function is based either on a clinical assessment using pre-specified tests (e.g.: walking on a 4-meter straight path) or on a collection of data through interviews and questionnaires. Small accelerometer-based activity tracking devices worn for a week, for example, can be used to estimate the total amount and the intensity of physical activity performed by a person in his/her environment. In second place, such instruments may allow to gather an objective measurement of several aspects that are often missed during the ambulatory evaluation of physical function[29]. For example, the Short Physical Performance Battery (SPPB) scores balance, gait speed and strength; however, information about the presence of retropulsion during the balance test, asymmetry of gait during the walking test, or difficulties during the leg extension phase in the chair stands test is either lost or only qualitatively described. Several instruments can help to quantitatively measure movement used to adjust balance during balance tests, spatiotemporal parameters of gait (such as left or right single-support phase duration or stride length), or proxies of lower limb power during chair stands. Sensors and devices are also likely to offer greater reliability in the measurement, in comparison to

routine clinical assessment; inter- and intra-operator variability are likely to be reduced by the implementation of such technologies[30,31]. As consequence, the instrumental evaluation of physical function is indeed able to offer new possibilities for conducting longitudinal assessments, as it would make easier to routinely and reliably collect data.

However, new challenges arise when these instruments are implemented in clinical and research practice. In first place, the number of available technological solutions is relatively high (and is increasing) and each device has its own advantages and disadvantages concerning both the technology itself and the application context; technical characteristics (such as sampling frequency, accuracy, resolution, etc.), size, cost, usability (including wearability, for instance) and acceptability by patients/study participants must be taken into consideration when choosing a specific system, together with the application field and quantification objectives[32]. Furthermore, different devices may return slightly different results even when employed to obtain the same metric from the evaluation of the same function because of their technical characteristics (e.g., accelerometer vs optical motion capture)[31]. For wearable devices, the location where the sensor is worn is another important factor that can impact on the output obtained from the sensor, since report information that can vary with respect to the motion realized; the sensitivity of each position with respect to the developed task can indeed be very different. In addition, the analysis of data derived from such devices poses significant technical and methodological challenges; the amount of data produced by each device depends upon its sampling frequency and the number of information retrieved (e.g., number of leads, channels, axes, etc.). For example, a simple tri-axial accelerometer with a sampling frequency of 20 Hz produces 60 data points per second per subject; therefore, monitoring a single patient for 24 hours/day for a week produces almost 3.6 x 10^7 data points that – working at 32 bits – correspond about 150 MB; therefore, the solutions for data storing, transferring, and processing should be carefully evaluated before the implementation of such devices in clinical and research practice (in particular, when applied to a significant number of patients/study participants). Moreover, the data retrieved from such instruments often need to be pre-processed prior to analysis; data filtering, de-noising, smoothing, and detrending are among the most commonly employed techniques, but their implementation significantly depends upon the aims, the study population, the device, and the function evaluated. Lastly, standardized or shared protocols for technology deployment, setup (including, for instance, position of the sensors), data pre-processing, and analysis are still lacking with respect to the context; an important heterogeneity can be found in the literature, making the generalizability of results and the clinical implementation of instrumental evaluation of physical function in clinical practice difficult.

An example of a wearable device for instrumental evaluation of mobility: the accelerometer

Accelerometers are among the most used instruments for non-invasive tracking of older persons' movement and activity and are mentioned or used in all the studies presented in this PhD thesis. Accelerometers are tools designed to measure acceleration (i.e.: the rate of change in velocity) of a body. In the simplest model, accelerometers are built linking a mass (m) to a spring that is attached to the accelerometer's case (**Figure 1A**). The spring is characterized by a constant factor k (i.e.: stiffness). Once a force F is applied, the mass m accelerates (**Figure 1B)**: force F is equal to mass m times acceleration (a). By Newton's law, F is equal to the elastic force Fs, which, in turn, is directly proportional to mass' displacement (x), corrected by factor k (**Figure 1C**). The acceleration is then estimated through the measurement of the mass position in consideration of the dynamic equilibrium, where the spring force is equal to the inertial one (as shown in **equation 1** and **2**).

$$ma = kx$$

Equation 1: m = mass, a = acceleration, k = spring stiffness, x = mass' displacement.

$$a = f(x)$$

Equation 2: acceleration is a function of mass' displacement.

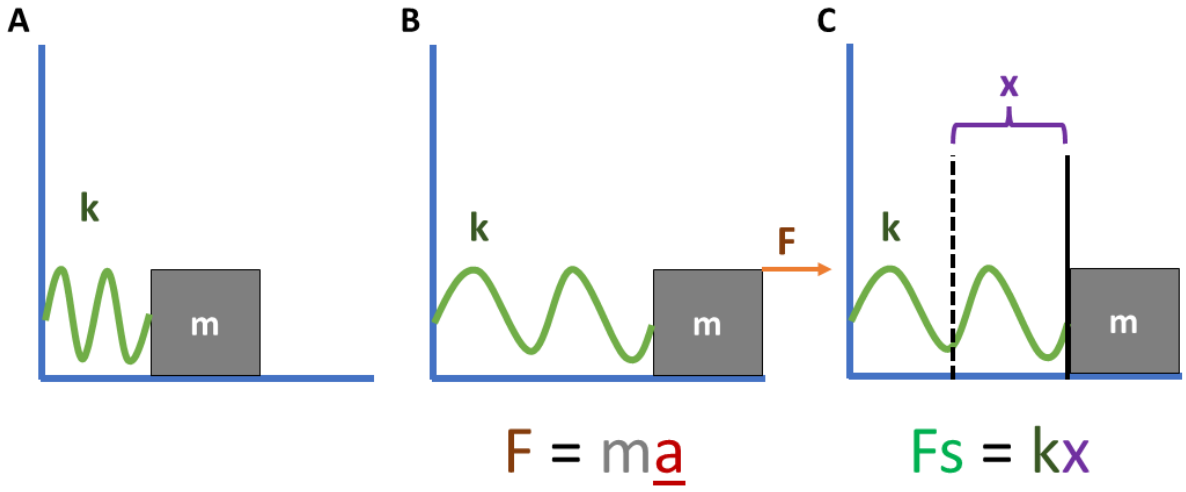

Figure 1: **A**: accelerometer at rest: a spring (green) is attached to the case (blue) and to a mass *m*. **B**: a force *F* is applied to the mass. **C**: the elastic force is equal to the mass's displacement (*x*) times spring's stiffness *k*.

In electronic devices, the mass' displacement *x* can be measured using different methods, including resistive, capacitive, or inductive techniques.

Considering the aforementioned functioning, some issues are worth mentioning in order to correctly interpret the outputs obtained from such devices. In first place, an accelerometer measures accelerations (both "static" and "dynamic") and not "movement" or "speed"; for example, an accelerometer resting in vertical position on a surface will always measure an acceleration (9.81 m/s^2) because of gravity. Furthermore, let's take into consideration the example of an object that, from a still position, is accelerated till a certain speed is reached. While moving in the same direction, the speed is decreased and then maintained constant for a certain amount of time. Lastly, the object is again decelerated till it stops. The output of the accelerometer (once cleaned from vibrations, noise, and the acceleration of gravity) will show a positive acceleration followed by the absence of any acceleration, a negative acceleration, absence of any acceleration and, lastly, another negative acceleration. Linking accelerometric signal to the performed movement is not a straightforward operation, in particular when the accelerometer is worn by a person who walk (a movement characterized by cyclic accelerations in different directions). In addition, these devices measure accelerations in their own instantaneous coordinates' frame, without using a fix set of coordinates; in other words, a tri-axial accelerometer will measure accelerations on three orthogonal axes according to its case, and not to the surrounding environment. A tri-axial accelerometer attached to the hip of a person who is walking will measure acceleration in the vertical, antero-posterior, and latero-lateral axes; however, these axes will not always correspond to the body reference frame of the subject. In fact, the axes will change their orientation following the leg's movements (similar to an inverted pendulum), as shown in **Figure 2**.

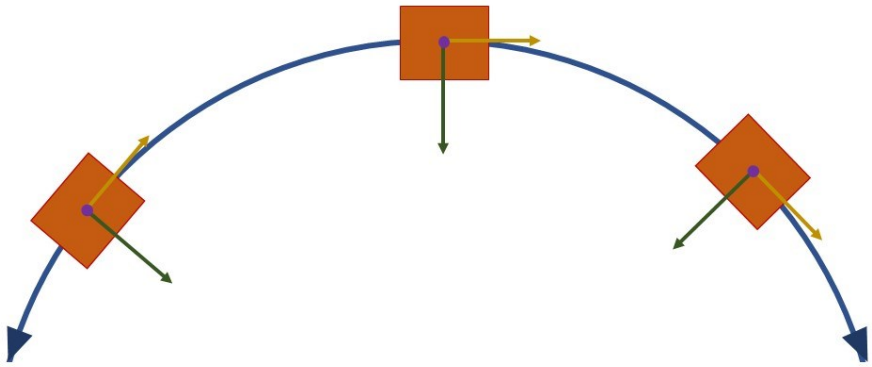

Figure 2: an accelerometer (orange) is attached to the hip a person who is walking. Accelerometers' axes (vertical – green, antero-posterior – yellow, and latero-lateral – purple), rotate relatively to the surrounding environment, following the inverted pendulum movement that characterizes gait.

These two considerations about the accelerometers' functioning are the main reasons why accelerometers alone are seldom used to precisely describe persons' movement. Indeed, to describe how a person (or better is centre of mass) moves in space using accelerometric data, acceleration (m/s^2) of his/her pelvis should be used to estimate velocity (m/s) – through integral analysis - and, in turn, speed should be used to estimate the linear displacement in space (m). Because of the relationship between the output of the accelerometer, the desired measure, and time, the presence of noise in the measurement and of small fluctuation in time may result in considerable imprecision in the estimation of movement in space. Furthermore, the direction of such movements should be estimated using the accelerations on different axes but, as described before, axes may change their orientation during movement itself and information about axes' orientation is lacking in simple accelerometers. To solve these problems, accelerometers are often combined with other sensors (i.e., magnetometers and gyroscopes) in instruments called "inertial measurement units" (IMU) that may be used to (more) precisely investigate human movement. IMUs can be combined in body area networks to obtain both joint kinematics and the estimation of "spatiotemporal parameters" of gait[31]. In the estimation of spatiotemporal parameters, meaningful moments of the gait cycle are identified from the signal. In particular, the heel-contact (HC) and toes-off (TO) moments are detected, either by inspection or using validated algorithms. Such moments allow to classify different segments of the IMU signal into phases of gait, such as leg swing and single or double leg support (for the right and left limb). The estimation of the time spent in each phase and of the distance covered (by integration of the accelerations retrieved from the IMU) allows the assessment of spatiotemporal parameters. Conversely, single accelerometers are mostly employed to collect data about physical activity for longer periods of time; considering accelerations beyond certain thresholds and on defined combination of axes, the number of steps made in certain amount of time (e.g., whole recording period, a week, a day, or a minute) can be estimated. This information can be used to calculate the total amount of physical activity performed by a person and, using some *a-priori* modelling, the caloric expenditure of such activity[33].

Study Abstracts

Study 1 - Technologies employed for the functional evaluation of persons affected by Chronic Obstructive Pulmonary Disease: a Systematic Review of the literature.

This study aimed to systematically review the technologies currently used to assess physical function in persons affected by COPD. In total, 24 studies were included. A variety of devices were used, such as wearable accelerometers, instrumented mattresses, motion capture and gait analysis systems, as well as surface electromyography and near-infrared spectroscopy. Gait was the most commonly assessed function, although evaluation protocols varied across studies (on treadmill, during the 6-minute walking test, straight walking on short paths). The parameters retrieved from the instrumental evaluation were heterogeneous: spatiotemporal parameters of gait, signal features (median, ranges, root mean squared, variance), simple activity counts (i.e.: number of steps) and measures of cadence were among the most evaluated metrics. A variety of devices, with different technical and economical characteristics, are currently employed in the instrumental evaluation of persons with COPD; however, small sample sizes and the lack of standardization in the protocols used for the functional evaluation hinder the implementation of instrumental assessment of physical function in current practice.

Study 2 - Frailty and objectively measured physical activity in older persons: results from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K)

Using data from a large Swedish population-based study, we aimed to investigate the association between frailty and objectively measured metrics of physical activity (PA) in older community-dwellers. Frailty was assessed using a validated frailty index, whereas several metrics of PA volume, intensity, fragmentation, and time spent in different positions (i.e.: sitting) were retrieved from tri-axial accelerometers worn by 656 persons for at least 4 days. Frailty was linearly associated with the majority of the PA metrics investigated. As secondary aim, we proposed a model (ridge-penalized logistic regression) able to identify older persons affected by severe or severe-to-moderate frailty exploiting only metrics derived from the accelerometers. In the internal validation subsample, both models exhibited good-to-optimal discriminative ability in the identification of persons with frailty.

Study 3 - Gait smoothness in persons with increased risk of falling: a pilot case-control study

In a small age-sex-matched case-control study conducted in Montichiari (Brescia, Italy), we investigated the role of movement smoothness in discriminating older persons at high and low risk of falling. In total, 10 participants (5 persons who reported an injurious fall in the previous 2 years and 5 controls) underwent a physical and cognitive evaluation (including short physical performance battery, frailty phenotype, mini-mental state examination, trail making test A). All physical tests were conducted while wearing an inertial measurement unit (IMU): movement smoothness was estimated by the spectral arc length (SPARC), a validated measure based on spectrum complexity of the acceleration signal retrieved by the IMU. Although strongly limited by the sample size, cases seemed to exhibit a significant worse movement smoothness during the turn phase of walking path, in comparison with controls. Movement smoothness measured in the straight phases of the same walking path seemed to be similar between cases and controls.

Study 1 - Technologies employed for the functional evaluation of persons affected by Chronic Obstructive Pulmonary Disease: a Systematic Review of the literature

Introduction

COPD is a chronic respiratory condition characterized by a high prevalence and a strong association with disability and mortality; it has been estimated that almost 10% of the worldwide population[34] is affected by this disease and that, in high-income Countries, COPD is the fourth leading cause of death[35].

COPD has been shown to be associated with older age, frailty[36], sarcopenia[37], multimorbidity[38], polypharmacy[39], cognitive impairment[40], depression[41], and disability[42]. For this reason, the clinical management of persons affected by COPD is often complex; these patients may be affected by other chronic conditions, may exhibit a low adherence to treatment, may be exposed at greater risk of hospitalization or institutionalization, and may report a variety of symptoms and symptoms' severity not always fully explained by air flow limitation's grade. Lastly, respiratory function has been also associated with decreased physical function even in absence of a severe reduction of respiratory and/or lower limb muscle strength, suggesting that the respiratory system and physical function may be linked by intricated and complex mechanisms[43]. It follows that those affected by COPD may represent an illustrative paradigm of persons who may benefit from personalized diagnostic- and therapeutic-pathways and patient-centred care.

Although the diagnosis of COPD is based on the identification of an airflow limitation that is not reversible (or only partially reversible) with bronchodilator[44], physical function tests are important for the evaluation of the severity of disease[45,46], the risk of exacerbation[47,48], and to quantify the impact of the disease on the quality of life of those affected[49]. Current guidelines, for example, highlight the role of objective exercise impairment measurement (e.g.: assessing the reduction of self-walked distance or during incremental exercise testing) as powerful indicator of general health status and mortality in persons with COPD, remaking the importance its assessment[44]. In theory, several devices may be used to investigate the physical functions that are typically evaluated in persons affected by COPD: gait, for example, is one of the most assessed functions, using the 6-minute walking test (6MWT), in this setting and a vast variety of sensors may be used for its instrumental evaluation (e.g.: wearable IMUs, instrumented mattresses, gait analysis laboratories, and so on). However, information about the devices, the metric obtained, and the tests implemented for the instrumental evaluation of physical function in persons with COPD, in the clinical and research settings, is lacking.

Therefore, in this study we aimed to systematically review the available literature about the implementation of technologies for the evaluation of physical function in persons with COPD.

Methods

Study selection and search strategy

We reviewed studies providing information about the instrumental evaluation of physical function in persons affected by COPD, regardless of study design. We included only studies that 1) addressed either a function (such as walking) or a physical function test (such as the 6MWT) (studies evaluating an isolated movement or characteristic - e.g.: hand-grip strength evaluated using a dynamometer- were excluded), 2) that reported quantitative measures derived from the instrumental assessment of physical function, and 3) that were conducted either in ambulatory or laboratory setting (e.g.: studies assessing physical activity using accelerometer worn at home for several day were excluded). This review was limited to articles in English or Italian, published between January 2001 and December 2020. The literature search was conducted in PubMed, Web of Science, Embase, and Scopus, adapting the same search query (available in the **supplementary material**). References and additional files from selected articles were checked to identify further studies eligible for inclusion. An ethical committee's approval was not needed for the conduction of this study.

Abstract screening, full-text screening, and data extraction

Two assessors independently screened articles' titles and abstracts, after duplicate exclusion. Conflicts were resolved via consensus. In case a consensus was not reached, a third assessor was included in the discussion. Full texts were screened and selected using the same procedure. An online application[50] was used to simplify the process of abstract and full-text screening. Study characteristics and information were independently extracted from selected papers by two assessors. Extracted data were then compared and possible inconsistencies were resolved.

Presentation of results

The selected studies were divided into two groups: the first one included those that employed technology-derived metrics to describe the functional characteristics of COPD participants, to compare healthy and COPD participants, or to investigate the association between physical function and other health-related outcomes. This group of studies was named "application studies". The second group of studies, including those articles aiming to evaluate the performance (e.g.: reliability, measurement error, precision, validity) of the instrumental evaluation of physical function, was named "validation studies".

Study quality assessment

We assessed the risk of bias for the validation studies included employing the COSMIN Risk of Bias tool[51]. The tools offer two different sets of criteria for studies' evaluation, according to their aim (reliability studies and measurement error studies). The worst-score-count method was applied to determine the risk of bias. The risk of bias was independently evaluated by the two reviewers: conflicts were resolved by the third assessor.

Results

A total of 8461 articles were retrieved from the literature search. Out of these, 24 were included in the present study (**Figure 3** depicts the selection flow-chart). A total of 21 articles were considered application studies, whereas 4 were defined validation studies. One study was included in both groups due to its double aim.

The application studies are listed in **Table 1**. The majority (N = 19) of the studies were observational and 16 aimed at comparing the functional characteristics of participants with COPD with those of persons without this condition (mostly, healthy controls). A recent COPD exacerbation was reported as an exclusion criterion in 9 studies whereas hypoxemia or chronic oxygen supplementation were considered as an exclusion criterion by 3 studies. The presence of comorbidities able to interfere with physical function tests was reported as exclusion criteria in the majority of studies (N = 16). Most studies (N = 16) reported that the diagnosis of COPD was made in accordance with GOLD guidelines.

Table 2 shows the general characteristics of the populations included in the application studies. The number of participants with COPD included ranged between 14 and 80, their mean age of ranged between 62.2 and 71.3 years old. The proportion of female participants was comprised between 0.0 and 52.9%. When reported, the mean ratio between the Forced Expiratory Volume in the first second and its predicted value (FEV1% pred) ranged between 0.37 and 0.58.

Eleven application studies employed a single device for the evaluation of physical function, whereas in the remaining papers, multiple instruments were used, as shown in **Table 3**. Accelerometers (either alone or in combination with other devices) were employed in five studies and force plates or instrumented mattress were used in eight papers. The employment of surface electro-myography (sEMG) was reported in five studies. Gait analysis systems, 3d motion captures systems, or high-speed cameras were employed in seven studies, and two studies reported the utilization of Near-Infrared Spectroscopy (NIRS). Walking was the most commonly assessed function in application studies (15 articles). The other application studies evaluated a variety of tests and functions: 6-minute step test, pegboard and ring test, balance and perturbation tests, and domestic activities of daily living (simulated in the laboratory setting).

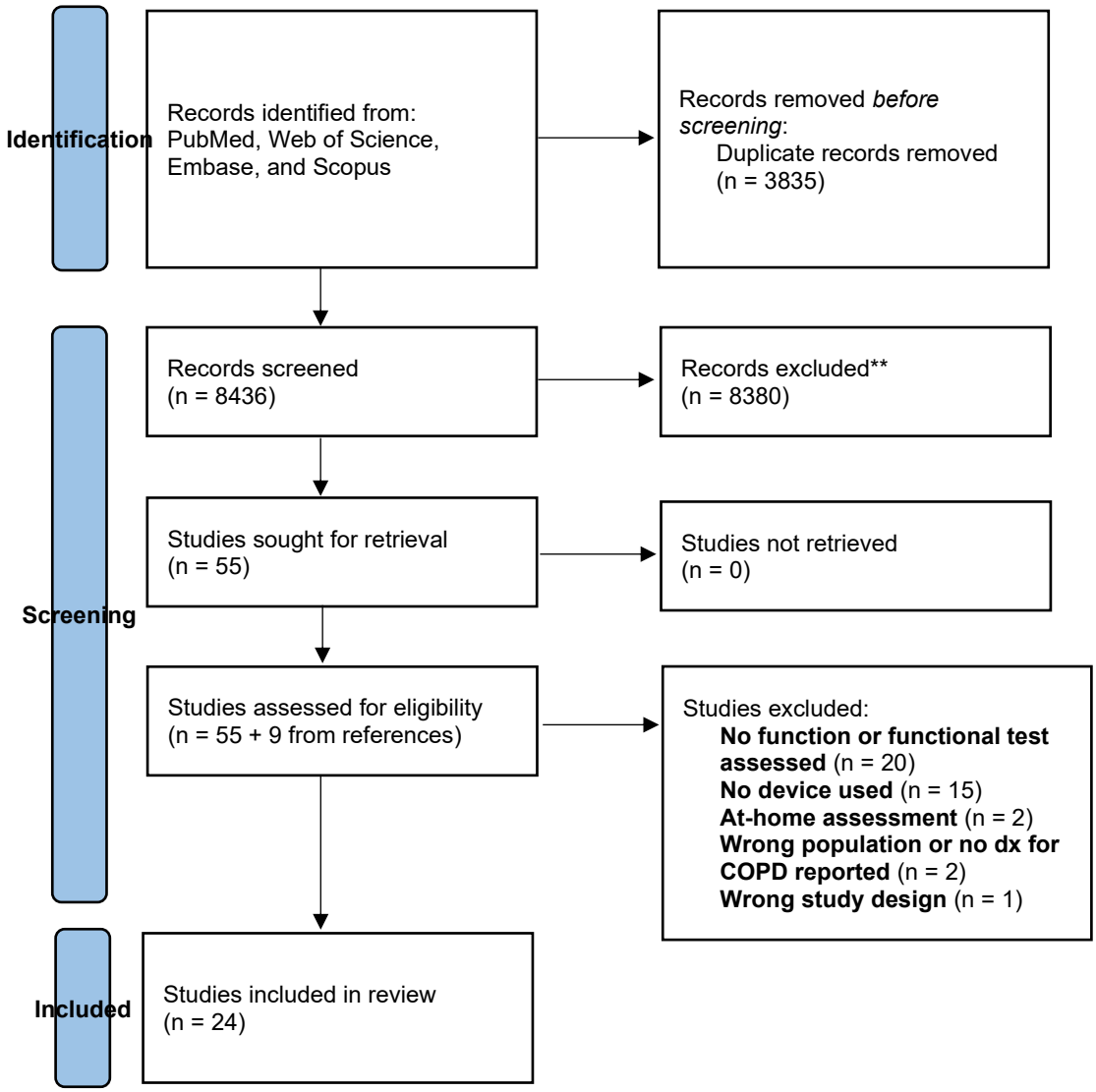

Figure 3: PRISMA 2020 flow diagram of the systematic review.

Table 1: Characteristics of the application studies

Study's first Author	*Year*	*Country*	*Study design*	*Exclusion criteria*	*Study population*	*COPD diagnosis*
Annegarn[52]	2012	the Netherlands	Cross-sectional	Exacerbation < 4 weeks, use of rollator, not able to complete 6MWT	Mixed: - COPD: outpatients recruited during a pre-rehabilitation assessment - Healthy subjects from previous trials conducted in the same centre	according to GOLD
Beauchamp[53]	2012	Canada	Cross-sectional	Inability to communicate, use of medications that may have increased the risk of falls, conditions that limited mobility	Mixed: - COPD: outpatients - Healthy age-sex-matched controls	according to GOLD
Canuto[54]	2010	Brazil	Cross-sectional	Exacerbation < 4 weeks, comorbidities that are contraindicated to physical therapy assessment	- COPD: outpatients	Clinical and spirometric (FEV1 < 50%)
Dos Reis[55]	2020	Brazil	Cross-sectional	Exacerbation < 2 months, conditions that prevent from performing the experimental protocols	Mixed: - COPD: outpatients - Healthy subjects	according to GOLD
Fallahtafti[56]	2020	USA	Cross-sectional	Injury or surgery affecting mobility and/or a diagnosis of neurological, muscoloskeletal, cardiovascular diseases or other pulmonary disorders	Mixed: - COPD: outpatients - Healthy subjects from general population	according to GOLD
Gloeckl[57]	2017	Germany	Randomized Clinical Trial (3-week pulmonary rehabilitation protocol)	Major surgery, bone fracture or deep vein thrombosis, arterial aneurysm, exacerbation < 4 weeks, conditions that prevented the completion of the protocol	Inpatients with COPD stage III or IV (GOLD)	according to GOLD
Iwakura[58]	2019	Japan	Cross-sectional	Diagnosis of dementia or other mental disorders, inability to communicate, use of any walking aid, use of medication(s), conditions that limit mobility, long-term oxygen therapy, exacerbation < 3 months	Mixed: - COPD: outpatients - Healthy subjects: age-matched, from local community centre	according to GOLD
Janssens[59]	2014	Belgium	Cross-sectional	Balance problems, spinal surgery, lower limb, muscoloskeletal problems	Mixed: - COPD: outpatients - healthy subjects	Unspecified

Liu[60]	2019	the Netherlands	Cross-sectional	Other lung diseases, neuromuscolar or orthopaedics problem affecting the gait, walking aid usage, need for supplemental oxygen	Outpatients referred for a pulmonary rehabilitation program in a specialized rehabilitation centre	according to GOLD
Liu[61]	2020	USA	Cross-sectional	History of injury or disease that affected their mobility or other comorbidities that may affect the musculoskeletal, neurological, pulmonary or cardiovascular systems	Mixed: - COPD: outpatients recruited from a medical centre and a veterans' affairs healthcare centre - healthy subjects from the community	according to GOLD
Liu[62]	2017	the Netherlands	Cross-sectional	Walking aids, chronic oxygen therapy, comorbidities affecting walking patterns, other lung diseases	Mixed: -COPD: outpatients referred for a pulmonary rehabilitation program in a specialized rehabilitation centre - Healthy subjects from previous trials conducted in the same centre	according to GOLD
Marquis[63]	2009	Canada	Cross-sectional	PaO2 < 60 mmHg at rest	Mixed: - COPD: outpatients - Healthy sedentary subjects	FEV1 % pred < 60 and FEV1/FVC < 70% and current or past smoking history
McCamley[64]	2017	USA	Cross-sectional	Co-morbidities affecting gait	Mixed: - COPD: outpatients from the pulmonary clinical studies unit of university - Healthy elderly - bilateral peripheral artery disease (Fontaine II): from medical centres	according to GOLD
Meijer[65]	2014	the Netherlands	Cross-sectional	Exacerbation < 4 weeks, conditions that could impair physical activities in daily life	Mixed: - COPD: outpatients - healthy subjects	according to GOLD
Morlino[66]	2017	Italy	Cross-sectional	Drug known to affect attention or sensory-motor function, diabetes mellitus	Mixed: - COPD: outpatients - healthy subjects (age-sex matched)	according to GOLD

Munari[67]	2020	Brazil	Cross-sectional	Diseases that could prevent the performance of the evaluation, COPD exacerbation during the protocol, smoking cessation < 6 months, participation to pulmonary rehab protocol < 6 months	- COPD: outpatients	according to GOLD
Rutkowski[68]	2014	Poland	Cross-sectional	Not listed	Mixed: -COPD: inpatients from specialist hospital - healthy individuals	Clinical and spirometric diagnoses, posed by physician
Terui[69]	2018	Japan	Cross-sectional	Walking with aids (canes), comorbidities that impaired behaviour, not able to understand the purpose of the experiment	Mixed: - COPD: outpatients, who previously undergone pulmonary rehabilitation -Healthy individuals	according to GOLD
Vaes[70]	2012	the Netherlands	Randomized crossover study	6-minute walking distance > 500 m, exacerbation < 4 weeks, comorbidities	- COPD: outpatients, recruited during pre-rehabilitation assessment	Clinical and spirometric diagnosis
Yentes[71]	2015	USA	Cross-sectional	Back or lower extremity injury/surgery affecting mobility or other process limiting the ability to walk, including neurological disease or impairments	Mixed -COPD outpatients recruited from local hospitals - healthy subjects: matched for age, height, and weight	according to GOLD
Yentes[72]	2017	USA	Cross-sectional	Injury or disease affecting mobility or processes limiting ability to walk. Conditions that impact on the ability to walk. Need for supplemental oxygen. Exacerbation < 4 months	Mixed - COPD outpatients recruited from outpatients clinics - Healthy subjects	according to GOLD

Table 2: Characteristics of the study populations investigated in application studies.

Study's first Author	*Year*	*COPD subjects N (%)*	*Age mean (SD)*	*Female %*	*Spirometric characteristics*
Annegarn	2012	79 (76.7)	64.3 (8.9)	40.5	Mean (SD) FEV1 % pred = 53.5 (18.7) GOLD 1 = 10.1% GOLD 2 = 45.6% GOLD 3 = 35.4% GOLD 4 = 8.9%
Beauchamp	2012	37 (64.9)	71 .0 (7.0)	54	Mean(SD) FEV1%pred = 39.4 (16.3) FEV1/FVC = 40.5 (15.1) On oxygen = 35%
Canuto	2010	14 (100)	68.9 (4.6)	NA	Mean (SD) FEV1 % pred = 39.4 (9.3)
Dos Reis	2020	30 (46.9)	68.0 (7.6)	33.3	Mean (SD) FEV1 % pred = 42.1 (16.4) FEV1/FVC = 0.55 (0.11) FVC = 2.1 (0.7)
Fallahtafti	2020	17 (42.5)	64.3 (7.6)	52.9	Mean (SD) FEV1/FVC = 55.1 (13.7)
Gloeckl	2017	74 (100)	64.0 (8.5)	32.5	Mean (SD) FEV1 % pred = 35.1 (10.1)
Iwakura	2019	34 (68.0)	71 (8.0)	0	Mean (SD) FEV1 % pred = 57.0 (28.0) GOLD 1 = 23.5% GOLD 2 = 29.4% GOLD 3 = 29.4% GOLD 4 = 17.7%
Janssens	2014	18 (50)	65 (7.0)	33.0	Mean (SD) FEV1 % pred = 51.0 (19.0) FEV1/FVC = 45.0 (13.0)
Liu	2019	44 (100)	62.2 (7.5)	43.2	Mean (SD) FEV1 % pred = 55.88 (19.73) FEV1/FVC = 0.42 (0.12) GOLD 1 = 13.6% GOLD 2 = 40.9% GOLD 3 = 38.6% GOLD 4 = 6.8%
Liu	2020	22 (50)	62.7 (9.0)	40.9	Mean (SD) FEV1 % pred = 53.7 (18.5) FEV1/FVC = 0.55 (0.12) FVC =3.2 (1.1)
Liu	2017	80 (67.8)	62.3 (7.2)	40.0	Mean (SD) FEV1% pred = 55.8 (19.4) FEV1/FVC = 0.41 (0.11) GOLD 1 = 12.5% GOLD 2 = 43.8% GOLD 3 = 36.3% GOLD 4 = 7.5%
Marquis	2009	10 (47.6)	62.7 (5.6)	10	Mean (SD) FEV1 % pred = 37.0 (13.0) FEV1/FVC = 36.0 (9.0) FVC = 2.71 (0.82)
McCamley	2017	16(24)	63.8 (8.8)	NA	NA
Meijer	2014	18(54.5)	62.4 (8.1)	44.4	Mean (SD) FEV1 % pred = 50.1 (20.1) FVC = 3.40 (0.9)
Morlino	2017	40 (58.8)	70.7 (7.1)	27.5	Mean (SD) FEV1/FVC = 49.9 (14.9) FEV1 % pred = 50.2 (21.1)
Munari	2020	36 (100)	67.0 (7.0)	19.4	Mean (SD) FEV1/FVC = 0.46 (0.08) FEV1 % pred = 51.1 (13.6) FVC = 3.39 (0.71)

					GOLD 2 = 44.4% GOLD 3 = 52.8% GOLD 4 = 2.8% GOLD A = 33.3% GOLD B = 27.8% GOLD C = 8.3 % GOLD D = 30.5%
Rutkowski	2014	33 (40.7)	65.7 (10.4)	15.3	NA
Terui	2018	16 (38.1)	71.3 (9.2)	0.0	Mean (SD) FEV1 % pred = 58.4 (20.1) FEV1 / FVC = 51.0 (15.7) GOLD 1 = 18.7% GOLD 2 = 43.8% GOLD 3 = 37.5% GOLD 4 = 0.0%
Vaes	2012	21 (100)	64.2 (10.1)	47.6	Mean (SD) FEV 1 = 1.1 (0.3) FEV 1 % pred = 42.0 (15.0) FEV1 /FVC = 37.3 (10.2) GOLD 1 = 0.0% GOLD 2 = 14.2% GOLD 3 = 42.9% GOLD 4 = 42.9%
Yentes	2015	17	63,8 (8,55)	35.3	Mean (SD) FEV1/FVC = 0.51 (0.16) FEV1 % pred = 50.2 (21.0)
Yentes	2017	20 (50.0)	63,6 (9,7)	20	Mean (SD) FEV1/FVC = 0.52 (0.12) FEV 1 % pred = 54.3 (19.2)

Table 4 shows the parameters derived from the employment of each technology: accelerometers were used mainly to obtain information about activity intensity (i.e.: n. counts/unit of time) or volume (i.e.: total n. counts or steps), although some spatiotemporal parameters were inferred from accelerometric data (step length, step time, gait speed). Spatiotemporal parameters of gait were mainly obtained using instrumented mattress and gait analysis systems. Force plates were employed in a variety of test (among which sit-to-stand tests, perturbed balance test, and jump tests). The parameters obtained from such technologies were strongly related to the test performed: they ranged from duration of meaningful function segments (such as the time taken for standing from the sitting position) to inferred measures of muscle power. Surface EMGs and NIRSs were employed to investigate specific muscles' activation time, duration, signal intensity, or infer oxygen consumption during the execution of functional tests.

Four studies were included among the validation studies (**Table 5**). The number of participants affected by COPD ranged between 6 and 61 and their mean age ranged between 61.9 to 71 years. The proportion of female participants was comprised between 0.0 and 83.0%. Walking, evaluated using different test, was assessed by all validation studies.

As shown in **table 6**, the validation studies were heterogeneous in terms of technology employed and aim, ranging from mobile phone app to 3d motion analysis system and from validation against gold standard to test-retest reliability studies. The risk of bias in the validation studies, according to the COSMIN tool, was doubtful in 3 studies and inadequate in one study.

Table 3: devices employed and functions/parameters estimated in application studies.

Study's first Author	*Year*	*Device*	*Protocol for technology application*	*Functional test/function*	*Parameter(s)*	*Parameters' value(s)*
Annegarn	2012	Accelerometer (Minimod, McRoberts, The Hague, The Netherlands), 100 Hz sampling frequency	Accelerometer was attached to the trunk at the level of the sacrum	6MWT	Walking intensity, counts/min Cadence, strides/min Autocorrelation *Anterior-Posterior, % *AC-Vertical, % *AC-Mediolateral, %	Mean (SD) 8658 (2971) 57 (6) *79.0 (10.7) *84.2 (10.2) *63.2 (14.0)
Beauchamp	2012	Force plates (Advanced Medical Technology Inc): two plates in parallel + one (in front of the subject. sEMG (gastrocnemius, tibialis anterior): pre-amplified signal at 500 gain + amplification by 1000. Signal digitally filtered from 20-250 Hz with 2nd order dual pass Butterworth	Force plates were used to capture footfall during perturbations-evoked reactions. sEMG was recorded bilaterally	Perturbation-Evoked Reactions: subjects wore a harness with a cable attached posteriorly and were instructed to lean forward. Five perturbation trials were completed.	Foot-off time, ms Foot contact time, ms Swing time, ms Anticipatory postural adjustment (APA) duration, ms Integrated APA size, mm X ms	Mean (SD) 372 (78) 500 (89) 128 (28) 192 (52) 339 (253)
Canuto	2010	sEMG (analogical signals were amplified with 1000 gain. The signal was filtered with 10-500 Hz band-pass filter)	Electrodes positioned on the motor point of the rectus femoris, vastus lateralis, tibialis anterioris, and soleus during STS and 6MWT	6MWT and sit-to-stand (STS) test	STS muscle fatigue, AC (angular coefficient of medium frequency, degrees) 6MWT muscle fatigue, AC	Mean (SD) Initial; Final -11.6 (4.6); -18.3 (5.3) -11.9 (4.5); 14.5 (3.3)
Dos Reis	2020	sEMG (Myomonitor IV, DelSys, Boston, Massachusetts) at 2000 Hz NIRS (OXYMON MK III, Artinis Medical System, Elst, The Netherlands) at 250 Hz	Four muscle groups were assessed with EMG: sternocleidomastoid, intercostal muscles, anterior deltoid, and trapezius. EMG signal was obtained for 6 min while the	6-min pegboard and ring test	Root mean square, mV - intercostal muscles - sternocleidomastoid - trapezius - anterior deltoid Mean Frequency, Hz - intercostal muscles - sternocleidomastoid - trapezius - anterior deltoid	Ranges 0.0046; 0.0051 0.0029; 0.0044 0.0543; 0.0587 0.073; 0.0844 54.85; 57.27 84.48; 88.08 73.17; 75.67 67.68; 73.03

			subject was performing the 6PBRT. NIRS was placed on intercostal muscles and anterior deltoid muscles.		Oxyhaemoglobin, Δ[O2Hb] - intercostal muscles - anterior deltoid deoxyhaemoglobin, Δ[HHb] - intercostal muscles - anterior deltoid total haemoglobin, Δ[tHb] - intercostal muscles - anterior deltoid	 -0.266; 0.357 -6.306; -2.58 -0.189; 0.169 6.757; 9.73 -0.494; 0.262 0.938; 7.051
Fallahtafti	2020	Gait analysis (12-camera Raptor system, Motion Analysis Corp., Santa Rosa, CA, USA), using anteroposterior trajectory of retro-reflective marker attached to the right heel.	Retro-reflective spherical markers were attached bilaterally to lateral and medial metatarsophalangeal joint, base of the second toe, calcaneus, heel, lateral and medial malleoli, midshank, tibial tuberosity, lateral and medial knee joint centre, top of thigh, midthigh, greater trochanter, anterior and posterior superior iliac spine, and sacrum. Marker trajectories were analysed for the last four minutes of each trial.	Walking for 6 min on a treadmill at self-selected walking speed (SSWS) + 1 slow and 1 fast (-20% and +20% SSWS) walking trials	 Step width, m Step time, s Step length, m	Mean (SD) -20%SSWS; SSWS; +20%SSWS 0.09 (0.03); 0.09 (0.03); 0.02 (0.03) 0.84 (0.17); 0.71 (0.14); 0.69 (0.12) 0.42 (0.11); 0.45 (0.13); 0.52 (0.13)
Gloeckl	2017	Force platform (Leonardo Mechanograph®, Novotec Medical, Pforzheim, Germany) with 8 force sensors (800 Hz)	Postural balance and muscular power were assessed using the ground reaction force platform. The best test was used for analysis	Postural balance (Romberg, semitandem, one foot beside and behind the other, one-leg stance) Muscle power (two-legged jump).	 Romberg stance/eyes closed absolute path length (APL), mm Semi tandem stance/eyes closed, APL, mm	Mean (SD) Intervention; Controls 446 (231); 413 (273) 971 (457); 800 (364)

					Semi tandem stance/eyes open, APL, mm One-leg stance/eyes open, APL, mm Two-legged jump, peak W/kg body mass Two-legged jump, jump height, cm	382 (161); 349 (180) 898 (366); 780 (257) 23.1 (7.1); 25.5 (6.0) 21.2 (8.0); 24.8 (8.4)
Iwakura	2019	A tri-axial accelerometer system (Mimamori-gait system, LSI Medience Corporation, Japan)	The accelerometer was fixed to a belt around the level of the subject's third lumbar vertebra.	Ten-metre walk test (14 m)	 Gait speed, m·s−1 Step length, m Cadence, step·min−1 Walk ratio Acceleration magnitude, g Step time SD, s	Mean (SD) 1.09 (0.22) 0.60 (0.08) 109 (10) 5.53 (0.69) 0.23 (0.08) 0.03 (0.01)
Janssens	2014	Six-channel force plate (Bertec, OH, USA), sampled at 500 Hz, filtered using low-pass filter (5 Hz)	Participants sit barefoot on a stool on the force plate. The vision of the participants was occluded. Participants were asked to perform five STS movements.	5-STS	 Sit duration, s Sit-to-stand duration, s Stand duration, s Stand-to-sit duration, s	Mean (SD) 0.87 (0.36) 0.14 (0.08) 1.79 (0.78) 1.08 (0.88)
Liu	2019	3D motion analysis system with a dual-belt, instrumented treadmill and a virtual reality 180 degrees projection screen (GRAIL, Motekforce Link, Amsterdam, the Netherlands) with integrated force plates (Forcelink, 12 channels, sample frequency 1000 Hz)	Patients performed a GRAIL-based 6MWTs on a split-belt instrumented treadmill within a virtual reality environment.	6MWT, on treadmill	 Mean stride time, s Mean stride length, m Mean step width, m Sample entropy stride length Sample entropy step width	Pre-PR; Post- PR 1.02 (0.08); 1.00 (0.08) 1.45 (0.19); 1.48 (0.18) 0.18 (0.05); 0.18 (0.05) 1.17 (0.17); 1.21 (0.17) 1.43 (0.04); 1.43 (0.05)
Liu	2020	High-speed motion capture system (Motion Analysis, Santa Rosa, California) at 60 Hz	Retroreflective markers were placed on bony landmarks of the body, bilaterally. Subjects were asked	3,5 min at self-selected walking speed (SSWS), 1 trial at speeds 20% slow and 1 trial at speed 20% fast - on treadmill	Range of motion (degrees) *Ankle *Knee	Mean (SD) -20%SSWS; SSWS; +20%SSWS *26.2 (5.9); 26.5 (6.0); 27.7 (6.0) *57.1 (8.8); 57.6 (8.7); 59.1 (7.2)

			to walk on a treadmill a their SSWS. 3d marker data were used to calculate sagittal joint angle time series for the ankle, knee, and hip. The range of motion (RoM) was calculated for every right and left step from the joint angle time series		*Hip Sample entropy RoM *Ankle *Knee *Hip Local divergence exponent joint angle *Ankle *Knee *Hip	*35.5 (5.6); 36.5 (5.1); 37.9 (4.9) *1.53 (0.38); 1.46 (0.40); 1.57 (0.51) *1.70 (0.42); 1.62 (0.39); 1.58 (0.36) *1.72 (0.23); 1.66 (0.23); 1.64 (0.29) *1.14 (0.11); 1.12 (0.17); 1.11 (0.15) *1.46 (0.14); 1.39 (0.16); 1.40 (0.17) *1.73 (0.18); 1.66 (0.18); 1.66 (0.19)
Liu	2017	3D motion analysis system with a dual-belt, instrumented treadmill and a virtual reality 180 degrees projection screen (GRAIL, Motekforce Link, Amsterdam, the Netherlands) with integrated force plates (Forcelink, 12 channels, sample frequency 1000 Hz)	25 reflective markers were placed on anatomical landmarks of each participant. Each participant performed two 6MWT's using the GRAIL	6MWT, on treadmill	 Cadence, steps/min Double support time, s Stride time, s Stride length, m Step width, m	Mean (SD) 118.6 (10.3) 0.28 (0.04) 1.02 (0.09) 1.43 (0.18) 0.18 (0.04)
Marquis	2009	sEMG signals with a wireless amplifier system (TeleMyo2400T; Noraxon, Inc., Scottsdale, AZ), high pass filtered (10 Hz) and pre-amplified near electrodes. Band-pass filter 10-500 Hz and amplification at the receiver box	sEMG signals from the soleus, tibialis anterior, medial gastrocnemius, vastus lateralis, and rectus femoris muscles of the right lower limb were measured during the 6 MWT	6MWT (30-meter long course according to the procedures recommended by ATS)	For each stride in each muscle: Median frequency of sEMG signal -soleus -tibialis anterior -gastrocnemius -vastus lateralis -rectus femoris Integrated EMG -soleus -tibialis anterior -gastrocnemius -vastus lateralis -rectus femoris	Ranges derived from figures 85-110 80-90 85-90 55-70 50-61 20000-25000 30000-40000 20000-25000 12000-20000 4000-5000

McCamley	2017	3-dimensional marker trajectories (Motion Analysis Corp, Santa Rosa, CA; 60 Hz) and ground reaction forces (600 Hz; Kistler Group, Winterhur, Switzerland)	33 retro-reflective markers on specific anatomical locations.	10-m walk: Subjects walked over a 10 m path at their self-selected speed	Peak Angles, degrees Peak Forces, N/Body Weight Peak Moments, N*m/kg Peak Powers, J/kg Impulse, N*s/kg	Mean (SD) of joint angles 4.2 (4.6); 36.5 (6.8) 0.03 (0.02); 1.09 (0.09) -0.75 (0.28); 1.41 (0.15) -0.90 (0.35); 2.49 (0.50) -0.40 (0.16); 0.40 (0.16)
Meijer	2014	Two triaxial accelerometers (CIRO Activity Monitor (CAM); Maastricht Instruments B.V., Maastricht) and a Programmable Ambulant Signal AcQuisition system (PASAQ; Maastricht Instruments B,V,) for sEMG	A common ground electrode was placed on the ulnar styloid process. The cables from the electrodes were taped to the skin and placed into the PASAQ, which the participant wore in a small backpack	12 domestic activities of daily life (cleaning windows, writing on a board, cleaning sink, pouring water and drinking, stretching arms, shaking hands, drawing picture, folding towels, put towel on top shelf, walking, face care, sweeping the floor)	Arm intensity Arm elevation Leg intensity	Ranges derived from figures: 5.5; 70 -9.8; 19.1 1.6; 40.6
Morlino	2017	Instrumented mattress (GAITRite®, CIR Systems, USA)	Participants walked at comfortable speed along a 4 m long instrumented mattress, four trials were evaluated	4 m walk	Speed (cm/s) Cadence (step/min) Step length (cm) Duration of the single-support (%Gait Cycle duration) Duration of the double-support (%Gait Cycle duration)	Mean values derived from figures: 100 110 57 38 25
Munari	2020	PortaMon near-infrared spectroscopy device (Artinis Medical Systems)	NIRS was positioned on the vastus lateralis muscle of the dominant lower limb approximately 10 cm from the knee.	6-min step test (6MST): 20 - cm high step. Two trials performed with an interval of 30 min. Test was stopped once HR > 85% predicted max HR or SpO2 < 85% and resumed once the condition for safe trial were met again.	Oxyhaemoglobin (O2Hb) Deoxyhaemoglobin (HHb) Total haemoglobin (THb) Tissue saturation index (TSI), %	6-min difference (t0 = reference), Mean (SD) −5.40 (6.11) 7.73 (6.54) 2.33 (6.93) −7,34 (5,30)
Rutkowski	2014	Instrumented mattress (GAITRite®, CIR Systems, USA)	From the 5th meter, there was a four-meter GaitRite mat placed in the corridor. Analysis included 3	6MWT: 30-m (evaluation on 4 m GaitRite)	Pace of gait (m/s) Stride length (cm) Stride duration (s)	Mean (SD) 156.6 (18.8) 74.8 (6.8) 0.48 (0.04)

			measurements taken at 3 points during the test duration.			
Terui	2018	Wireless triaxial accelerometer (MG-M1110; LSI Medience, Tokyo, Japan)	The accelerometer was fixed to a belt at the level of the subject's L3.	10 meters walk (1-m spare walkway area at the start and the end)	Difference in the absolute value for lateral acceleration (Δx lateral) Difference between vertical acceleration when the right leg is in the stance phase and vertical acceleration when the left leg is in the stance phase (Δy lateral) Lissajou index, %	Mean (SD) 0.22 (0.15) 0.15 (0.11) 34.2 (19.2)
Vaes	2012	Two tri-axial accelerometer (KXP94, Kionix inc, Ithaca New York, USA) and the signal acquisition system for ambulant measurements (PASAQ, Maastricht Instruments B.V., Maastricht, The Netherlands)	Accelerometers were placed two fingers above the lateral malleolus of the right ankle and on the lower back and were connected with the PASAQ. Patients were randomly assigned to walk with rollator or modern draisine during the 6MWT	6MWT (with rollator or modern draisine)	Number of strides, n Stride length, m Stride frequency, strides/s Root mean square of the acceleration	Mean (SD) Draisine; Rollator 245.3 (60.9); 300.3 (49.1) 1.27 (0.14); 1.89 (0.73) 0.76 (0.14); 0.88 (0.11) 0.10 (0.03); 0.19 (0.07)
Yentes	2015	high-speed motion capture system (Motion Analysis Corp., Santa Rosa, CA; 60 Hz) and piezoelectric force plate (Kistler Instrument Corp., Winterthur, Switzerland)	Reflective markers were placed on defined anatomical locations, bilaterally.	10-meter walk at normal pace. The subjects were asked to walk at normal pace (rest condition) or immediately after reporting breathlessness or muscle tiredness (provoked by treadmill walking with 10% incline) (no rest condition)	Speed (m/s) Step Length (m) Step Width (m) Step Time (sec) Stance Time (sec) Support Time (sec) Stride Length (m) Stride Time (seconds)	Mean (SD) Rest; no rest 1.11 (0.17); 1.15 (0.18) 0.66 (0.06); 0.66 (0.06) 0.11 (0.04); 0.12 (0.04) 0.58 (0.06); 0.59 (0.06) 0.69 (0.09); 0.70 (0.10) 0.11 (0.03); 0.12 (0.04) 1.31 (0.13); 1.33 (0.13) 1.15 (0.11); 1.18 (0.13)

Yentes	2017	Infrared cameras (60 Hz; Motion Analysis Corp., Santa Rosa, CA)	3,5 minutes of walking on the treadmill at their self-selected pace and at two additional speeds (± 20%)	Normal, fast and slow walking (on treadmill)	Step length (m) Step time (s) Step width (m)	Ranges derived from figures 0.3-0.6 0.55-0.90 0.07-0.13

Table 4: parameters estimated from different devices.

Device	*Parameters*	*Study's first Author*
Accelerometers	cadence (steps/min)	Annegarn, Iwakura
	cadence (strides/min)	Annegarn, Vaes
	Autocorrelation AP	Annegarn
	Autocorrelation V	Annegarn
	Autocorrelation ML	Annegarn
	Gait speed	Iwakura
	Step length	Iwakura
	Step length/cadence (walk ratio)	Iwakura
	Acceleration magnitude	Iwakura, Vaes
	Step time	Iwakura
	Intensity (upper limbs)	Meijer
	Intensity (lower limbs)	Meijer
	Relative muscle effort	Meijer
	difference in absolute ML acceleration	Terui
	difference between V acceleration in right stance and left stance	Terui
	Lissajou index (symmetry evaluation)	Terui
	total amount of strides	Vaes
	Stride length	Vaes
Force plates	Foot-off time	Beauchamp
	Foot contact time	Beauchamp
	Swing time (foot-off time - foot contact time)	Beauchamp
	Anticipatory postural adjustment	Beauchamp
	Integrated APA size	Beauchamp
	absolute path length	Gloeckl
	peak W/kg during jump	Gloeckl
	jump height	Gloeckl
	sit duration in STS	Janssens
	sit-to-stand duration in STS	Janssens
	stand duration in STS	Janssens
	stand-to-sit duration in STS	Janssens
Instrumented mat	Speed	Morlino, Rutkowski
	Step length	Morlino, Rutkowski
	Cadence	Morlino
	Single support duration	Morlino
	Double support duration	Morlino
	Stride duration	Morlino
sEMG	angular coefficient of medium frequency	Canuto
	mean frequency	Dos Reis
	RMS frequency	Dos Reis
	median frequency	Marquis
	integrated frequency	Marquis
NIRS	delta [O2Hb]	Dos Reis, Munari
	delta [HHb]	Dos Reis, Munari
	delta [tHb]	Dos Reis,Munari
Gait analysis/camera	Step width	Fallahtafti, Liu (2019), Liu (2017), Yentes (2015), Yentes (2017)
	Step duration	Fallahtafti
	Step length	Fallahtafti, Yentes (2015), Yentes (2017)
	Stride time	Liu (2019), Liu (2017), Yentes (2015)

Stride length	Liu (2019), Liu (2017), Yentes (2015), Yentes (2017)
Step time	Yentes (2015)
Stance time	Yentes (2015)
Stride sample entropy width	Liu (2019)
Stride sample entropy length	Liu (2019)
ROM	Liu (2020)
sample entropy ROM	Liu (2020)
Local divergence exponent joint angle	Liu (2020)
Cadence (steps/min)	Liu (2017)
Double support time	Liu (2017), Yentes (2015)
Speed	Yentes (2015)
Peak angles	McCamley
Peak forces	McCamley
Peak moments	McCamley
Peak power	McCamley
Impulse	McCamley

Table 5: validation studies and study populations' characteristics.

Study's first Author	*Year*	*Country*	*Study design*	*Population*	*N (%)*	*Mean age*	*% Female*
Cheng[73]	2013	USA	Validation study	Mixed: - COPD: outpatients - Healthy subjects	6(50.0)	NA	83
Iwakura[58]	2019	Japan	Test-retest reliability	COPD	20 (100.0)	71 (8)	0
Liu[74]	2016	The Netherlands	Cross-sectional	Mixed: - COPD: outpatients (pre-rehabilitation assessment) - Healthy subjects	61 (56.0)	61.9 (6.8)	38.7
Sant'Anna[75]	2012	Brazil	Cross-sectional	COPD	30 (100)	67 (7)	43

Table 6: devices employed, function(s) evaluated, parameters retrieved, and comparison metric(s) used in validation studies.

Study first Author	*Year*	*Device*	*Test/biomech fx*	*Parameter(s)*	*Comparison device*	*Comparison Metric(s)*	*Comparison value*	*Quality of the study*
Cheng	2013	Phone app running on a Samsung Galaxy Ace	6MWT	Walking speed (estimated by SVM)	Clinical measurement	Root mean square error	Range 0.032; 0.133 (different SVM models)	Inadequate
Iwakura	2019	A tri-axial accelerometer system (Mimamori-gait system, LSI Medience Corporation, Japan), 100 Hz sampling rate	10-metre walk test	Gait speed Step length Cadence Walk ratio Acceleration magnitude Step time	No	Intra-class correlation coef.: Gait speed (m·s−1) Step length (m) Cadence (step·min−1) Walk ratio Acceleration magnitude Step time SD	ICCs (95%CI) 0.97 (0.93 - 0.99) 0.97 (0.92 - 0.99) 0.96 (0.90 - 0.98) 0.97 (0.92 - 0.99) 0.97 (0.92 - 0.99) 0.91 (0.79 - 0.96)	Doubtful
Liu	2016	3D motion analysis system with a dual-belt, instrumented treadmill and a virtual reality 180 degrees projection screen (GRAIL, Motekforce Link, Amsterdam, the Netherlands) with integrated force plates (Forcelink, 12 channels, sample frequency 1000 Hz)	6MWT	walking speed	Clinical evaluation (overground 6MWT)	Intra-class correlation coefficient	ICCs (95%CI) 0.74 (0.51 - 0.86)	Doubtful
Sant'Anna	2012	Power Walker 610 (Yamax, 1-5-7, Chuo-cho, Meguro-ku, Tokyo 152-8691 Japan): pedometer combined with accelerometer	Walking protocol	Number of steps (n) Walking distance (m) Intensity (m/min) Energy expenditure (Kcal)	Video recording and SenseWear Armband (for energy expenditure estimation)	Pearson correlation coefficient: Number of steps -fast -slow Walking distance -fast -slow Walking intensity (speed) -fast	rho 0.95 0.79 0.48 0.63 0.47	Doubtful

-slow	0.61
Energy expenditure	
-fast	0.83
-slow	0.65

Discussion

In this study we have evaluated the implementation of different technologies for the ambulatory or laboratory assessment of physical function in persons affected by COPD. We found a variety of technologies employed for the assessment of physical function: small wearable devices (such accelerometers) as well as cumbersome gait analysis laboratory were employed.

Our study highlights a significant implementation of technologies for the instrumental evaluation of physical function in persons with COPD over the last two decades. We also found that there was a significant heterogeneity in terms of type of device used, applications, function(s) tested, and metrics retrieved. This finding is of particular interest, given that the lack of standardization and device-dependence assessment results was deemed as among the most important factors that hinders technology-aided assessments of physical function[76].

In particular, we found that similar metrics were retrieved using a variety of devices. For example, spatiotemporal parameters of gait were obtained from accelerometers, gait analysis systems, and instrumented mattress. The validity of measures obtained by different technologies is of pivotal importance for the implementation of an instrumental evaluation of mobility. Instrumented mattresses and walkway of force plates have been reported as valid technologies for the assessment of spatiotemporal parameters in healthy individuals, when compared with video-based systems as gold standards[77,78]. The spatiotemporal parameters of gait obtained from a tri-axial accelerometer located near the centre of gravity and from instrumented mattresses have also been shown to exhibit good-to-excellent collinearity in healthy individuals[79,80]. In addition, a recent meta-analysis[31] showed that the validity of IMU-derived spatiotemporal parameters was generally excellent (using either instrumented walkway, instrumented mattresses, or motion capture systems as reference). However, the authors of the latter study, highlighted how this finding was strongly limited by quality of the investigated studies, generally characterized by low statistical power. Our systematic review extends the issue of the absence of high-quality studies investigating the validity of instrumental evaluation of physical function to the setting of COPD. In addition, only one study included in this systematic review compared measurements obtained from an accelerometer with a video-based assessment of gait: the collinearity between the methods for simple characteristics of gait (total distance walked and intensity) were moderate-to-low (Pearson's' rho ranging between 0.47 and 0.61). It is likely that the validity of an instrumented evaluation of function in persons affected by chronic conditions is lower than the one reported for healthy individuals. A recent study[81] comparing gait events recognition obtained from magneto-IMUs and instrumented mattresses, for example, showed that the errors in the estimation of the initial contact, stride time, and step time were significantly lower for healthy older adults, in comparison with participants affected by Parkinson's disease. This result is likely to be explained be the higher heterogeneity that can be found in pathological patterns of gait and the consequent difficulty in finding rules and algorithm for the identification of gait events.

It is also worth mentioning that, to the best of our knowledge, the impact of possible measurement errors in the instrumental evaluation of physical function in clinical or research practice is unknown. The totality of the application studies included in our systematic review were cross-sectional, mostly with a case-control design: the possible association of specific device-derived metrics with meaningful clinical outcome was not investigated, as well as possible confounders that may explain the differences found in terms of device-derived metrics between persons with COPD and healthy controls. It is crucial, for the implementation of technologies in clinical practice, to deeply investigate the role of device-derived metrics in the prediction of poor health-related outcomes or in the identification of groups of persons affected by COPD that may benefit from specific diagnostic or therapeutic approach.

We also found a significant variability in the protocols used to assess the same function, for example gait (the most evaluated function). Out of eighteen studies (including both application and validation) evaluating this function, 8 were conducted by performing the 6MWT. The 6MWT is suggested by

current guidelines as a simple and reliable test to investigate exercise tolerance in persons with COPD: subjects are asked to cover the maximum distance possible during 6 minutes on a straight path, typically 30-meter long. In most of these cases, Authors evaluated spatiotemporal parameters of gait: however, fatigue has been previously shown to possibly modulate such parameters[82]. Indeed, Rutkowski and colleagues[68] reported that, both in participants with COPD and healthy controls, stride lengths were higher at the beginning of the test in comparison with those measured after 3 minutes. They also reported that stride length seemed to revert to baseline values at the end of the 6MWT, probably due to the effect of the provided instructions and motivation. Liu and colleagues[62] reported the coefficients of variation (i.e.: standard deviation divided by mean) of several spatiotemporal parameters of gait obtained during the whole 6MWT (performed on a treadmill and investigated using a gait analysis laboratory): they ranged between 2% for stride time up to 14% for step width, although the temporal patterns of such variations were not investigated. Interestingly, these authors showed, in a sub-analysis (N = 28) of participants with comparable walking speeds, that the mean values of spatiotemporal parameters of gait were similar between participants with COPD and healthy controls, but the variability of stride length, double support time, and step lengths seemed to be higher among cases. These findings may be worth some considerations: in first place, the functional test used for the assessment of gait may have a major impact on the metric of interest. The lack of standardized protocols for the instrumental evaluation of mobility may hamper the generalizability of results and, therefore, the implementation of technologies in clinical and research settings. A previous study, for example, reported the important role of distance walked on the parameters retrieved and, in particular, on those linked to gait rhythmicity[83]. In second place, these findings suggest that the variability of specific spatiotemporal parameters may be an early sign of deterioration of the gait pattern in persons with COPD, as already described for the general population of older adults[84–86].

Our systematic review highlight that a significant number of devices may be used for the instrumental evaluation of physical function in persons with COPD. Several factor should be taken into consideration before implementing a technology for the instrumental evaluation of physical function in ambulatory or research practice. In first place, size and cost may be considerably different from one instrument to another: tri-axial accelerometers are easily worn on different parts of the body and are generally affordable, whereas 3D gait analysis systems typically need dedicated spaces or infrastructures and their cost is significantly higher. The physical test or function that needs to be objectively measured is another important factor for the choice of the system to implement: some gait labs are combined with treadmills that allows a detailed evaluation of gait or run, whereas force plates are often used both for balance tests' evaluation (e.g.: posturography) and assessment of strength or power during functional tests involving the lower limbs (e.g.: jumps, chair stands). The possibility to assess different functions with the same device may be also worth to be considered: among the application studies included in this systematic review, instrumented mattresses have been implemented only for the evaluation of gait, whereas force plates, accelerometers, NIRS, sEMG were employed to retrieve parameters from a variety of tests and function (i.e.: gait, balance, jump, replication of domestic activities). In addition, the aim of an instrumental evaluation of function should be clearly defined before the implementation of any technology. For example, in our study, we found that accelerometers have been used to obtain data about the intensity of gait (cadence), spatiotemporal parameters of gait (stride length, step length, gait speed) and measures of gait symmetry. Obviously, such data cannot be retrieved using NIRS sensors or sEMGs which, in turn, have been implemented to obtain detailed information about the activation and usage of particular muscles (or muscular groups) during the performance of specific actions or functions.

Another result of our study is that the majority of studies included recruited a limited number of participants. Indeed, 9 out of twenty-four papers included less than twenty COPD participants. Beside the sample size, most authors selected their study population by excluding individuals affected by conditions potentially impacting the performance in physical function tests: cardiological, neurological, and musculoskeletal comorbidities were the most cited exclusion criteria. Interestingly, COPD is known

to be frequently associated with multiple other conditions: in particular, due to shared risk factors, cardiological and neuro-vascular diseases are frequent co-morbidities of COPD. COPD is also associated with an increased risk of developing sarcopenia, frailty, and disability. These considerations suggest that the results from the studies included in this systematic review may not be directly generalizable to a significant share of older persons affected by this respiratory condition.

In conclusion, novel devices are more and more used to investigate physical function in persons affected by COPD and a variety of potentially interesting metrics can be retrieved from such instrumental evaluation. However, a general lack of standardization and limitations in study design and sample size hinders the implementation of the instrumental evaluation of function in clinical practice.

Study 2 - Frailty and objectively measured physical activity in older persons: results from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K)

Introduction

Frailty, a state of increased vulnerability caused by the reduction of physiological reserve in several organs and systems, is considered one of the most important geriatric syndromes and is often considered a reliable proxy of biological age[87].

The relationship between frailty and physical activity (PA) has been highlighted since one of the first frameworks for the definition and assessment of frailty has been proposed; indeed, the reduction of PA plays a critical role in the "frailty cycle", proposed by Fried L. and colleagues in a seminal paper in 2001[12]. New technologies allow to objectively measure PA in the "real world", overcoming the limitations posed by anamnestic questionnaires/interviews or ambulatory assessment protocols. Large implementation of such devices may help to better characterize the relationship between low PA and frailty. Measures of PA volume (i.e.: total PA performed), intensity (i.e.: PA performed in units of time), and possibly time spent in certain positions (i.e.: sitting, standing, laying) are easily calculated from the output obtained from these devices. Previous studies showed that frailty is generally associated with reduced PA measures obtained from wearable devices: low PA intensity and volume have been positively associated with frailty. However, such results were not always concordant[88]. In addition, another accelerometer-derived metric for the measurement of PA in older persons gained consensus in the last years. Such measure, named PA fragmentation, is thought to be linked to the inability to maintain longer bouts of physically demanding activities and has been already associated with lower functional ability, higher mortality risk[89], and fatigability[90]. It follows that it is likely that a link between PA fragmentation and frailty exists, although this topic has been seldom explored so far[91].

Furthermore, wearable accelerometers are, nowadays, largely available, economically affordable, and well tolerated by older persons[92]. The identification of potentially frail individuals in the general population by exploiting data obtained from real life PA is of particular interest as it may allow to screen a large share of the population using simple and non-invasive devices. Given the importance of frailty in the personalization of care pathways for older persons and in the design of impactful public health policies, to investigate the potential role of accelerometer-derived metrics in modelling the risk of frailty is a valuable step toward large-scale implementation of wearable technologies in older persons.

Thus, in this study we aimed to 1) evaluate the association between a robust and validated measure of frailty with several measures of PA volume, intensity, and fragmentation, and 2) to develop and internally validate a model that, exploiting accelerometer-derived metrics, may help to identify older persons affected by frailty.

Methods

Study population

We used data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K). The study design and protocol are explained in detail elsewhere[93]. Briefly, persons older than 60 years old and living in the central area of Stockholm (Sweden), either in the community or nursing homes, were asked to participate to the study in 2001. Those who agreed, underwent an in-depth assessment involving physicians, nurses, and neuropsychologists. Interviews, questionnaires, physical, and instrumental examination were administered to the participants, as well as the collection of bioumoral samples and linking with Regional and National registries. Each participant was followed up according to age: those younger than 72 were followed up every 6 years, whereas those older were followed up every 3 years. At the follow-up examination held in 2016-2018, 1280 participants were evaluated.

Nurses identified 680 participants who were suitable to wear an accelerometer for the following week. The clinical criteria employed for this sample selection were the ability to move autonomously indoor (even using a walking aid) and the absence of major cognitive impairment. The selected participants were instructed by the nurse on how to wear the accelerometer and were provided with a log-sheet, tape for accelerometer positioning, and a pre-paid envelope to mail the accelerometer after data recording.

Evaluation of physical activity

The device employed in this study is the ActivePAL (PAL technologies Ltd). ActivePAL is a wearable tri-axial accelerometer able to collect data about PA volume and intensity, as well information about the time spent in different positions (e.g.: sitting, standing, laying). The device was worn on the thigh during all waking hours, excluding bath, showering, or swimming time. The data were collected with a sampling frequency of 20 Hz and were downloaded using the proprietary software (PALanalysis). Data were visually inspected, as explained in a previous work[94], to identify possible misplacements or discrepancy with information about activity reported in the log-sheet. Only participants whose accelerometer recorded at least four valid days of data were considered eligible for inclusion in this study. A day was considered valid if at least 10 hours of recordings were available. From the data recorded, the following metrics were calculated:

- PA volume:
  - *%stepping*: proportion of recording time spent stepping. Calculated as the total time spent stepping divided by the total wearing time
- PA intensity:
  - *%MVPA*: proportion of recording time spent stepping with a cadence higher than 100 steps/min (threshold for moderate-to-vigorous PA). Calculated as the total time spent stepping with cadence ≥100 steps/min divided by the total wearing time.
  - *%LPA*: proportion of recording time spent stepping with a cadence lower than 100 steps/min or spent in standing position (thresholds for light PA). Calculated as the sum of the total time spent stepping with a cadence < 100 steps/min and the total time spent standing without stepping, divided by the total wearing time.
  - *Time spent stepping with cadence in different intervals*: total time spent stepping in different intervals of cadence. In particular: ≥130 steps/min, between 80 and 100 steps/min, between 80 and 50 steps/min, lower than 50 steps/min.
  - *Maximum cadence reached in bouts lasting at least 120 seconds.*
- Time spent in different positions:
  - *Number of sitting bouts lasting less than 30 minutes*: averaged per day.
  - *Number of sitting bouts lasting at least 30 minutes*: averaged per day.
  - *Median time spent sitting*: taking into consideration the whole observation time.
  - *Maximum time spent sitting*: taking into consideration the whole observation time.
- PA fragmentation:
  - *Total number of stepping bouts*: taking into consideration the whole observation time.
  - *Median* $P(Rest_{t+1}|Active_t)$: median conditional probability of a participant being at rest (laying, sitting, or standing without stepping) at any time $t+1$ given that he/she was active (stepping) at time t. More details are available in the appendix.
  - *Median* $P(Active_{t+1}|Rest_t)$: median conditional probability of a participant being active at any time $t+1$ given that he/she was resting at time t. More details are available in the appendix.
  - *Active Gini Index*: a measure of the inequality in the distribution of active bouts' (stepping ≥ 5 seconds) durations, as described in previous papers[95,96].
  - *Resting Gini Index*: a measure of the inequality in the distribution of resting bouts' (laying, sitting, or standing without stepping or stepping < 5 seconds) durations, as described in previous papers[95,96].

All metrics, when checked for collinearity one with the other, exhibited an absolute Spearman coefficient lower than 0.85.

Frailty

We assessed frailty employing a frailty index (FI). A FI is a simple ratio between the deficits exhibited by the participant and the total number of deficits taken into consideration by the researchers. Deficit is a broad definition that tries to include every possible damage that may accumulate in different organs and systems; for these reasons, chronic conditions, symptoms, signs, physical or cognitive function tests' results, biomarkers, and results from instrumental tests are all considered deficits. For this study, we used a previously proposed FI whose list of deficits was built and validated using SNAC-K baseline data. The proposed FI was developed implementing an optimization algorithm to identify deficits able to increase its discriminative ability in the prediction of mortality and hospitalizations, both in the whole SNAC-K baseline study population and in its age- and sex- subsamples. When compared with a FI previously built using clinical criteria for the selection of the deficits, the FI based on the optimization algorithm showed better areas-under-the-curve for all outcomes and in all subsamples. The same list of 40 deficits was then shifted to the study population for the present study, updating the values of each deficit according to the last available follow-up assessment. Due to the lack of updated registry data for the 2016-2018 assessment, the resulting FI contained 39 deficits (information about hospitalizations in the previous year was unavailable). In sensitivity analyses run using baseline data, the predictive performance for mortality of the resulting 39-deficit deficit did not significantly change in comparison with the one from the original 40-deficit FI. The complete list of deficits included in the FI is available in the original article. In this study, we categorized frailty as "no or mild", "moderate", and "severe". The cut-offs for such classification were identified by assessing the 5-year mortality in baseline data. In the baseline data, those with "no or mild" frailty ($FI < 0.07$) exhibited a 5-year mortality lower than 5%, those with moderate frailty ($0.07 \leq FI < 0.16$) showed a 5-year mortality of 22.4%, and those affected by severe frailty ($0.16 \leq FI < 0.33$) exhibited a 5-year mortality higher than 50%. Those with $FI > 0.33$ (i.e.: the maximum value registered in the accelerometer cohort), showed a 5-year mortality higher than 90%.

Statistical analysis

Study population's characteristics were described using median and interquartile range (IQR) or count and proportion, as appropriate. Linear regression models, employing the FI as independent variable, were used to investigate the association between frailty and accelerometer-derived metrics. The models were adjusted by major confounders. For the development of the prediction model, the dataset was randomly split into two subsamples: 75% as train subsample and 25% for testing subsample. The train subsample underwent a mixed over- and under-sampling approach to synthetically solve class imbalance prior to model fitting[97]. We fitted a penalized (ridge) logistic regression model including all accelerometer-derived metrics on the train dataset. The penalization coefficient (λ) was identified using a cross-fold ($k = 5$, repeated 3 times) grid search and using the area under the curve as performance indicator. The fitted model was then applied to test subsample and its performance was evaluated. All analyses were conducted with R 4.0.5 and an alfa-level = 0.05.

Results

The final analytical sample for this study comprised of 656 persons. Twenty-four participants were excluded because the number of valid days (i.e.: 10+ hours of recording time/day) was lower than 4. The median age of those included was 66.5 years old (first and third quartile, Q1-Q3: 66.1-81.2) and 64.0% were female (**table 7**). The 17.1% of the study population was widowed and 15 participants (2.3%) had primary education. The prevalence of multimorbidity (i.e.: 2+ chronic diseases) was 90.4% and the median Mini-Mental state examination (MMSE) score was 29 (Q1-Q3: 28-30). The median proportion of waking time spent stepping each day was 12.3% (Q1-Q3: 9.1-15.0) and the median proportion of waking time spent performing MVPA was 3.1% (Q1-Q3: 1.3-5.2). The median time spent sitting each day was 30.1 minutes (Q1-Q3: 24.4-39.1) and the median maximum cadence reached during the whole observation time (in bouts lasting 2+ minutes) was 117.5 (Q1-Q3: 109.8-125.4).

Almost 65% of the study participants (N = 425) had a FI lower than 0.07 ("no/mild frailty"), whereas 27.7% and 7.5% were considered affected by moderate and severe frailty, respectively (**Table 7**). The median age of those affected by no/mild, moderate and severe frailty were 66.2 (Q1-Q3: 66.1-67.1), 81.2 (Q1-Q3: 67.4-84.3), and 84.2 (Q1-Q3: 82.2-90.0) years old, respectively. The proportion of female participants raised from 62.1% among those without or with mild frailty to 73.5% among those with severe frailty. The proportion of widowed participants ranged from the 7.5% (no/mild frailty) to 55.1% (severe frailty), similarly to the proportion of persons with primary education, which raised from 0.2% among those with no/mild frailty to 16.3% among those with severe frailty. The median number of chronic conditions ranged between 3 (Q1-Q3: 2-5) for those with no/mild frailty to 10 (Q1-Q3:8-11) for those with severe frailty. Among those with no/mild frailty, the median proportion of waking time spent stepping and performing MVPA were 13.1% (Q1-Q3: 10.6-16.0) and 3.8 (Q1-Q3: 2.2-6.1), respectively. The median time spent sitting in this group, each day, was 29.5 minutes (Q1-Q3: 23.7-36.4) and the maximum cadence reached in bouts lasting at least 2 minutes was 120.6 steps/min (Q1-Q3:114.2-126.9). Among those with severe frailty, the median proportion of time spent stepping and performing MVPA were 6.5% (Q1-Q3:4.6-9.0) and 0.1 (Q1-Q3:0.0-0.6), respectively. In median, 39.9 minutes/day were spent sitting by those participants affected by severe frailty (Q1-Q3: 29.3-44.0). The median maximum cadence reached in bouts lasting 2+ minutes was 97.3 (Q1-Q3: 89.2-107.7).

Table 8 shows the results of linear regressions using each accelerometer-derived metric as dependent variable and the FI as independent one, both unadjusted and adjusted for age, sex, body mass index (BMI), education, widowhood, and total accelerometer wearing time. The FI was found to be linearly associated with all accelerometer-derived metrics even after adjustment, with the exclusion of the number of sitting bots lasting less than 30 minutes, the time spent stepping with a cadence higher than 130 steps/min, and the resting Gini Index. In particular, each 0.1 FI increase was associated with 2.4 points reduction in the proportion of time spent stepping (95% confidence intervals – 95%CI= 1.75-3.0), to a reduction of almost 45 stepping bouts in the total amount of stepping bouts recorded (95%CI = 28.3-61.5), and to a reduction of 9.7 steps/min in the maximum cadence reached in bouts lasting 120+ seconds (95%CI = 7.8-11.6). In general, a higher FI score was associated with a reduction in the time spent stepping with different cadences (with the exclusion of cadence higher than 130 steps/min). The median transition probability between active and resting status increased by 1% for each 0.1 FI score increase.

Table 7: characteristics of the study population, stratified according to frailty classes.

	Overall *N = 656*	*no/mild frailty* *N = 425 (64.8)*	*moderate frailty* *N = 182 (27.7)*	*severe frailty* *N = 49 (7.5)*
Age (median (IQR))	66.51 (66.11, 81.24)	66.21 (66.06, 67.12)	81.18 (67.41, 84.32)	84.23 (82.24, 90.00)
Female sex (%)	420 (64.02)	264 (62.12)	120 (65.93)	36 (73.47)
Education (%)				
-primary	15 (2.29)	1 (0.24)	6 (3.30)	8 (16.33)
-secondary	266 (40.55)	162 (38.12)	82 (45.05)	22 (44.90)
-tertiary	375 (57.16)	262 (61.65)	94 (51.65)	19 (38.78)
Widowed (%)	112 (17.07)	32 (7.53)	53 (29.12)	27 (55.10)
BMI; kg/m^2 (median (IQR))	25.15 (22.93, 27.78)	25.18 (22.96, 27.82)	25.18 (22.83, 27.55)	25.04 (22.92, 27.13)
N. chronic diseases (median (IQR))	4.00 (3.00, 7.00)	3.00 (2.00, 5.00)	6.00 (5.00, 8.00)	10.00 (8.00, 11.00)
2+ chronic diseases (%)	593 (90.40)	365 (85.88)	179 (98.35)	49 (100.00)
Walking speed; m/s (median (IQR))	1.20 (1.00, 1.50)	1.20 (1.20, 1.50)	1.00 (0.75, 1.20)	0.61 (0.61, 0.75)
Use any walking aid (%)	82 (12.54)	7 (1.65)	41 (22.65)	34 (69.39)
MMSE score (median (IQR))	29.00 (28.00, 30.00)	29.00 (28.00, 30.00)	29.00 (27.00, 29.00)	28.00 (27.00, 29.00)
FI (median (IQR))	0.05 (0.03, 0.08)	0.03 (0.00, 0.05)	0.10 (0.08, 0.13)	0.21 (0.18, 0.24)
% stepping	12.28 (9.06, 14.96)	13.08 (10.65, 16.02)	10.17 (7.78, 13.35)	6.51 (4.57, 8.98)
% MVPA	3.07 (1.33, 5.23)	3.81 (2.25, 6.08)	2.05 (0.83, 4.14)	0.15 (0.04, 0.60)
% LPA	35.96 (29.24, 42.42)	37.03 (30.74, 43.73)	34.44 (27.91, 39.42)	31.49 (22.73, 37.34)
N. sitting bouts lasting < 30 minutes, per day	38.33 (30.00, 48.18)	38.86 (31.00, 48.86)	37.87 (29.89, 47.96)	31.86 (26.14, 40.57)
N. sitting bouts lasting ≥ 30 minutes, per day	4.71 (3.71, 5.71)	4.57 (3.57, 5.43)	5.00 (4.14, 5.85)	5.71 (4.86, 6.57)
N. stepping bouts	359.14 (287.86, 430.41)	382.14 (313.57, 448.71)	329.07 (255.68, 409.68)	256.57 (191.33, 331.40)
Median time spent sitting, per day (minutes)	30.13 (24.39, 39.10)	29.53 (23.71, 36.38)	30.48 (24.83, 40.83)	39.86 (29.30, 44.02)
Maximum time spent sitting, per day (minutes)	132.61 (106.39, 166.93)	130.47 (105.95, 159.63)	134.09 (105.48, 168.63)	143.00 (112.41, 190.83)
Maximum cadence reached in bouts lasting ≥ 120 seconds	117.55 (109.81, 125.41)	120.61 (114.18, 126.91)	114.17 (107.79, 122.36)	97.28 (89.19, 107.74)
Time spent stepping with a cadence ≥ 130 steps/min (minutes)	0.08 (0.05, 0.16)	0.10 (0.06, 0.21)	0.06 (0.04, 0.12)	0.03 (0.02, 0.07)

Time spent stepping with a 80 ≤ cadence < 100 steps/min (minutes)	24.90 (17.99, 34.66)	26.61 (19.45, 36.69)	23.23 (17.66, 33.38)	13.74 (7.71, 27.47)
Time spent stepping with a 50 ≤ cadence < 80 steps/min (minutes)	31.16 (23.81, 39.09)	32.72 (25.35, 42.24)	27.84 (21.60, 35.17)	22.94 (18.36, 32.91)
Time spent stepping with a cadence < 50 steps/min (minutes)	12.28 (9.16, 15.91)	13.05 (10.02, 16.82)	11.06 (7.87, 13.93)	9.39 (6.16, 13.59)
Median $P(Rest_{t+1} \mid Active_t)$	0.04 (0.03, 0.04)	0.03 (0.03, 0.04)	0.04 (0.03, 0.05)	0.05 (0.04, 0.06)
Median $P(Active_{t+1} \mid Rest_t)$	0.03 (0.02, 0.03)	0.03 (0.02, 0.03)	0.03 (0.02, 0.03)	0.02 (0.02, 0.03)
Gini index (active bouts)	0.68 (0.63, 0.72)	0.69 (0.65, 0.73)	0.66 (0.62, 0.71)	0.62 (0.56, 0.67)
Gini index (sedentary bouts)	0.81 (0.79, 0.83)	0.81 (0.79, 0.83)	0.81 (0.78, 0.83)	0.81 (0.78, 0.83)

Abbreviations: BMI: body mass index; MMSE: mini-mental state examination; FI: frailty index; MVPA: moderate-to-vigorous physical activity; LPA: light physical activity

Supplementary tables 1 and 2 show the results of the same adjusted analyses, stratified for sex and age (cut-off = 72 years old), respectively. A higher FI score was negatively associated with the number of sitting bouts lasting less than 30 minutes among female participants, but such association disappeared among males. Conversely, maximum time spent sitting significantly increased among male participants with increasing FI (+19 minutes per 0.1 FI increase, 95%CI = 7.1-31.0) but not among female ones. The median and maximum time spent sitting increased with FI among participants older than 75 years, but such association was not seen among those younger.

In test subsample, the ridge-penalized logistic regression model was able to identify participants with severe frailty (versus no, mild, or moderate frailty) with an area under the curve of 0.91, using the predicted probability as a continuous variable (**Table 9**). Using a cut-off = 0.5 of predicted probability to identify those with severe frailty, the accuracy was 0.82 and sensitivity and specificity of 0.87 and 0.82, respectively. The positive predictive value (PPV) was 0.32 (severe frailty prevalence in the test dataset = 0.09) and the negative predictive value (NPV) was 0.98. The model developed to identify participants affected by moderate-to-severe frailty (vs no or mild frailty) showed an AUC of 0.81. The accuracy was 0.72 and sensitivity and specificity were 0.77 and 0.69, respectively. The PPV was 0.61 (moderate-to-severe frailty prevalence in the test dataset = 0.39), whereas the NPV was 0.82. The further inclusion of age and sex in the model identifying severe frailty led to a non-significant increase in its discriminative ability (AUC difference: +0.01, $p = 0.644$). In the model aimed at identifying moderate-to-severe frailty, the inclusion of age and sex positively impacted on its discriminative ability (AUC difference: +0.07, $p = 0.011$).

Table 8: impact of 0.1 increase in FI on accelerometer-derived metrics in unadjusted and adjusted models. Models adjusted for age, sex, education, civil status, bmi, and total time of accelerometer wearing.

	Beta for 0.1 increase in FI	
	Unadjusted	Adjusted
% stepping	-3.42 (-3.92 - -2.91)*	-2.38 (-3.01 - -1.75)*
% MVPA	-1.98 (-2.32 - -1.65)*	-1.26 (-1.68 - -0.85)*
% LPA	-3.83 (-5.05 - -2.61)*	-4.33 (-5.89 - -2.76)*
N. sitting bouts lasting < 30 minutes, per day	-2.60 (-4.42 - -0.78)*	0.13 (-2.17 - 2.42)
N. sitting bouts lasting ≥ 30 minutes, per day	0.64 (0.46 - 0.81)*	0.50 (0.28 - 0.72)*
N. stepping bouts	-66.82 (-80.32 - -53.32)*	-44.90 (-61.51 - -28.30)*
Median time spent sitting, per day (minutes)	5.21 (3.74 - 6.67)*	3.49 (1.62 - 5.37)*
Maximum time spent sitting, per day (minutes)	7.92 (2.01 - 13.83)*	11.49 (3.83 - 19.14)*
Maximum cadence reached in bouts lasting ≥ 120 seconds	-12.46 (-13.99 - -10.92)*	-9.71 (-11.63 - -7.79)*
Time spent stepping with a cadence ≥ 130 steps/min (minutes)	-0.64 (-1.06 - -0.21)*	0.00 (-0.54 - 0.55)
Time spent stepping with a 80 ≤ cadence < 100 steps/min (minutes)	-5.91 (-7.67 - -4.15)*	-4.79 (-7.06 - -2.52)*
Time spent stepping with a 50 ≤ cadence < 80 steps/min (minutes)	-5.37 (-7.03 - -3.70)*	-2.83 (-4.94 - -0.71)*
Time spent stepping with a cadence < 50 steps/min (minutes)	-2.25 (-2.93 - -1.56)*	-1.39 (-2.25 - -0.53)*
Median $P(Rest_{t+1} \mid Active_t)$	0.01 (0.01 - 0.01)*	0.01 (0.01 - 0.01)*
Median $P(Active_{t+1} \mid Rest_t)$	0.00 (0.00 - 0.00)*	0.00 (0.00 - 0.00)*
Gini index (active bouts)	-0.04 (-0.05 - -0.03)*	-0.04 (-0.05 - -0.03)*
Gini index (sedentary bouts)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)

* = $p < 0.05$; Abbreviations: MVPA: moderate-to-vigorous physical activity, LPA: light physical activity

The relative importance of the variable included in the models are reported in **table 10**. The maximum cadence reached in bouts lasting at least 120 seconds is the most important variable in both models (the one identifying severe frailty and the one identifying moderate-to-severe frailty). The proportion of time spent performing MVPA was the second most important variable for the model aiming at identifying severe frailty. In the same model, the activity fragmentation index based on transition conditional probability (Median $P(Rest_{t+1} \mid Active_t)$) was the third most important variable, whereas the number of sitting bouts lasting more than 30 minutes was penalized and excluded from the model (beta coefficient = 0.0). The second and third most important variables for the model aiming at identifying participants with moderate-to-severe frailty were the time spent stepping with a low cadence (lower than 50 steps/min) and, again, the activity fragmentation index based on transition condition probabilities. In this model, the resting fragmentation index (Median $P(Active_{t+1}|Rest_t)$) was excluded.

Table 9: performance of the prediction models for the identification of severe frailty and moderate-to-severe frailty in the test dataset.

	AUC	*Accuracy*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Positive LLR*	*Negative LLR*
	Identification of severe frailty							
Accelerometer-derived metrics alone	0.91	0.82	0.87	0.82	0.32	0.98	4.78	0.16
Including age	0.91	0.84	0.87	0.83	0.34	0.98	5.17	0.16
	Identification of moderate-to-severe frailty							
Accelerometer-derived metrics alone	0.81	0.72	0.77	0.69	0.61	0.82	2.47	0.34
Including age	0.86	0.80	0.83	0.78	0.71	0.88	3.76	0.22

Abbreviations: AUC = area under the curve, PPV = Positive Predictive Value, NPV = Negative Predictive Value, LLR = Likelihood Ratio

Table 10: standardized betas and relative variable importance for all variables used in the prediction models.

	Severe frailty		*Moderate-to-severe frailty*	
	Standardized beta	Relative variable importance	Standardized beta	Relative variable importance
% stepping	-0.06	5.34	-0.15	62.86
% MVPA	-0.86	90.09	-0.15	64.02
% LPA	0.30	31.49	-0.01	1.21
N. sitting bouts lasting < 30 minutes, per day	0.10	9.76	0.17	69.42
N. sitting bouts lasting ≥ 30 minutes, per day	0.00	0.00	0.04	17.58
N. stepping bouts	-0.46	48.31	-0.16	65.81
Median time spent sitting, per day (minutes)	0.28	29.48	0.08	33.62
Maximum time spent sitting, per day (minutes)	0.10	10.40	-0.02	6.94
Maximum cadence reached in bouts lasting ≥ 120 seconds	-0.95	100.00	-0.24	100.00
Time spent stepping with a cadence ≥ 130 steps/min (minutes)	-0.19	20.09	0.01	4.54
Time spent stepping with a 80 ≤ cadence < 100 steps/min (minutes)	0.14	14.53	-0.08	34.62
Time spent stepping with a 50 ≤ cadence < 80 steps/min (minutes)	0.23	24.08	-0.02	8.23
Time spent stepping with a cadence < 50 steps/min (minutes)	0.04	3.37	-0.21	89.41
Median $P(Rest_{t+1} \mid Active_t)$	0.59	62.09	0.19	79.18
Median $P(Active_{t+1} \mid Rest_t)$	0.11	11.29	0.00	0.00
Gini index (active bouts)	-0.13	13.74	-0.15	60.34
Gini index (sedentary bouts)	-0.08	7.98	-0.08	33.93

Abbreviations: MVPA: moderate-to-vigorous physical activity, LPA: light physical activity

Discussion

In this study, we showed that frailty, measured using a validated frailty index, is linearly associated with a variety of metrics derived from the instrumented monitoring of physical activity obtained using tri-axial accelerometers in older adults. Furthermore, we propose two models exhibiting good performances in the identification of severe and moderate-to-severe frailty employing only metrics derived from such devices.

The relationship between frailty, physical function, and physical activity is well established in the literature. Frailty, indeed, is often considered a pre-disability status and has been shown to be associated with a reduced function and PA. In the "frailty cycle", proposed by Fried LP and colleagues to support the development of the physical frailty phenotype, the reduction of muscle mass is suggested to be an important cause leading to a decreased physical function and, consequently, to a reduced activity[12]. In turn, low physical activity promotes the loss of muscle mass, sustaining the progression of physical frailty. Our results confirm that the relationship between frailty and low PA holds even when a "deficit accumulation model" is used to assess frailty, as shown by other authors[98,99]. This study further strengthens the idea that several organs and systems, beyond the musculo-skeletal one, are involved in the performance of PA and function and that, in turn, reduced PA is likely to have a detrimental effect on the whole organism. Recent systematic reviews[88,100,101] reported that frailty has been found to be negatively associated with different objective measures of physical activity obtained using wearable devices, although the results are not always concordant. For example, PA volume has been shown to correlate with frailty by some authors, but such relationship was not found in all studies. MVPA is another instrument-derived metric that has been often shown to be associated with frailty. Our findings may help to expand such results. Firstly, we showed a linear association between frailty, and measures of PA volume and intensity, even after adjustment for several potential confounders. In their systematic review, Tolley APL and colleagues[100] showed that LPA and measures of related to sedentary bouts were inconsistently associated with "multifactorial" (i.e.: measured using a FI) frailty. However, in our study, frailty was found to be associated, even after adjustment, with LPA. The reasons for such variability in the association between LPA and frailty reported in the literature is unknown, but it is likely that the employment of different threshold for the definition of LPA may impact the studies' findings. Furthermore, the qualitative characteristics of the FI used to assess frailty may impact on the ability to highlight association between instrumental PA measurers and FI. In our study, we also found that the FI was not linearly associated with the time spent stepping with a very high cadence. In our study population, the total time spent stepping with cadence higher than 130 steps/min was extremely low, suggesting that this cadence cut-off may be inadequate for older persons. This issue may, again, impact on the selection of meaningful threshold for the identification of LPA and MVPA in older persons. Interestingly, some authors[102] suggested that even the cut-off used to identify non-wearing time in the automated software used for PA analysis may be too low for their application to older persons: a careful evaluation of the cut-offs used by different software for PA intensity is of pivotal importance to allow the implementation of instrumental evaluation of PA in older persons. In second place, we also considered two metrics of activity fragmentation (sometimes referred to as "PA patterns" or "PA behaviour") and shown that frailty is also linearly associated with them. PA intensity and a measure of PA fragmentation were also among the most important variables retained by the two models identifying severe and moderate-to-severe frailty, further confirming the aforementioned results. Activity fragmentation, measured as the reciprocal of the average active bout duration, has been associated with higher odds of being affected by frailty, according to the physical phenotype[91]. Our study expands such results to other metrics of PA fragmentation and to a deficit-accrual model for frailty identification. The reasons for such association are still uncertain. PA intensity is often considered a proxy of energy expenditure. PA fragmentation, in turn, may be thought as a measure of "energy management": older persons affected by increasing frailty may be prone to interrupt long activities because of the inability to sustain long periods of activity. It is worth mentioning that walking, the activity that is most likely to be assess using wearable accelerometers for long periods, has been shown to be negatively impacted

by low speed, from an energetic point of view. In other words, when walking is performed under certain cadence, the increased energetic cost of maintaining balance outperform the reduction in the caloric expenditure obtained by walking at low speed[103,104]. Older persons affected by low or moderate frailty may try to maintain the usual PA levels but, due to an increased caloric expenditure, they may need to frequently interrupt such activity. Further longitudinal studies may help to disentangle the intricate relationship between PA intensity, PA fragmentation, and frailty.

In our study we developed and internally validated two models able to identify older persons affected by frailty with a high discriminative ability. The identification of frail individuals is pivotal due to their increased risk of developing several poor health-related outcomes. However, the assessment of frailty, even if several tools have been proposed, is not always straightforward. For example, some assessment scores require instruments, training, time, or spaces that are seldom available in settings such as primary care. Other instruments, i.e., the frailty index, need a significant number of variables for their calculation which are hardly always available. Our findings suggest that information retrieved by monitoring PA for 7 days using a simple, affordable, non-invasive device may be used to reliably identify frail older adults.This result is in line with other studies; Kumar DP and colleagues[105], for example, employed data retrieved from accelerometers worn 48h to identify participants with prefrailty or frailty using a logistic regression model. The implemented model included age, BMI, stride variability, the main frequency from the spectral analysis of signal, and the maximum number of continuous steps in a single active bout reaching an AUC of 0.84, although an internal or external validation was not performed. Schwenk M and colleagues[106] investigated the role of several device-derived metrics for the identification of frailty, assessed using the frailty phenotype. Among the variables retrieved from 24-hour worn accelerometers, the variability in bout duration was the most important in the discrimination of robust, prefrail, and frail participants (assessed using a multinomial logistic regression fitted on the whole dataset). In our study, age and sex increased the discriminative ability of the model aimed at identifying older persons with moderate-to-severe frailty, but not the one exhibited by the model for severe frailty alone. It is possible that persons with moderate frailty exhibit subtler and heterogeneous changes in their PA pattern and quality, in comparison with those affected by well-established frailty status. Further studies are needed to investigate the trajectories of accelerometer-derived metrics according to frailty status. In the future, the information retrieved via instrumental evaluation of real-life physical activity may be used to screen the general population: an inexpensive device, or an application exploiting the accelerometers implemented in mobile phones, may help general practitioners to identify those individuals who are likely to benefit from an in-depth clinical screening for frailty.

This study should be read in light of some limitations. In first place, due to the study design, our results cannot provide information about the temporal or causal relationship between frailty and PA. Although our study provides information about the association between PA-measures and frailty beyond the presence of several confounders, future longitudinal studies are warranted. Furthermore, although we used a validated measure of frailty and we identified frailty cut-off based on 5-year mortality, such data were based on the baseline participants' characteristics. Future follow-up examination may help us to investigate the relationship between mortality, frailty and objective measure of PA. In addition, although we provide an internal validation of the predictive model aimed at identifying older persons with different level of frailty, an external validation of such models is lacking; future studies should investigate the generalizability of models based on accelerometric-measures for the identification of frail individuals. Lastly, although the post-test probabilities for frailty exhibited by the proposed models are consistently higher than the pre-test ones, a careful estimation of costs and an external calibration of the models is warranted prior to the possible large-scale implementation: if applied to population characterized by a high prevalence of frailty, it is likely that these models will be proven to be more useful to exclude persons free from frailty rather than for screening purposes.

In conclusion, our study strengthens the current knowledge about the association between objective metrics of PA and frailty, extending such results to other metrics of PA fragmentation and a validated

FI, in large cohort of community-dwelling older adults. Our study further suggests that accelerometer-derived PA metric may be easily used for the identification of older adults affected by frailty.

Study 3 - Gait smoothness in persons with increased risk of falling: a pilot case-control study

Introduction

Falls are among the most common and harmful events for older adults and are considered a geriatric syndrome, characterized by a complex and multifactorial pathogenesis[107]. Indeed, several factors may impact on the risk of falling; female sex, older age[108], specific medications and polypharmacy[109], multimorbidity[110], frailty[111], and sarcopenia[112] are among some of conditions the have been associated with this syndrome. Several characteristics of balance and gait have also been strongly linked with the risk of falling[113,114]. Novel technologies and methodological approaches may help to quantify several aspects of balance and gait that are generally qualitatively described during routine clinical examination. For example, among older persons with Parkinson's disease, several spatiotemporal parameters have been already associated with an increased risk of falling (either measured using gait analysis systems, inertial measurement units, or instrumented walkways and mattresses); lower walking speed, lower cadence, lower step and stride length, as well as higher step and stride time and time variability have been shown to be consistently present among persons with an history of falling[115]. Beside spatiotemporal parameters, other metrics may be inferred from the instrumental evaluation of gait; for example, smoothness, perceived when a movement is conducted uninterruptedly and in a continuous fashion, has been associated higher degree of sensorimotor control and can be calculated from the signal retrieved from accelerometers worn while performing a movement[116]. However, results about the association between gait smoothness and mobility dysfunctions were not always concordant[117]. Although several metrics for the evaluation of smoothness have been suggested, the spectral arc length (SPARC) proposed by Balasubramanian S. and colleagues[118] is gaining more and more consensus because of its high validity invariability to movement duration. For this reason, SPARC has been increasingly implemented also in studies investigating gait smoothness. For example, gait smoothness has been associated with poor balance in persons with Parkinson's disease[119] and as a potential metric for the identification of older persons with increased risk of falling[120]. Novel and invariant metrics, such as SPARC, may help to better investigate this issue in the population of older adults, characterized by a significant heterogeneity in terms of walking speed and gait pattern's quality.

In this study, we preliminary explore the role of gait smoothness, both in straight and turn walking phases, in discriminating persons with high and low risk of falling.

Methods

Study design and study population

We conducted an age- and sex-matched case-control study. Cases were identified by reviewing the electronic health registries of the Emergency Department and of the Geriatric ward of Montichiari hospital (ASST Spedali Civili, Brescia – Italy). We searched records of persons who had a triage diagnosis (free text) of "fall" and who were admitted to the Geriatric ward between 2019 and 2021. The following exclusion criteria were used to select the study population: age lower than 65 years old, falls caused by a cardiovascular condition (e.g. arrhythmia), suspected or definitive, according to the discharge chart, a Mini-Mental state examination (MMSE) score at discharge lower than 24, a diagnosis of atrial fibrillation, having a pace maker, lower limb amputation(s), Parkinson disease or parkinsonism, para- hemi- or tetra-plegia, not being able to walk alone indoor, and severe peripheral neuropathies. The eligible participants were contacted by hospital staff via telephone and in case of acceptance to participate the study, they were invited to the hospital for the evaluation. Controls were identified from the geriatric ward registries; in addition to the aforementioned exclusion criteria, no previous fall should have been reported in the discharge letter and the Tinetti scale evaluation at discharge should have reported values higher than twenty points. Controls were matched to cases by sex and age (± 3 years). The study was approved by the local ethical committee.

Assessment protocol

A medical history questionnaire was administered to all study participants by a resident in geriatric medicine; diagnoses and drugs reported by the participants were compared with those listed in the most updated discharge letter available in our electronic system. In case of conflict, the resident in geriatrics evaluated all available medical documents, further interviewed the study participant and, if available, her/his caregiver. The first assessment of physical function was conducted by performing the Short Physical Performance Battery (SPPB). Each item of the SPPB was visually demonstrated and verbally explained by the resident in geriatric medicine to the participant. All time were measured using a stopwatch and noted. A turn test path was used to evaluate walking speed: a 4-meter straight path followed by a 180° left turn (1-meter radius) and another 4-meter straight path. The time needed to complete the first 4 meters was noted and used for the calculation of SPPB score (walking speed). The participants underwent a further neuropsychological assessment, including the Mini-Mental state examination (MMSE), the clock drawing test (evaluated according to Shulman 6-point scale), the digital symbol substitution test (DSST), and the trail making test part A (TMT-A). An evaluation of the risk of sarcopenia was also performed employing the SARC-F questionnaire. Hand grip strength for the left and right arm was evaluated from the seated position using a digital dynamometer and the highest value was recorded. Left and right calf circumferences were measured by applying a non-rigid tape to the widest part of the calf from the seated position, employing the minimum possible amount of pressure. Frailty was assessed according to the physical frailty phenotype. Five criteria were considered: unintentional weight loss of more than 4.5 kg in the last year, engaging in light physical activity (i.e.: walking, light house chores) less than one time per week in the last 3 months, reporting feeling exhausted more than one time per week in the last 3 months, walking speed lower than the height- and sex-adjusted cut-offs proposed by Fried LP and colleagues, and hand grip strength lower than the BMI- and sex-adjusted cut-offs cited in the same study.

Instrumental assessment

The BTS G-walk (BTS Bioengineering – Milano, Italy) is a small, wireless, wearable inertial movement unit. As such, it is composed by a tri-axial accelerometer, tri-axial gyroscope, and tri-axial magnetometer. The device weights 37 grams and is applied, using a belt, to the back of the subject at the level of the 2nd lumbar vertebra. The sensor collect data with a frequency of 100 Hz and transfer them to a personal computer using a wireless connection. Data are visualized and stored using the proprietary software. The data can be exported in comma-separated-value (CSV) format. For this study, this device was worn by the participants during the whole evaluation.

Movement smoothness analysis

Movement smoothness was calculated using the Spectral Arc Length (SPARC). SPARC is based on the intuition that a smooth movement is mainly composed by low-frequency components, whereas an unsmooth movement will exhibit more higher-frequency ones[118]. Such differences in the composition of movement will also be reflected by the profile of the Fourier magnitude spectrum of the movement. Arc length (i.e., the length along the curve defined by the spectrum itself) is used to measure the complexity of Fourier spectrum and SPARC was defined as the negative arc length of the amplitude and frequency-normalized Fourier magnitude spectrum of the speed profile (**Figure 4**). In this study, as suggested by other authors[119], we calculated SPARC using the root mean squared (RMS) acceleration on the three axes, after removing the mean value of the acceleration on each axis. The calculation of SPARC was done using a personalized script in R, based on a freely available Python script coded by the original authors of the algorithm[121]. SPARC needs two parameters to filter the spectrum before calculating smoothness; we specifically used a higher bound frequency threshold of 5 Hz (i.e.: $\omega = 10\pi$) and a lower bound normalized amplitude threshold of 0.03, to limit the impact of possible signal noise. The straight and turn walking phase were pre-identified using the gyroscope signal as guidance and the exact phase time cut-off was identified upon visual inspection. The straight phase gait smoothness was calculated as the average SPARC obtained in the two straight segments of the turn test.

Statistical analysis

Data were described as count and proportion or median and first/third quartile as appropriated. Differences between cases and controls were investigated using Fisher's exact e test or Kruskal-Wallis test, as appropriate. Turn and straight phase SPARC were used as dependent variables in linear regression testing the association with all covariates, tested one at the time. All analyses were conducted in R (4.0.5).

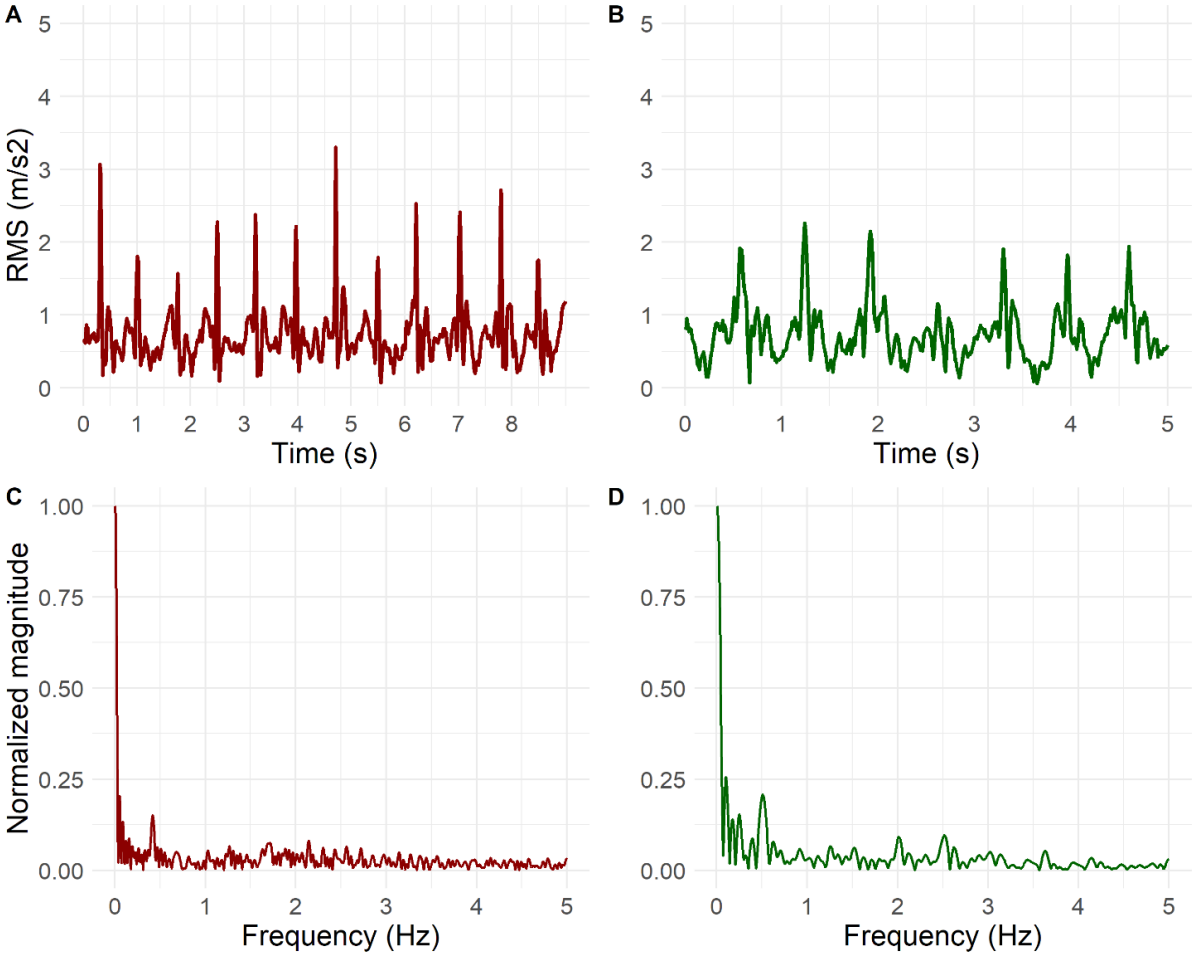

Figure 4: Example of RMSs (panels A and B) and frequency spectra (C and D) of a participant with a previous injurious fall (in red) and a control (in green), during the turn phase

Results

Table 11 shows the characteristics of the study population. The median age was 79.5 (1st quartile, 3rd quartile – Q1-Q3 = 75.8-82.3) years old and 80% of the study population was female. More than half of the participants had primary education. The median number of drugs chronically prescribed was 5.5 (Q1-Q3 = 5.0-7.0) with a median anticholinergic burden score of 0.5 (Q1-Q3 = 0.0- 2.5). Ten percent of participants were robust according to the frailty phenotype, whereas 80% and 10% were pre-frail and frail, respectively. The median walking speed measured on a 4-meter straight path using a stopwatch was 0.61 m/s (Q1-Q3 = 0.44, 0.86) and the median score in the SPPB was 8.5 (Q1-Q3 = 6.5, 10.0). The median MMSE score was 27.5 (Q1-Q3 = 23.3-28.8): study participants took, in median, 134 (Q1-Q3 = 52.4-146.0) seconds to complete the TMT-A and correctly completed a median of 15.5 (Q1-Q3 = 9.0-30.5) symbols during the 90-second DSST.

Table 11: characteristics of the study participants

	Overall N = 10	*Controls* N = 5	*Cases* N = 5	*p*
Age (median [IQR])	79.50 [75.75, 82.25]	79.00 [78.00, 80.00]	80.00 [75.00, 83.00]	0.753
Sex = M (%)	2 (20.0)	1 (20.0)	1 (20.0)	1.000
Primary education (%)	7 (70.0)	3 (60.0)	4 (80.0)	1.000
N. drugs (median [IQR])	5.50 [5.00, 7.00]	5.00 [5.00, 6.00]	7.00 [5.00, 8.00]	0.195
ACB (median [IQR])	0.50 [0.00, 2.50]	0.00 [0.00, 1.00]	1.00 [0.00, 3.00]	0.432
BMI (median [IQR])	42.25 [37.65, 46.27]	43.80 [40.70, 44.40]	37.60 [34.40, 46.90]	0.465
Walking speed, m/s (median [IQR])	0.61 [0.44, 0.86]	0.77 [0.73, 0.89]	0.43 [0.41, 0.48]	0.076
Hand grip, kg (median [IQR])	20.80 [18.58, 26.53]	20.90 [20.70, 25.70]	19.70 [17.80, 26.80]	0.602
Calf circumference, cm (median [IQR])	35.00 [33.50, 36.75]	37.00 [36.00, 38.00]	35.00 [30.00, 35.00]	0.045
SPPB (median [IQR])	8.50 [6.50, 10.00]	10.00 [9.00, 11.00]	6.00 [6.00, 8.00]	0.045
MMSE (median [IQR])	27.50 [23.25, 28.75]	28.00 [28.00, 29.00]	22.00 [21.00, 27.00]	0.073
TMT-A (median [IQR])	134.00 [52.40, 146.00]	64.00 [52.40, 134.00]	142.50 [114.00, 152.00]	0.624
DSST (median [IQR])	15.50 [9.00, 30.50]	20.00 [20.00, 34.00]	9.00 [6.00, 11.00]	0.141
Turn SPARC (median [IQR])	-5.66 [-6.60, -4.92]	-4.90 [-4.99, -4.69]	-6.61 [-6.81, -6.55]	0.028
Straight SPARC (median [IQR])	-5.16 [-5.71, -4.45]	-5.06 [-5.26, -4.35]	-5.73 [-6.56, -4.77]	0.347
Frailty phenotype (%)				0.167
frail	3 (30.0)	0 (0.0)	3 (60.0)	
prefrail	6 (60.0)	4 (80.0)	2 (40.0)	
robust	1 (10.0)	1 (20.0)	0 (0.0)	
SARC-F (median [IQR])	1.0 (1.00, 3.25)	1.0 (0.00, 1.00)	4.0 (1.0, 5.0)	0.034

Abbreviations: ACB: anticholinergic burden; BMI: body mass index; SPPB: short physical performance battery; MMSE: mini-mental state examination; TMT-A: trail making test, form A; DSST: digital symbol substitution test; SPARC: spectral arc length

Cases exhibited lower median calf circumferences (35.0 vs 37.0 cm) and lower scores at the SPPB (6 vs 10 points). A trend for lower median score in the walking speed (0.43 vs 0.77 m/s), MMSE score (22 vs 28 points), higher median time taken to complete TMT-A (142.5 vs 64.0 seconds), and lower median score in the DSST (9 vs 20 symbols) was also observed. The median value of movement

smoothness in the turn phase was lower among cases, in comparison with controls (-6.6 vs -4.9, p = 0.028). In the straight segment of the walking path, the median SPARC value was similar between cases and controls (-5.7 vs -5.1, p = 0.347). **Table 12** shows the results from linear regressions between several covariates and SPARC values (turn and straight phases). The MMSE score showed a linear association both with straight phase (beta = 0.17, p = 0.016, R^2 = 0.53) and turn phase SPARC (beta = 0.18, p = 0.030, R^2 = 0.46). A trend of association was detected between SARC-F score and straight phase SPARC (beta = -0.24, p = 0.052, R^2 = 0.39): such association was significant for turn phase SPARC (beta = -0.31, p = 0.019, R^2 = 0.52). A trend of association was also detected between straight phase SPPB and SPARC (beta = 0.225, p = 0.057, R^2 = 0.38).

Table 12: results of linear regression models investigating the relationship between smoothness (turn and straight phases) and participants' characteristics.

	TURN SPARC			*STRAIGHT SPARC*		
	Beta coef.	*p*	R^2	Beta coef.	*p*	R^2
Age	0.018	0.762	0.01	-0.011	0.836	0.01
Sex	1.078	0.199	0.20	0.04	0.96	0
Education	-0.858	0.325	0.24	1.228	0.112	0.34
N. drugs	-0.283	0.202	0.19	-0.116	0.575	0.04
ACB	-0.273	0.169	0.22	0.293	0.087	0.32
BMI	-0.014	0.753	0.01	-0.013	0.754	0.01
Walking speed	0.211	0.874	0.00	1.915	0.074	0.34
Hand grip	0.077	0.181	0.21	0.058	0.265	0.15
Calf circumference	0.075	0.468	0.07	0.088	0.327	0.12
SPPB	0.199	0.154	0.24	0.225	0.057	0.38
MMSE	0.181	0.03	0.46	0.173	0.016	0.53
TMT-A	0.005	0.34	0.13	0.001	0.872	0
DSST	0.008	0.759	0.01	0.028	0.236	0.17
Frailty phenotype (score)	-0.476	0.148	0.24	-0.493	0.084	0.33
SARC-F	-0.31	0.019	0.52	-0.241	0.052	0.39

Abbreviations: ACB: anticholinergic burden; BMI: body mass index; SPPB: short physical performance battery; MMSE: mini-mental state examination; TMT-A: trail making test, form A; DSST: digital symbol substitution test

Discussion

In this small age- and sex-matched case-control exploratory study, we found that turn phase gait smoothness seemed to be different among persons with an history of injurious falls and controls. Our results may also suggest that global cognition and gait smoothness are associated.

Our study is strongly limited by the sample size and its cross-sectional design. However, some cautious observations can still be inferred from our findings. First, the characteristics of our study participants seem to adhere to those of the general population at risk of falling; we have included persons affected by frailty, characterized by low walking speed, high risk of sarcopenia, and prescribed with a significant number of drugs. Indeed, our findings seem to confirm the results from other studies when it comes to characteristics of persons at high risk of falling[108].

Our study explored the role of gait smoothness in older persons at high and low risk of falling. Smoothness is a metric that is gaining interest as it may allow to quantitatively measure a characteristic of gait that is, at the moment, only seldom qualitatively described in clinical practice. Although the risk of falling have been associated with walking speed, it is likely that measures of gait pattern's quality may allow to gain a deeper understanding of the characteristics of gait that are associated with the risk of falling. Previous studies measuring other aspects of gait patterns, such as variability and symmetry, have already shown that such characteristics are different in persons with problem in the control of motor function (such as Parkinson's disease) when compared with healthy controls[117,122]. In addition, two previous studies evaluated movement smoothness during walking in persons affected by Parkinson's disease[119,123]. The average reported values of SPARC are comparable with our findings. In another study[120], evaluating SPARC in persons older than 85 at risk of falling, the ranges of SPARC reported for straight and turn phases of a timed up-and-go test (TUG) were slightly higher than the one we found: whether this difference is due to different study population's characteristics or issues related to sample numerosity needs to be further evaluated. Furthermore, in the latter study, the authors report a significant difference in SPARC values between fallers and not-fallers both for the straight and turn phases, whereas our findings show a difference only for the turn phase. However, the difference found by these authors was higher during turning phase: these findings altogether may confirm that the sensorimotor control needed to turn while walking is particularly strenuous and that assessment of the turn phase may help to elicit differences between physiological and pathological gait patterns. Indeed, the turn phase during walking has drawn interest in the last years and different strategies for turning have been reported in the literature[124]. Interestingly, these different strategies seem to be used by persons with different characteristics (i.e.: age, body weight) in different situations (i.e.: walking at higher or lower speed in comparison with usual speed)[125,126]. Due to the impact of different turning strategies on the stability and biomechanical cost of the action, it is likely that turning phase may play an important role in the risk of falling[127].

Our study also confirms the probable association between SPARC values and MMSE score, at least for turn phase SPARC, as shown by Figueiredo AI and colleagues[120]. We did not find any association between SPARC values and other cognitive test (such as the TMT-A and DSST): however, these results need to be confirmed on larger sample. In addition, although we applied an exclusion criterion based on the MMSE score evaluated in the prior two years, cases and controls showed a significantly different global cognition performance. This finding suggest that cognitive trajectories between fallers and followers may be extremely different, further complicating the intricate relationship between cognition, falls, and movement smoothness. Our study also highlights a possible linear association between SPARC values and SARC-F score: due to the limitation of this study, a possible association between gait smoothness and sarcopenia is difficult to investigate. In particular, measures of strength (such as hand grip or the time needed to complete five chair stands in the SPPB) were not associated with neither measure of SPARC. In addition, we found no association between SPARC values and frailty phenotype or walking speed, that are likely to reflect the functional status of the study participants.

SPARC is a metric of gait smoothness that can be easily calculated using the output from wearable sensors such as accelerometers and IMUs. Interestingly, SPARC can be calculated on any signal of acceleration or speed derived from such devices: other metrics, such as spatiotemporal parameters of gait can be calculated only after meaningful moments of the gait cycle are identified in the signal (recall **introduction** and the discussion of **study 1**). However, such action is not always straightforward when the population of interest is composed by older persons characterized by high cognitive and functional heterogeneity: errors in the identification of heel-contact/toe-off moments may lead to wrong estimations of several spatiotemporal parameters. Because of its mathematical definition, SPARC seems to easily adapt to the variability of gait patterns that can be found among older adults.

Lastly, it is worth noticing that during the whole study, none of the participants reported any acceptability issue with the wearable device. Although we faced some minor technical issues (e.g.: mild connectivity problems solved by the attending physicians), our study suggests that the implementation of wearable devices for the evaluation of physical function in clinical practice for older persons is feasible, even when frailty, increased risk of falling, and mild cognitive deficits are present.

In conclusion, this study shows that the instrumental evaluation of mobility using a IMU is feasible and strengthens our knowledge about the importance of gait smoothness in the evaluation of older persons at risk of falling.

Final remarks

Some considerations can be drawn from the three studies included in this PhD thesis. In first place, novel sensors and devices are more and more employed for the instrumental evaluation of physical function in research practice. Although some technical limitations still exist, it is likely that the most important challenges we'll have to face for a large-scale implementation of such devices in clinical practice are methodological. Common protocols for the instrumental evaluation of physical function need to be proposed and tested, similarly to what happened prior to the application of instrumental techniques currently used in clinical practice, such as echography or 24-hour EKG monitoring. Such implementation protocols would help physicians to identify suitable patients for the instrumental evaluation of physical function, to identify criteria for the interpretation (and interpretability) of the results, and to understand how to possibly modify the care path of patients according to the information retrieved from devices. An effort, shared between health professionals, engineers, and researchers is required to obtain the data needed for the development of implementation protocols: high quality research, based on comparable longitudinal studies with large sample numbers and investigating meaningful outcomes, is a fundamental first step towards this goal. In second place, information about physical function and activity acquired in the "real world" may help research and clinic to overcome the limitations posed by current clinical assessment. Thanks to data obtained from wearable devices, we can gain an objective insight into the behavioural patterns that characterize physical activity in older persons. This information cannot be retrieved from interviews, medical history, or ambulatory testing and can help us to better understand how physical function and mobility are preserved even when several organs and systems are impaired Investigating how mobility is preserved may be important to disentangle the complex relationship between behavioural strategies, health deficits accumulation, chronic conditions, and disability. Lastly, wearable devices seem to be well tolerated by older persons: in the next future, these instruments are likely to be easily worn during routine evaluation of function in clinical practice. In this way, high quality data can be collected while performing a standard assessment: the simultaneous integration of instrumental data with observations and judgment of skilled physicians and health professionals may help to increase the effectiveness and the efficiency of the comprehensive geriatric assessment.

A strong interdisciplinarity, supported by a profound collaboration between health professionals, policy makers, and engineers, is likely to be one of the key elements to shape the future of the person-centred care model.

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Supplementary material

Study 1

Search strategy (Pubmed): **#1 AND #2 AND #3 AND #4 NOT #5**

1. **#1 Construct search**

("Walking"[Mesh] OR "Walking Speed"[Mesh] OR "Gait"[Mesh] OR "Motion"[Mesh] OR "Posture"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Movement"[Mesh] OR "Lower Extremity"[Mesh] OR "Upper Extremity"[Mesh] OR "Muscle Contraction"[Mesh] OR "Muscle, Skeletal"[Mesh] OR "Muscle Strength"[Mesh] OR "Muscle Fatigue"[Mesh] OR "Exercise Tolerance"[Mesh] OR "Physical Endurance"[Mesh] OR "Time Factors"[Mesh] OR "Biomechanical Phenomena"[Mesh] OR "Acceleration"[Mesh] OR "Energy Metabolism"[Mesh] OR "Motor Activity"[Mesh] OR "Physical Functional Performance"[Mesh] OR "Joints"[Mesh] OR "role function"[tiab] OR "activit*"[tiab] OR "physical"[tiab] OR "function*"[tiab] OR "performance"[tiab] OR "biomechanic*"[tiab] OR "functional screening"[tiab] OR "implementation"[tiab] OR "step*"[tiab] OR "stand*"[tiab] OR "walk*"[tiab] OR "distance"[tiab] OR "balance"[tiab] OR "grip"[tiab] OR "handgrip"[tiab] OR "sit"[tiab] OR "lift*"[tiab] OR "gait"[tiab] OR "locomot*"[tiab] OR "stair*"[tiab] OR "rise"[tiab] OR "elevation"[tiab] OR "joint kine*"[tiab] OR "sit to stand"[tiab] OR "velocity"[tiab] OR "speed"[tiab] OR "power"[tiab] OR "rate of force development"[tiab] OR "strength evaluation"[tiab] OR "strength assessment"[tiab] OR "muscle evaluation"[tiab] OR "muscle assessment"[tiab] OR "endurance evaluation"[tiab] OR "endurance assessment"[tiab] OR "normative data"[tiab] OR "kinematic characteristic*"[tiab] OR "measurement propert*"[tiab] OR "clinical evaluation"[tiab] OR "clinical assessment"[tiab] OR "motion"[tiab] OR "motor"[tiab])

2. **#2 Population search**

("pulmonary disease, chronic obstructive"[Mesh] OR "Pulmonary emphysema"[Mesh] OR "chronic obstructive pulmonary disease*"[Title/Abstract] OR "chronic obstructive lung disease*"[Title/Abstract] OR "chronic obstructive airway disease*"[Title/Abstract] OR COPD[Title/Abstract] OR COAD[Title/Abstract])

3. **#3 Instrument search**

("Motion/instrumentation"[Mesh] OR "Actigraphy/instrumentation"[Mesh] OR "Movement/instrumentation"[Mesh] OR "Accelerometry/instrumentation"[Mesh] OR "Accelerometry/methods"[Mesh] OR "Software"[Mesh] OR "Mobile Applications"[Mesh] OR "Cell Phone"[Mesh] OR "Computers, Handheld"[Mesh] OR "Walk Test/instrumentation"[Mesh] OR "Micro-Electrical-Mechanical Systems"[Mesh] OR "Wearable Electronic Devices"[Mesh] OR "Technology/instrumentation"[Mesh] OR "Biomedical Technology"[Mesh] OR "Gait Analysis"[Mesh] OR "Exercise Test/instrumentation"[Mesh] OR "Exercise Test/methods"[Mesh] OR "Exercise Therapy/instrumentation"[Mesh] OR "Muscle Contraction/instrumentation"[Mesh] OR "Muscle Strength Dynamometer"[Mesh] OR "Resistance Training/instrumentation"[Mesh] OR "Equipment and Supplies/rehabilitation"[Mesh] OR "Equipment and Supplies/instrumentation"[Mesh] OR "Equipment and Supplies/methods"[Mesh] OR "Clinical Nursing Research/instrumentation"[Mesh] OR "Spectroscopy, Near-Infrared"[Mesh] OR "Electromyography/instrumentation"[Mesh] OR "near infrared spectroscopy"[tiab] OR "NIRS"[tiab] OR "gait analysis"[tiab] OR "performance-based test"[tiab] OR "wearable*"[tiab] OR "pedometer"[tiab] OR "acceleromet*"[tiab] OR "instrument*"[tiab] OR "tool*"[tiab] OR "smartphone*"[tiab] OR "smart-phone*"[tiab] OR "technolog*" OR "kinematic analysis"[tiab] OR "kinetic analysis"[tiab] OR "kinematic parameters"[tiab] OR "robot*"[tiab] OR "virtual"[tiab] OR "motion analysis"[tiab] OR "inertial sensor*"[tiab] OR "quantitative measure*"[tiab] OR "quantitative analysis"[tiab] OR "electromyograph*"[tiab] OR "EMG"[tiab])

4. **#4 Filter for measurement properties**

(instrumentation[sh] OR methods[sh] OR Validation Study[pt] OR Comparative Study[pt] OR ‘‘psychometrics’’[Mesh] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR "outcome assessment, health care"[Mesh] OR outcome assessment[tiab] OR outcome measure*[tw] OR ‘‘observer variation’’[Mesh] OR observer variation[tiab] OR ‘‘Health Status Indicators’’[Mesh] OR ‘‘reproducibility of results’’[Mesh] OR reproducib*[tiab] OR ‘‘discriminant analysis’’[Mesh] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR ‘‘internal consistency’’[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tiab] OR precision[tiab] OR imprecision[tiab] OR ‘‘precise values’’[tiab] OR test–retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intraobserver[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR

inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR repeatab*[tiab] OR ((replicab*[tiab] OR repeated[tiab]) AND (measure[tiab] OR measures[tiab] OR findings[tiab] OR result[tiab] OR results[tiab] OR test[tiab] OR tests[tiab])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR ''known group''[tiab] OR factor analysis[tiab] OR factor analyses[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR item discriminant[tiab] OR interscale correlation*[tiab] OR error[tiab] OR errors[tiab] OR ''individual variability''[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR ''standard error of measurement''[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR meaningful change[tiab] OR ''ceiling effect''[tiab] OR ''floor effect''[tiab] OR ''Item response model''[tiab] OR IRT[tiab] OR Rasch[tiab] OR ''Differential item functioning''[tiab] OR DIF[tiab] OR ''computer adaptive testing''[tiab] OR ''item bank''[tiab] OR ''cross-cultural equivalence''[tiab])

5. **#5 Exclusion filter**

(''biography''[Publication Type] OR ''case reports''[Publication Type] OR ''comment''[Publication Type] OR ''directory''[Publication Type] OR ''editorial''[Publication Type] OR ''festschrift''[Publication Type] OR ''interview''[Publication Type] OR ''legislation''[Publication Type] OR ''letter''[Publication Type] OR ''news''[Publication Type] OR ''newspaper article''[Publication Type] OR ''patient education handout''[Publication Type] OR ''consensus development conference''[Publication Type] OR ''consensus development conference, nih''[Publication Type] OR ''practice guideline''[Publication Type]) NOT (''animals''[Mesh Terms] NOT ''humans''[Mesh Terms])

Study 2

Physical activity fragmentation

Median $P(Rest_{t+1}|Active_t)$ and median $P(Active_{t+1}|Rest_t)$:

These two measures of PA fragmentation are based on a modification from the previous work by Lim ASP and colleagues (Sleep, 2011). We defined an activity bout as a period of observation time longer than 5 seconds and containing at least one activity count (i.e.: one step). Resting bouts were defined as periods of time either with no activity counts or shorter than 5 seconds. Therefore, the sum of the duration of all activity and resting bouts was equal to the whole observation time. For *median $P(Rest_{t+1}|Active_t)$* (i.e.: the median transition probability from an active status to a resting one), we tabulated the frequencies of the duration of all activity bouts (e.g.: 100 bouts lasted 5 seconds, 70 bouts lasted 7 seconds, 70 bouts lasted 30 seconds and so on). For each possible activity bout duration t (e.g.: 5 seconds, 7 seconds, 30 seconds, and so on), we calculated N_t, defined as the number of active bouts lasting at least t (e.g.: 240 for t = 5, 140 for t = 7, 70 for t = 30, and so on). Therefore, $N_{min(t)}$ (the minimum value of t for activity bouts is 5 second, by definition) was equal to the total number of activity bouts. We ordered all possible t from the smallest to the largest (e.g.: $t_1 = 5$, $t_2 = 7$, $t_3 = 30$, and so on) and we proceeded to define $P(Rest_{t(i+1)}|Active_{t(i)})$ as follows:

$$P\left(Rest_{t_{t+i}}\middle|Active_{t_i}\right) = \frac{N_{t_i} - N_{t_{i+1}}}{N_{t_i}}$$

Once $P(Rest_{t(i+1)}|Active_{t(i)})$ was calculated for all possible t, we defined *median $P(Rest_{t+1}|Active_t)$* as the median value of all $P(Rest_{t(i+1)}|Active_{t(i)})$. The same methodology was applied to resting bouts.

Supplementary table 1 (analyses are adjusted for age, education, civil status, bmi, and total time of accelerometer wearing) and stratified by sex

	Beta for 0.1 increase in FI	
	Females	Males
% stepping	-3.35 (-3.94 - -2.77)	-3.59 (-4.58 - -2.59)
% MVPA	-1.91 (-2.29 - -1.54)	-2.18 (-2.9 - -1.47)
% LPA	-3.4 (-4.81 - -1.99)	-5.79 (-8.14 - -3.45)
N. sitting bouts lasting < 30 minutes, per day	-3.76 (-5.78 - -1.74)	0.32 (-3.5 - 4.15)
N. sitting bouts lasting ≥ 30 minutes, per day	0.64 (0.43 - 0.85)	0.68 (0.34 - 1.01)
N. stepping bouts	-71.84 (-87.53 - -56.15)	-60.15 (-86.14 - -34.17)
Median time spent sitting, per day (minutes)	5.42 (3.74 - 7.1)	4.74 (1.8 - 7.68)
Maximum time spent sitting, per day (minutes)	4.16 (-2.59 - 10.9)	18.99 (7.01 - 30.97)
Maximum cadence reached in bouts lasting ≥ 120 seconds	-13.65 (-15.45 - -11.84)	-9.26 (-12.21 - -6.32)
Time spent stepping with a cadence ≥ 130 steps/min (minutes)	-0.65 (-1.08 - -0.22)	-0.53 (-1.54 - 0.47)
Time spent stepping with a 80 ≤ cadence < 100 steps/min (minutes)	-5.26 (-7.25 - -3.28)	-7.12 (-10.74 - -3.5)
Time spent stepping with a 50 ≤ cadence < 80 steps/min (minutes)	-5.85 (-7.77 - -3.93)	-4.05 (-7.39 - -0.71)
Time spent stepping with a cadence < 50 steps/min (minutes)	-2.36 (-3.15 - -1.56)	-2.2 (-3.53 - -0.86)
Median $P(Rest_{t+1} \mid Active_t)$	0.01 (0.01 - 0.01)	0.01 (0.01 - 0.01)
Median $P(Active_{t+1} \mid Rest_t)$	0 (0 - 0)	0 (0 - 0)
Gini index (active bouts)	-0.04 (-0.05 - -0.03)	-0.04 (-0.06 - -0.03)
Gini index (sedentary bouts)	0 (0 - 0.01)	0 (-0.01 - 0.01)

Supplementary table 2 (analyses are adjusted for sex, education, civil status, bmi, and total time of accelerometer wearing) and stratified by age

	Beta for 0.1 increase in FI	
	Age ≤ 75 years old	Age > 75 years old
% stepping	-2.85 (-4.1 - -1.6)	-2.51 (-3.16 - -1.85)
% MVPA	-1.16 (-2.04 - -0.27)	-1.44 (-1.83 - -1.06)
% LPA	-5.47 (-8.55 - -2.39)	-3.85 (-5.46 - -2.25)
N. sitting bouts lasting < 30 minutes, per day	0.7 (-3.61 - 5.01)	-0.36 (-2.93 - 2.22)
N. sitting bouts lasting ≥ 30 minutes, per day	0.57 (0.14 - 1.01)	0.5 (0.27 - 0.74)
N. stepping bouts	-60.64 (-95.3 - -25.99)	-46.67 (-63.45 - -29.89)
Median time spent sitting, per day (minutes)	2.94 (-0.17 - 6.06)	4.25 (1.89 - 6.61)
Maximum time spent sitting, per day (minutes)	6.55 (-7.44 - 20.53)	11.76 (3.15 - 20.36)
Maximum cadence reached in bouts lasting ≥ 120 seconds	-3.49 (-6.77 - -0.2)	-12.89 (-15.27 - -10.52)
Time spent stepping with a cadence ≥ 130 steps/min (minutes)	0.03 (-1.26 - 1.33)	-0.14 (-0.31 - 0.04)
Time spent stepping with a 80 ≤ cadence < 100 steps/min (minutes)	-4.72 (-9.05 - -0.39)	-5.52 (-7.95 - -3.09)
Time spent stepping with a 50 ≤ cadence < 80 steps/min (minutes)	-6.93 (-11.15 - -2.72)	-2.44 (-4.56 - -0.32)
Time spent stepping with a cadence < 50 steps/min (minutes)	-2.86 (-4.61 - -1.1)	-1.04 (-1.89 - -0.19)
Median $P(Rest_{t+1} \mid Active_t)$	0.01 (0 - 0.01)	0.01 (0.01 - 0.01)
Median $P(Active_{t+1} \mid Rest_t)$	0 (-0.01 - 0)	0 (0 - 0)
Gini index (active bouts)	-0.04 (-0.05 - -0.02)	-0.04 (-0.05 - -0.03)
Gini index (sedentary bouts)	0.01 (0 - 0.02)	0 (-0.01 - 0.01)

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