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Marco Inzitari

Determinants of mobility disability in older adults

Evidence from population-based epidemiologic studies

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Foreword

I write to express my enthusiastic admiration for the research accomplishments of Dr. Marco Inzitari, who served as a Pepper Research Scholar at the University of Pittsburgh during the 2006 to 2007 academic year. In the following paragraphs I will comment on his scholarly abilities and activities during his year here in Pittsburgh, as well as his subsequent research collaborations with us.

I am Principal Investigator of the NIH funded Pittsburgh Pepper Center, which is dedicated to research on mobility and balance among the aged. Dr. Inzitari applied and was accepted to serve as a Pepper Scholar in order to further his knowledge of cutting edge research in this area and to advance his skills in carrying out independent research.

Within a short time after his arrival, it became clear that he was very well trained and prepared to function at a high level in our program. He was cognizant of the many core concepts regarding the role of mobility in health in the aged, as well as complex models of interacting causation and consequences. In addition, he demonstrated a high level of skill in data management and statistical analysis that allowed him to aggressively and independently pursue two major and several additional research questions using existing data from our studies of aging.

In both his study of coronary calcification and his study of anemia and brain white matter disease, he was able to independently formulate a rigorous research hypothesis, prepare and submit manuscript plans, carry out analyses and prepare the manuscripts for submission to high quality journals. He used his extensive knowledge of the issues, additional reading and conferences with our investigators to specify main independent, dependent and cofactor variables for his models. His analytic skills are of a very high level. He was able to plan careful examinations of data quality and variable distributions. He independently proposed complex modeling approaches that incorporated assessments of confounding and effect modification. He himself planned and carried out the statistical analyses using univariate and multivariate models. I was also impressed with the quality of his writing. He prepared well organized and clearly presented work that was comparable to the level of sophistication of our research faculty.

In addition to these major components of his research with us, he was also deeply engaged in the scientific discussions of our investigators. He took the lead on several small projects where he helped plan new projects related to assessment of mobility and interventions to promote mobility. Throughout his work with us, he was always exceptionally professional, collaborative and responsive to ideas and suggestions of others.

Since returning to Florence and subsequently working in Barcelona, he has continued to pursue related research with us. He is engaged in a complex analysis of the effect of combined disorders of cognition, movement and mood on functional capacity, on

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another project assessing gait speed as a predictor of survival in multiple data sets and is working with me on a novel exercise intervention to promote physical and cognitive health in older women.

I consider Dr. Inzitari to be an exceptional candidate for the doctoral degree. I have served on the thesis committees for over 20 doctoral candidates and consider him to be in the top 10% of all of them. I believe Dr. Inzitari, through your training program, has prepared himself to become an international leader in aging research with exceptional capacity for creative ideas and rigorous science.

Finally I would like to thank the leaders of your program for sharing this outstanding individual with us. We are impressed with your program and would welcome further such collaborations in the future.

Stephanie Studenski MD MPH
Professor, University of Pittsburgh

Abstract

Background Mobility and gait are cardinal to retain independence in daily living at old ages. An impairment in these functions could represent a critical point in the transition to disability and dependency. Systems implicated in mobility and gait regulation are redundant, and are characterized by complex interactions with each other. For this reason, detecting a single cause of progressive mobility disability is a challenge for both researchers and clinicians, with the consequence of limited preventive and therapeutic strategies. Chronic processes under the threshold for clinical appearance can impair organs and systems which are involved in mobility and gait control. The study of factors contributing to the development of progressive mobility disability could be relevant to develop preventive strategies to prevent disability in older adults.

Aim To assess the determinants of progressive mobility disability and gait impairment in older adults living in the community.

Methods This work is the result of three years of investigations, conducted in Italy and in the United States using data from four major epidemiologic studies from these two countries. The studies had different primary outcomes, but all were designed to enrol community-dwelling older adults, and all included similar objective measures of physical performance. We focused on the impact on mobility and gait of subclinical dysfunctions in the central and peripheral nervous systems and in the cardiovascular system. We took advantage of the peculiarities of each study to test specific hypotheses: for example, the role of the nervous system and of the vascular systems were assessed in the ILSA study and in the CHS, which were respectively designed to assess the epidemiology and consequences of neurological diseases and cardiovascular diseases in the elderly.

Results In the ILSA study, depression and peripheral neuropathy independently predicted a decline in mobility over three years in initially well-functioning older adults. In the first analysis included in this work, cognitive impairment no-dementia was not associated with physical performance decline. Investigating more in detail the role of specific cognitive functions, attention and psychomotor speed, but not global cognitive function and memory, predicted mobility decline in this study. The reverse association was demonstrated in the Health ABC study, in which slow gait speed predicted a decline in attention over five years. This might indicate that the two measures could share a common substrate. In the ICARe Dicomano study we demonstrated the impact of neurological damage load, measured as the number of neurological findings at a standard neuroexam in people without overt neurological diseases, on functional and cognitive decline. Looking at vascular disease, in CHS participants without a history of cardiovascular disease, we found an association between coronary artery calcium, which has a strong correlation with systemic atherosclerosis, and physical performance

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in older women. In the same study, anemia was associated with the progression of neurological damage measured as white matter disease at a brain MRI.

Conclusion Taken together, our results indicate that subclinical dysfunctions in the nervous and cardiovascular systems are associated with the onset of progressive mobility disability in older adults living in the community. These findings might add relevant information to understand the disablement process, but may have implications for clinical practice too, since vascular disease, which might be also implicated in the pathogenesis of subtle neurological damage, is potentially preventable.

Introduction

1. The demographic and epidemiological transitions

In the past century, an extraordinary increase in the lifespan of world population has been observed, unprecedented across the whole history of human beings. The constant prolongation in life expectancy started in Europe at the end of the XIX century and continued constantly afterwards. In 1950, there were 205 million persons aged 60 or over throughout the World (**Figure 1**).

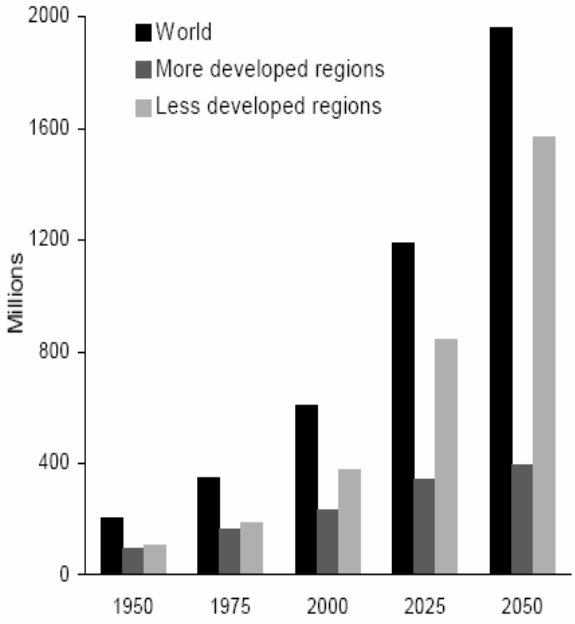

Figure 1 Projections of the World population as a whole and by more or less developed regions. *Source: UN, Department of Economic and Social Affairs Population Division*

At that time, only 3 countries, China, India and the United States of America, had more than 10 million people 60 or older. Fifty years later, the number of persons aged 60 or over increased about three times to 606 million. In 2000, 12 countries had more than 10 million people aged 60 or over. Over the first half of the current century, the global population 60 or over is projected to expand by more than three times to reach

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nearly 2 billion in 2050. Currently, the growth rate of the older population (1.9 per cent) is significantly higher than that of the total population (1.2 per cent). In the near future, the difference between the two rates is expected to become even larger as the baby boom generation starts reaching older ages in several parts of the world. By 2025-2030, projections indicate that the population over 60 will be growing 3.5 times as rapidly as the total population (2.8 per cent compared to 0.8 per cent). Europe is currently the world's major area with the highest proportions of older persons and is projected to remain so for at least the next 50 years. About 30 per cent of the European population is projected to be 65 or over in 2050, up from 15 per cent in 2000. People aged 60 or over currently constitute from one fifth to nearly one fourth of the population of Austria, Czech Republic, Greece, Italy, Japan, Slovenia and Spain (1). **In Italy**, for example, a further improvement of survival, compared to what the country has experienced in the last decades, is expected in the next future. This will place the country at the top of the ranking among EU countries. Mean life expectancy for men will increase from 77.4 years in 2005 to 83.6 years in 2050; for women, the change will be from 83.3 to 88.8 years. From 2005 to 2050, the prevalence of people 65+ years old will increase from 19.5% to 33.6%, whereas of those >85 years old from 2% to 4.7%. The ratio between older adults and the general population will shift from 1/5 in 2005 to 1/4 in 2030 for 65+ years old, and from 1/50 to 1/20 for >85 years old (2). **In the USA**, the country where the majority of research on aging has been conducted, in 2030, when all of the baby boomers will be 65 and older, nearly one in five residents is expected to be 65 and older. This age group is projected to increase to 88.5 million in 2050, more than doubling the number in 2008 (38.7 million). Similarly, the 85 and older population is expected to more than triple, from 5.4 million to 19 million between 2008 and 2050 (3).

The constant aging of the World's population has been paralleled and highly affected by the shift from acute to chronic diseases, which is usually indicated as the "epidemiological transition". The frequent occurrence, in late life, of chronic, non-fatal and coexistent diseases, including cardiovascular diseases, respiratory diseases, or depression (4) implies a progressive decline in the function of organs and physiologic systems. This, in turn, together with changes typical of "normal" aging, results in an increased risk of disability, i.e. the inability to carry out activities of daily living and, in a more restrictive use of this term, the consequent dependency for somebody else's help to do it.

Disability is frequent among older adults. Between 20 and 30% of people >70 years old in the general population in the USA (5) as well as in Europe (6) reports some form of disability, and the prevalence increases with older ages. Women have longer life expectancy at all ages, but usually spend more years of their life with disability. This sex difference is constant in different populations, increases with advancing age and is probably related to a different distribution of diseases by sex, with a higher prevalence of more lethal diseases in men (mainly cardiovascular diseases and some cancers) and a higher prevalence of more disabling diseases in women (7). Disability is a dynamic and in general progressive process, which, in some cases (defined as "**catastrophic**" disability) , appears suddenly, as a result of acute, severe diseases (stroke, myocardial infarctions, fractures etc). However, in many cases, the onset of disability is more gradual, as the result of chronic diseases or age-related changes in biology and physiology ("**progressive**" disability) (8).

1.1 Impairments of mobility and walking in the disablement process

Moving itself is one of the fundamental functions of daily life, and is pivotal to retain independency in all the other activities of daily life (9-11) and to maintain adequate

levels of social interaction (12;13) and emotional life (14;15). All these factors are cardinal for a good quality of life (16;17).

Epidemiology of mobility disability in older adults

The aging process is often associated with a reduction of mobility and gait. Among non disabled community-dwelling older adults, the prevalence of mobility disability, defined as combined impairments in gait, balance and muscle strength, is high (about 40%), and a relevant proportion has a severe impairment (10%). Gait disorders, regardless of their operative definition, which may encompass qualitative and quantitative methods, these are common findings in the elderly: their prevalence increases from 14% in apparently healthy subjects aged >65 years (18) to 50-80% in >85 years old (19;20). In a recent epidemiological survey of 468 participants aged 77 years (range 70-99), the prevalence of neurological gait abnormalities, defined on a clinical ground, was 16%; its incidence was 103 per 1,000 person-years in the whole series and increased sharply with aging. In a 5-year follow-up, the risk of institutionalization and death increased with the presence and the severity of gait disorders (21).

Changes in mobility and gait can remain completely subclinical, but often may have an insidious progression until they affect the ability of carry out the activities of daily living, either basic, self-care activities (such as transferring from the bed to a chair, using the toilet etc), or more complex ones (such as shopping, cleaning the house, preparing meals etc) which are fundamental to maintain independency outside the house. Mobility impairment could represent a critical threshold in the transition between independence to disability (22). It has been demonstrated that, even in initially non-disabled older adults, a dysfunction of mobility increases the likelihood of accelerated loss of independence, hospitalization, institutionalization or death (23-25).

2. Clinical consequences of mobility dysfunction and the onset of disability

From a clinical viewpoint, the most direct and severe consequences of mobility and gait dysfunctions and **falls and fractures**, which are often dramatic events in the life of older adults, and can be the trigger for the onset of **catastrophic** disability: according to estimates of the World Health Organization (WHO), accidental falls are the third cause of disability and dependency in the activities of daily living in older adults (26). Every year, 1/3 of people >65 years old experiences at least one fall, and 15% at least two falls (27-29). Of these falls, 5% results in a fracture, and another 5% in other serious lesions (30). Fear of falling, which is a frequent consequence of a fall, may worsen balance and gait (31), may lead to a reduction in mobility and finally have a negative impact on the quality of life (32). Fractures (mainly of the hip and femur) are the most serious consequences of falls. Around 90% of fractures in the elderly are caused by accidental falls (33). However, many falls apparently attributable to accidents are, in fact, the result of an interaction between environmental obstacles and individual susceptibility, stemming from aging and comorbid subclinical or clinical diseases. The broad category of gait disorders is the more common single and specific determinant of falls (10-25%), after the external or environmental factors (such as obstacles or slippery surfaces), and the most frequent intrinsic cause (34;35). Older ages have been associated with a more rigid, less coordinated gait, which is intuitively associated with a higher risk of negative clinical consequences. The impairment of balance control, of spatial orientation and reflexes, the reduction of muscle strength and tone and of step height can lead to an impairment in the ability of avoiding falls after an event such as slipping or stumbling (34).

Other clinical consequences of mobility and walking impairments could mediate the onset of more **progressive** disability in some older adults. A number of studies has demonstrated that movement and gait disorders are associated with a higher risk of incident cardiovascular disease (36) and also, in older adults without overt, clinical, neurological diseases, with a higher risk of cognitive decline (37;38) and dementia, of both Alzheimer (39) and vascular (40) types. Neuroimaging studies have suggested that degenerative and vascular brain diseases, which are responsible for different dementia subtypes, might affect specific cerebral cortical and subcortical areas involved in movement planning and execution (41;42). From a practical viewpoint, it is important to consider that impairment in physical functioning and gait is in most cases evident before cognitive impairment is detected: besides being contributing to discriminate between degenerative and vascular dementia (43;44), this might offer clues to early recognition of subclinical cognitive impairment. Finally, physical and gait dysfunctions are associated with a reduced survival, which might results from a combination of falls, reduction of cardiovascular performance and death due to underlying diseases (21;45-47). It is noteworthy that an improvement in mobility and gait over time independently predicts a reduction in mortality, suggesting that interventions aimed at modifying physical performance are potentially successful (48).

Walking is also a form of physical activity and exercise, which is especially recommended for older adults. Regular walking for at least 30 minutes a day for 5 days/week is recommended by the Center for Disease Control and Prevention (CDC) and by the American College of Sports Medicine (ACSM) (49). On the other hand, physical inactivity increases the risk of overweight and obesity, diabetes, hypertension, coronary heart disease, some types of cancer and osteoporosis (50), and this might in part explain the association between impairments in mobility and gait and cardiovascular and cerebrovascular diseases and other comorbidities. Finally, a reduced physical activity is associated with an excess mortality (51). In the United States, less than 50% of older adults (50) maintain regular physical activity, and the trend towards inactivity increases with advancing age (52).

The transition towards disability in apparently healthy older adults: mobility dysfunction as a central element of pre-disability or "frailty" status

Many studies have investigated the factors involved in the development of disability. The role of specific disabling diseases, which are likely responsible for the higher risk in the female sex (7;53) is clear. However, in a relevant proportion of older adults the onset of disability is appearently not precedented by any overt disease. Though still debated in the clinical and research arena, the concept of "frailty" can be useful to better understand the transition and the phatophysiologic pathway leading from independence to disability. Frailty is a dynamic concept and indicates an unstable equilibrium caused by the reduction of functional reserve and by the impairment of multiple physiological systems, with a consequent reduced ability to regain physiological homeostasis after stressful, destabilizing events, either endogenous or exogenous. These events can be either organic (e.g. a new disease or the reactivation of a pre-existing disease), psychological (loss of the partner) or social (moving to a different place). From a clinical viewpoint, frailty is a state of high vulnerability for accelerated physical and cognitive decline and of a higher risk of transition to disability, dependency, falls, institutionalization and death (54). Therefore, this term can not be equated to disability and comorbidity, as very often happens in the clinical setting (for this reason, some authors prefer the term "pre-frailty" to describe this "pre-disability" status, reserving "frailty" for more care-dependent older adults). Frailty can range from mild to severe stages and,

given its dynamic nature, transitions between grades of different severity are possible, and even improvements in the frailty status have been demonstrated. As a pre-disability condition, the concept of frailty might be cardinal to identify high risk older adults, in whom the transition towards adverse health outcomes can be potentially delayed with appropriate interventions (55). The reduction of reserve and the presence of subthreshold impairments responsible for frailty occur at multiple levels: with advancing age, different organs and systems experience a reduction in mass or in function, which may not reach the threshold for clinical appearance, but may be responsible for frailty: in other words, these changes could result in functional modifications which are initially not severe enough to become evident at a "clinical" level, or to significantly impact the instrumental (IADL) or the basic activities of daily living (BADL). Among others, the endocrine system (hypothalamus deregulation, reduction in steroid hormones and in IGF-1), the immune system and inflammatory response, the skeleton (ostopenia), the muscle (sarcopenia), and the nervous and cardiovascular systems are involved. According to this picture, frailty would result from the expression of these subtle multiple deregulations in different physiologic systems, age- and comorbidity-dependent. Although in the first phases this process can remain clinically silent, when the aggregation of impairments increases, this syndrome becomes detectable through biomarkers (PCR, hemoglobin levels etc.) or objective measures of physical performance.

The most important application of the frailty concept is probably the detection of individuals at high risk for incident disability, with the aims of possibly treating risk factors and finally preventing disability. Different authors have pursued operational definitions of frailty. Linda Fried and other investigators from the Cardiovascular Health Study (CHS) have provided a major contribution to this definition, developing a pathophysiologic model and proposing an operational output (56). They identified frailty as a constellation of signs and symptoms associated with changes in body composition and physical functioning. In their theoretical pathway, sarcopenia and muscle strength, by limiting mobility and physical activity, reduce total energy expenditure and nutritional intake, which in turn determine weight loss and further sarcopenia. These elements have been operationalized and validated in the context of the CHS cohort, by clustering the following items: unexplained weight loss, reduced grip strength, self-reported exhaustion, slow walking speed and low physical activity. According to Fried et al.'s definition (presence of >3 of the quoted criteria), 6.9% of the CHS participants were frail, and other 7.2% became frail in the following 4 years. This definition has been reproduced in other epidemiological settings using clinical markers for each of the domain listed in the Fried's definition: similar prevalence was found, for example, in the InChianti study, where 8.8% of participants were frail (57), and in the Women Health and Aging Study (WHAS-I and II) were 8.9% of participants were frail (58). The frailty phenotype, which is more prevalent among women and in older individuals, is an independent risk factor for falls self-reported mobility disability, hospitalization and death over 3 years (56), and is associated with a positive history of cardiovascular diseases. However, even in subjects without clinical cardiovascular diseases, frailty is associated with subclinical vascular disease, detected with non-invasive measures, such as carotid ultrasound, ankle-arm index, ECG, cardiac echocolor-Doppler and brain MRI. (59).

According to the CHS model and operational definition, mobility represents the objective, common outcome resulting from the reduction of functional reserve in different physiologic systems and declines early in the disablement process (54). The CHS model has been questioned by other authors (60;61) for being excessively mobility-centered, whereas other elements, such as cognitive decline, had a comparable impor-

tance in the disablement process. The issue of including cognitive decline in the frailty phenotype remains debated, but many criticisms have been raised, since cognitive decline, in its clinical expressions of mild cognitive impairment (MCI) and dementia, seem to have very specific pathologic and clinical aspects, and allow overt clinical manifestations and dramatic consequences even in the absence of multiple systems reserve reduction.

Different theoretical models have been developed and refined to describe the disablement process, or the transition from independence to disability, and to classify the different components to come up with a universal language for both theoretical and rehabilitative purposes. Probably, the most classical model was proposed by Nagi (62), and describes the transition from active pathology to disability through intermediate abnormalities in body structure and function. This framework, reflecting a purely medical idea of the disablement process, was subsequently extended by Verbrugge and Jette (63), who included sociocultural factors (i.e., social and physical environment) and personal factors (e.g., lifestyle behaviors and attitudes). Parallel in time, in Europe, the World Health Organization (WHO), in his International Classification of Impairments, Disabilities, and Handicaps (ICIDH), developed a similar model to account for the disabling consequences of chronic disease. This model was designed to become part of the WHO family of international classifications. Similar to the Verbrugge and Jette's revision of the Nagi's model, the ICIDH model was modified in the International Classification of Functioning, Disability and Health (ICF) (64). The ICF portrays human function and decreases in functioning as the product of a dynamic interaction between various health conditions and contextual factors. Within the ICF, contextual factors include aspects of the human-built, social, and attitudinal environment that create the lived experience of functioning and disability as well as personal factors such as sex, age, coping styles, social background, education, and overall behavior patterns that may influence how disablement is experienced by the individual. Both models provide definitions for the elements of the dynamic pathway from disease to various functional outcomes.

Limiting the model to biological/medical factors for the purpose of this work (Figure 2), active pathology refers to biochemical and physiologic abnormalities that are labeled as diseases in medical science; impairments are dysfunctions and structural abnormalities in specific body systems that can be evaluated through clinical examination, laboratory tests, imaging procedures, and symptoms reports: factors that affect the ability to walk are in this category; functional limitations are restrictions in performing fundamental physical and mental actions used in daily life: according to this definition, walking should be included in this category; disability is experienced difficulty doing activity in any domain of life due to a health or physical problem.

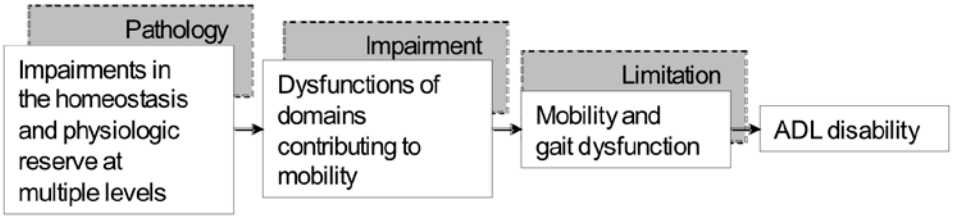

Figure 2 Models for the disablement process, revisited to highlight elements of mobility disability

3. Health care and social costs of impaired mobility

It is quite intuitive that mobility disability is associated with excessive costs. However, data on this topic are scarce and come only from the USA. A recent study has analyzed the costs of hospitalization, institutionalization, and palliative care associated with the incidence of mobility disability in a representative sample of 5,138 older adults participating in the multicentre Established Populations for Epidemiologic Studies of the Elderly (EPESE) (mean age 78 years) (65). Mean healthcare costs for an older adult with an initially preserved mobility and independency in the activities of daily living, who developed self-reported inability to walk 800 meters or to climb stairs in one year, was 2,000 USD, compared to 900 USD expense for age-, sex- and social status-matched elderly whose mobility remained preserved. In the year following the onset of mobility disability, the mean healthcare costs raised to 2,700 USD on average, ranging from 2,000 USD if the subject's mobility remained stably impaired, to 4,700 USD if it further worsened to affect his ability to perform daily living activities, up to 13,000 USD if the case of death. Using an objective measure of physical performance, such as the Short Physical Performance Battery, mean health care costs over 4 years increased with increasing baseline severity of mobility limitation, ranging from 7,000 USD for those with absent baseline mobility limitation, to 10,000 USD for those with moderate impairment to 12,000 USD for those with severe impairment. The 4 years mean healthcare costs were also associated with the progression of the mobility limitation over time, ranging, for example, from 3,000 USD for those with initially preserved mobility who remained stable over time to 10,000 USD for those with initially preserved mobility who finally developed severe limitations. This study gives a clear picture of the economic magnitude of the problem, to be born in mind, in a public health prospective, when the costs of interventions to prevent disability are quantified .

Looking at healthcare expenses related to mobility disability, it is also important to consider the costs associated with its major clinical consequences: according to a US recent report, the cost for diagnosis, treatment and follow-up of the consequences of a fall (traumatisms and fractures) ranges from 63 and 86,000 USD, with a mean cost of 6,000 USD (66).

Other studies investigated the relationship between mobility disability and health services utilization: older adults with mobility limitations are less likely to participate in screening and prevention programs (mammography, PAP test) (67), and in general express a lower satisfaction about health care, complaining in particular about lacking accuracy and communication from the physicians (68). In fact, movement and gait disorders represent a challenge in clinical practice: for example, even physical exam is more difficult for this kind of patients than for patients younger or with preserved mobility. This could reduce the time available to allow a proper communication between the physician and the patient.

In spite of the clear importance of movement and gait disorders and their relevant consequences, evaluation of gait and balance is still infrequent in the clinical practice: in the USA, only 23% of patients reporting mobility problems and – even worse - only 7% of those who reported a fall undergo a specific gait and balance evaluation (69).

4. Assessment of mobility in epidemiologic studies

Different methods have been used to describe mobility and gait impairments in the elderly, including both qualitative and quantitative assessments. Even if very different

in their characteristics, each seems to provide different, relevant, and possibly complementary information to detect abnormalities in mobility and gait. Self-reported measures of mobility (such as difficulty walking 400 m or climbing stairs) provide a macroscopic perspective, are simple, easy to administer and inexpensive, and therefore can be useful in epidemiological studies with a high number of participants (70;71). Obviously, these measures capture a relatively advanced stage of mobility and gait impairments, when the ability to perform the ADLs has been already altered, are limited by a low sensibility and do not provide detailed information. For this reason, these measures seem more useful as final outcomes to evaluate the effect of more subtle mobility impairments, than as intermediate factors along the pathway to disability. An important advancement in this field has been provided by the introduction of objective, quantitative measures of physical performance, which usually include a battery of tests, from stop-watch measured gait speed, to balance measures, simple assessments of muscle strength, ability to turn around etc. These measures are now largely used in research, and, even if very slowly, are penetrating the clinical routine and are more frequently included in the multidimensional assessment of the geriatric patient. Different batteries for the evaluation of lower extremity performance have been proposed and validated (23;27;72). This approach allows to explore more early stages of functional decline, preceding the onset of disability, and to identify older adults which have a still preserved global function, and still live independently, generally in the community, but have an increased risk of becoming disabled in a relatively short time. These measures are able to predict either catastrophic or progressive disability (73), in general predict disability accurately across diverse populations (25), and are able to predict falls, urinary incontinence, depression, institutionalization, and death (24;27;28;63;74), even in initially non-disabled older adults (75). This is why the measures of physical performance are largely considered a pivotal element to define the frailty phenotype. Among other measures, gait speed over a short course (3 or 4 meters) seems to perform, alone, almost as well as other comprehensive batteries in predicting incident disability (25). This measure is easy and not time consuming, and clinically meaningful cut-offs have been proposed for either the absolute value or for the change over time. For example, the threshold of 1 m/s in the measures gait speed consistently predicts persistent lower extremity limitations, falls, hospitalizations, requirement of a caregiver and death (76;77). On the other side, a prospective decline in gait speed of 0.1 m/s within 1 year increased the subsequent 5-year mortality rate (78). Thus, it is possible that gait speed might penetrate the consciousness of clinicians and providers more than more complex batteries. Extended walking tests, such as the 6-minutes-walking test and the 400 meters walking, have been also shown to predict disability in older adults (79-81). These tests are not substitutive but complementary to lower extremity batteries and short walks, since they can better account for the aerobic fitness component; however, the translation to different geriatric clinical settings appears more complex. Other more sophisticated techniques use gait analysis to collect more detailed information about gait. Relatively simple assessments can be obtained using short walkways with embedded pressure sensors (GaitRite or GaitMat systems) or other relatively low-tech tools (insole pressure sensors or accelerometers), which allow to collect spatial-temporal data of the gait cycle. These instruments are relatively expensive and need dedicated personnel and space. However, they start to be implemented in epidemiologic studies. Conversely, the use of more complex assessments, such as computerized gait analysis systems, are still limited to studies on biomechanics, conducted on small samples.

5. Determinants of mobility disability in older community-dwellers

In a relevant proportion of older adults living in the community, the decline in mobility is not related to a defined medical condition and often it does not receive proper medical attention until a late stage. In many other patients referring to the physician for the impairment in mobility, the presence of comorbidity more or less related to the decline in physical function makes challenges the identification of a primary cause and consequently reduces the chances of an effective treatment. Moreover, walking is such an important activity in human life, that the evolution has provided human beings of redundant physiologic systems to adapt to possible reductions in physiologic reserve, and these systems are able to work and interact in different ways to accomplish the same task (22). As a consequence, walking problems become clinically evident only when this large functional reserve is exhausted and even compensatory strategies have failed.

Many different factors, either non modifiable or modifiable, can play a role in mobility and gait dysfunction in older adults, and contribute to the onset of progressive disability. Demographic factors (older age, female sex), socio-economic status (lower education and income, widowhood), lifestyle (smoking habit, overweight and obesity) and comorbidity are recognized risk factors for incident mobility impairment (82). Among biologic factors, different clinical chronic diseases or subclinical processes affecting the structure or function of physiologic organs and systems are thought to contribute to dysfunction in mobility and gait. Luigi Ferrucci and colleagues (22) tried to summarize the theoretical role of possible contributors to mobility disability to design the InChianti study, an Italian epidemiologic survey on older adults from the Tuscan area of Chianti. At that time, the framework he designed was only partially support-

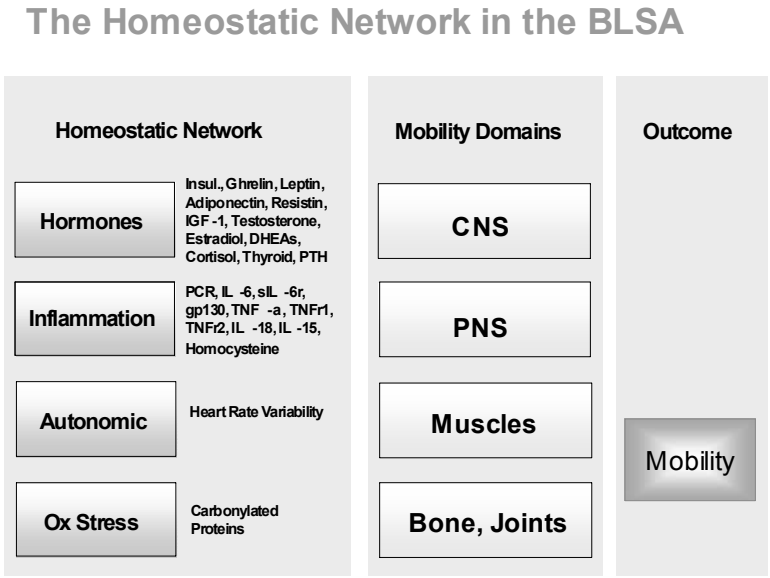

Figure 3 Physiologic domains contributing to mobility and gait, and the underlying homeostatic changes. The present thesis is focused on the right side of this figure, i.e. the clinical and subclinical determinants of progressive mobility disability in older adults. Reproduced by courtesy of Dr. Luigi Ferrucci.

ed by evidence. Afterwards, in the effort to reframe the Baltimore Longitudinal Study on Aging (BLSA), a long-running epidemiologic study from the National Institute on Aging of the USA, he revised the same theoretical model, and integrated the homeostatic changes that might underlie the dysfunction of the different physiologic domain contributing to mobility and gait. In this framework (**figure 3**), six systems are the major contributors to mobility and gait dysfunction, and the relative impairments could be responsible for a deregulation of these functions. These systems are: 1) the central nervous system (CNS), including the regulatory system for balance control 2) the peripheral nervous system (PNS) 3) perceptual systems (vision, hearing) 4) muscles 5) bone and joints 6) production and transportation of energy (cardiovascular and respiratory systems).

In cases of catastrophic disability, when a single event is responsible for the acute onset of mobility impairment, the treatment directed to correct that factor, if effective, should improve mobility; also, rehabilitative strategies are more effective when facing a sudden loss of function. However, some data suggest that appropriate interventions can substantially improve frailty-related walking ability in older persons [(83-85)], and that an improvement in mobility and gait is associated with more gains in the global health status of older adults (48). Understanding the determinants of mobility disability and gait impairment is of paramount importance to plan effective interventions directed, in the long run, at preventing disability in older adults.

Aims

This work aims at assessing the determinants of progressive mobility disability and gait impairment in older adults living in the community. For this reason, we focused on persons with relatively preserved function at baseline. Starting from the model described above (**Figure 3**) we conducted different analyses to assess the role of specific potential predictors and the relationships among them. In particular, with tried to disentangle the role of central and peripheral nervous systems and of the systems dedicated to energy production and transportation. In the first study (Inzitari M, et al., J Am Geriatr Soc. 2006; 54:318-24), using data from the Italian Longitudinal Study on Aging (ILSA) we aimed at assessing the predictors of mobility decline among factors which had been previously associated with poor motor performance in older adults. We decided that selecting people with optimal mobility at baseline might provide more accurate information about the factors independently involved in the onset of progressive mobility decline. In the second study (Inzitari M, et al., J Gerontol A Biol Sci Med Sci. 2007; 62:837-43) we focused more specifically on cognitive function as a potential predictor, investigating the role of specific cognitive domains in mobility decline in the same cohort of older adults. The hypothesis was that functions related to the executive domain, such as attention and psychomotor speed, could be involved in the decline of mobility more that other domains, such as memory. To further confirm the relationship between physical performance and cognitive function in the domains of attention and psychomotor speed, we also considered the reverse relationship, and analyzed the role of using gait speed as a potential predictor of cognitive decline in the cohort of the Health, Aging and Body Composition study (HABC) (Inzitari M, et al., Neuroepidemiology. 2007; 29:156-62). In the fourth study (Inzitari M, et al., Arch Intern Med. 2008; 168:1270-6) we looked at the burden of damage in the nervous system, and we assessed the association between neurological signs, physical performance, cognitive and affective decline and the incidence of disability in the activities of daily living in older community-dwellers without overt neurological disease at baseline. To answer this question, we used the data of the Insufficienza Cardiaca negli Anziani Residenti a Dicomano (ICARe Dicomano) study. In parallel, we looked at the effect of subclinical vascular disease, with a particular emphasis to its localization at the level of coronary arteries, and physical functioning, using data from the Cardiovascular Health Study (CHS) (Inzitari M, et al., J Gerontol A Biol Sci Med Sci. 2008; 63:1112-8). Finally, in the effort of investigating the interrelations between different domains contributing to mobility disability, we looked at the association between cardiovascular risk factors and anemia on one hand, and structural abnormalities of the brain white matter on the other, once again using data from the CHS (Inzitari M, et al., J Am Geriatr Soc. 2008; 56:1867-72).

Marco Inzitari, *Determinants of Mobility Disability in Older Adults : Evidence from Population-Based Epidemiologic Studies*, ISBN 978-88-8453-916-8 (print) ISBN 978-88-8453-758-4 (online)

Methods

This work is the result of three years of investigations conducted in Florence, Italy, and in Pittsburgh, PA, USA. The data used for these analyses were collected in four major epidemiologic studies from two Countries, Italy and the United States. These studies had different primary outcomes, but all were specifically designed to enrol community-dwelling older adults. The study designs had many similarities, which allowed us to maintain a certain homogeneity in the conduction of the different analyses. For example, even if we considered different potential predictors in the different analyses and following papers, the ways of measuring the outcome were similar, and we always took into account the role of comorbidity and other important variables included in the multidimensional geriatric assessment (socio-economic status, psychological aspects etc). On the other hand, we took advantage of the peculiarities of each study to test specific hypotheses: for example, the relationship between vascular disease and mobility was investigated using sophisticated measures of atherosclerosis, such as those included in the CHS, whereas the relationship between central nervous system function and physical performance was assessed using data from the ILSA study, which was specifically designed to assess the epidemiology and consequences of neurological problems in the elderly.

1. Populations

The participants included in these analyses were all community-dwelling adults aged 65 years old or older. The four studies described below were approved by the local institutional review boards, and participants gave informed consent. The "Insufficienza Cardiaca negli Anziani Residenti a Dicomano" (**ICARe Dicomano**) (86) is a longitudinal epidemiological survey of heart failure in older people. It was conducted in Dicomano, a small, rural town near Florence, Italy. In 1995 the study, which followed the principles of the Declaration of Helsinki, enrolled the entire unselected community-dwelling elderly (≥65 years) population recorded in the city registry office. The only exclusion criterion was living in a nursing home. The final number of enrolled subjects was 864. In 1999, participants were re-interviewed and underwent a follow-up visit. Vital status and hospitalizations were recorded until December 2003. The **Italian Longitudinal Study on Aging** (ILSA) (87) investigated frequency, determinants, and consequent dysfunctions of age-related cardiovascular and neurological diseases in a population-based cohort of older (>65 years) Italians. Following an equal allocation strategy, a sample of 5632 subjects was randomly selected from 8 municipalities across Italy, including both urban and rural environments. The baseline evaluation (1992) in-

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cluded a general interview (including demographics, socio-economic factors, medical history, medications etc) and a two-step visit: in the first step, all the participants underwent structured assessments risk factors and symptoms/signs suggestive of the diseases under study and a general assessment for cognitive and physical function. In a second phase, specialists of each discipline confirmed the diagnoses through a detailed clinical examination and medical records reviewing. A follow-up visit took place in 1995. The **Cardiovascular Health Study (CHS)** (88) enrolled 5888 community-dwelling older adults, including 5201 participants recruited in 1989-1990 and 687 minority participants recruited in 1992-1993. Participants were recruited from a random sample of the Health Care Finance Administration Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), Pa. Potential participants were excluded if they were institutionalized, wheelchair-bound in the home, or currently under treatment for cancer. The study protocol included a very broad assessment, ranging from cardiovascular function, which represented the specific focus of the study, to an extensive assessment of geriatric syndromes. Other more specific ancillary examinations were performed on subsamples of the study. Annual examinations included physical and cognitive assessments with periodic reassessment of medical history, including clinical and subclinical cardiovascular disease. Interim telephone and clinic contacts at 6 months were used to assess all hospitalizations and outpatient cardiovascular diagnoses. The **Health Aging and Body Composition** (Health ABC) study aimed at investigating if the changes in body composition acted as a common pathway by which multiple diseases affect morbidity, disability, and mortality. Between 1997 and 1998, the study enrolled 3.075 Medicare-eligible non-disabled men and women aged 70–79 years from Pittsburgh, PA, and Memphis, TN, USA. Exclusion criteria were difficulty walking one quarter of a mile or climbing 10 steps without resting, or walking without an assistive device.

2. Markers of different physiologic domains tested as potential predictors of mobility and gait dysfunction

2.1 Central and peripheral nervous systems

During the ILSA study baseline visit, a short battery for cognitive function was administered to the whole cohort, and included three paper-and-pencil tests: a screening measure for global cognition (the Mini Mental State Examination [MMSE] (89), one test for episodic memory, the Babcock recall story test (90), in which the participant is asked to remember the details of a short story, and one test attention and psychomotor speed, the Digit Cancellation Test (91), which consists of a matrix of number, in which participants have to cancel as many numbers as possible corresponding to a specific indicated number, during a definite time. In a second phase, subjects scoring less than 24 points on the MMSE underwent an extensive assessment comprising Sections B and H of the Cambridge Mental Disorders of the Elderly Examination, the Pfeffer Functional Activities Questionnaire, the Hamilton Depression Scale, a full neurological examination, and a review of clinical records. Final possible diagnoses were absence of cognitive impairment, dementia (based on Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, criteria), and cognitive impairment with no dementia (CIND) (92). The HABC study included a similar short battery, with the MMSE and a

paper-and-pencil test of attention and psychomotor speed, the Digit Symbol Substitution test, very similar to the Digit Cancellation Test included in the ILSA study, whose aim is to copy as many novel symbols corresponding to numbers as possible, in a given time. In the ILSA baseline visit, the whole cohort was screened for depressive symptoms using a 30-items Geriatric Depression Scale (GDS) (93). Again, in the ILSA study, a two-steps procedure allowed trained neurologists to reach or discard a diagnosis of distal symmetric neuropathy (DSN). In the screening phase, subjects were questioned as to whether they experienced symptoms such as pain, burning, tingling or sensory loss, cramps, weakness or fatigue, or muscle wasting in the legs or feet and about the time profile of the symptoms' presentation. Light touch, pinprick, position sense, and ankle jerk reflexes were examined. Subjects with a previous diagnosis, those having diabetes mellitus, and those positive for at least one of the above listed symptoms lasting more than 1 day or repeated over several days underwent a full neurological examination. Final diagnosis followed criteria previously established (94).

A neurological assessment was conducted by expert geriatricians at the baseline evaluation of the ICARe Dicomano study. It included elements of the classic neurological examination, such as tests of muscle strength (foot extensions, pronator drift or shift of one arm etc.), sensitivity (light touch at the foot plant etc.), deep tendon reflexes, plantar reflex and classic extra-pyramidal signs; in an extended vision, we considered part of the neurological exam two simple and quick instrumental tests, such as dynamometry for the evaluation of muscle strength (handgrip and hip flexion) and the Purdue pegboard, in which participants are timed while putting 10 small sticks into an equal number of holes in a tablet. This test, initially designed to assess manual dexterity, also explores frontal lobe cognitive function because it requires integrity of attention, sequencing, planning and motor coordination. To obtain a final score of neurological damage, we calculated, for each participant, the number of subtle neurological abnormalities summing up the positive signs resulted from the neurological exam. The term "subtle" was used because these signs neither related to definite neurological diseases – considered as exclusion criteria - nor were reported by the participants.

2.2 Energy production and transportation

Coronary artery calcium (CAC) disclosed by electron beam tomography (EBT), is a non-invasive measure of calcified atherosclerotic plaque, which correlates with underlying atherosclerosis (95). CAC seems more sensitive in capturing low levels of subclinical vascular disease than other non-invasive measures of atherosclerosis, such as ankle-arm index (AAI) or carotid intima-media thickness (96), which are associated with a decline of physical performance in the elderly (97), (98). Between 1998 and 2000, 614 of 727 older community-dwellers CHS participants from the Pittsburgh cohort underwent EBT to detect CAC. Coronary artery calcium (CAC) was assessed using an Imatron C-150 scanner and the Agatston scoring method (99), (100). In our analyses, CAC score was examined in quartiles (CAC score 0-34, 35-220, 221-659, >660 for increasing quartiles) and as log(CAC score). We also tested sex-specific quartiles.

Hemoglobin concentration was measured in fasting blood samples by automated coulter counters in laboratories close to each field center. Internal and external quality-assurance reports were examined, and concurrently obtained duplicate samples were analyzed for 3% of participants (101). Anemia was defined according to WHO criteria, as a hemoglobin concentration <13 g/dL in men and <12 g/dL in women.

2.3 Outcome variables: measures of physical performance and other variables

All the studies included an objective assessment of physical performance, which was usually a comprehensive battery including tests for gait, balance and muscle strength. In one case, the ICARe Dicomano study, the measures of physical performance were only available at baseline. In the other studies these measures were re-evaluated in at least one point in time after baseline. The ILSA study battery included 6 tests that, in a previous study, (27) proved to be independent predictors of falls. Three of them explore dynamic balance and coordination: time to stand from a chair unaided and without using the arms, the number of times a subject could step up onto a single 23-cm step in 10 seconds, the number of errors made in performing a tandem walk along a 2 meters line (5 cm wide). Three other tests assess static balance: time standing on one leg, number of steps and time spent to walk for 5 m and number of steps to complete a 180° turn. A total score, ranging from 0 (worst possible) to 14 (best possible performance), was obtained summing up single items' scores. This battery was administered at baseline (1992) and three years later. The ICARe Dicomano study used the classical Short Physical Performance Battery (SPPB) developed and validated by Guralnik and colleagues (23). This battery includes three sub-tests for balance, walking, and muscle strength. In the modified version used in this study (86), balance was evaluated as the time, up to a maximum of 10 sec, the participant was able to maintain standing equilibrium in five tasks of increasing difficulty. Walking ability was assessed as speed in a 4-m path (best of two trials). Lower extremity strength was indirectly evaluated as time required to stand up five times from a chair. A score from 0 (worst) to 4 (best performance) was adjudicated to each test, based on the quartile distribution of the test results in a reference older population. The SPPB summary performance score (range 0 to 12), which is the sum of individual tests scores, has been shown to predict incident disability and death independent of measures of comorbidity in the same population (102). The CHS also included different test for physical performance. Gait speed was calculated from the number of seconds it took a participant to walk a 15-foot course at usual pace starting from a standstill. Chair stand results were recorded as the number of seconds used to perform five consecutive stands from a seated position on a 45-cm tall chair with arms folded across the chest. The standing balance test measured the time a participant could stand in a tandem position (heel-to-toe) up to a maximum of 10 seconds. These measures were obtained at baseline (1992-93), and repeated yearly during the follow-up. Of the Health ABC physical performance battery, we used the single value of usual pace gait speed (m/s) over a 6-meter course is a valid and reliable indicator of physical performance, which predicts incident disability, hospitalization, institutionalization, falls, fractures and death in healthy elderly persons (25;77;103). Moreover, among other physical tests included in a previous HABC analysis, usual pace gait speed demonstrated the strongest association with cognition (104). In specific analyses, variables different from the measures of physical performance were used: in particular, in study 3, the outcome was the change in the attention and psychomotor speed score over five year; in study 4, since measures of physical performance were not available during the follow-up, increasing difficulty in the activities of daily living, change in the MMSE over time, deaths and cerebrovascular events were used as outcomes; finally, in study 6, the outcome variable we the progression of white matter hyperintensities on brain MRI scan over a 5 year follow-up.

3. Essential aspects of the statistical analysis

Linear (continuous variables) and logistic regression models (dichotomous variables as an outcome) were the common statistical techniques used across the different studies to evaluate changes in physical performance over time (dependent variable) as a function of the baseline different physiologic domains markers (independent variables). The outcome variable could be either the total score of the different physical performance batteries or the specific sub-tests, depending on the analysis. It could be usually modelled as either a categorical variable, based on percentile distribution or on accepted clinical cut-offs, or a continuous variable, as the difference between follow-up and baseline data (delta). Other statistical methods were punctually used in specific analyses (for example survival models in the fourth study).

Main results

Study 1

In the ILSA study, 1052 subjects performed normally on motor tests in 1992. Of these, 166 (15.8 %) had declined at the 1995 re-assessment. In the univariate analysis, older age, female gender, widowhood, a lower education, a lower MMSE score, CIND, dementia, parkinsonism, distal symmetrical neuropathy, depressive symptoms, heart failure, anemia and an increased difficulty in performing basic (BADL) and instrumental (IADL) activities of daily living were significantly associated with a higher risk of decline in physical performance decline using either the dichotomous (any worsening in the total score) or the continuous (delta) variable as an outcome. In multivariable logistic and linear regression models (**Table 1**), depressive symptoms and distal symmetrical neuropathy were associated with an increased risk of decline in physical performance over time. Other independent predictors were older age, female gender and lost baseline IADL activities. Interestingly, CIND was no longer associated with the outcome in multivariable analyses.

Table 1 Multivariate predictors of physical performance decline in the ILSA study

	Logistic regression. Outcome variable: decliners versus non-decliners.			Linear regression. Outcome variable: δ MP 1992-1995.		
Variables in the equation	OR	95% CI	p-value	Unstandardized coefficients		p-value
				B	SE	
Age				0.045	0.010	<0.001
70-74 Vs 65-69	1.66	1.08 - 2.55	0.022			
75-79 Vs 65-69	2.06	1.24 – 3.40	0.005			
80-84 Vs 65-69	3.84	2.14 - 6.88	<0.001			
Female sex	1.50	1.03 - 2.20	0.036	-0.171	0.110	0.118
DSN*	2.00	1.03 - 3.87	0.039	0.725	0.225	0.001
Depressive symptoms	1.85	1.17 – 2.92	0.008	0.324	0.138	0.019
Lost Instrumental ADL	1.22	1.08 - 1.37	0.001	0.174	0.036	<0.001

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Study 2

In the same cohort, we investigated more in detail the role of specific cognitive domains in the development of mobility disability over time. Participants who experienced a decline in mobility over three years had worse scores in all the three tests, the MMSE (global cognition), the Babcock recall story test (memory) and the Digit Cancellation Test (attention and psychomotor speed), compared with those who did not decline. However, after the adjustment for demographics, education, social status, comorbidities and functional status, only the Digit Cancellation Test score remained significantly associated with a decline in mobility (**Table 2**): participants in the lower quartile had a significantly increased risk of mobility decline, compared with those in the highest quartiles, and the risk increased with a dose-response trend across decreasing performance quartiles at this specific test. Among the specific sub-items of the physical performance battery, and adjusting for demographics and education, subjects in the lowest quartile of Digit Cancellation Test, compared with those in the highest quartile, had a two to threefold higher risk of decline in step-ups, walking speed, and 180°-turn steps, whereas the adjusted risk of decline in tandem walking was more than fivefold higher in subjects in the lowest quartile of Digit Cancellation Test.

Study 3

The relationship between cognitive function and gait found in the previous analysis (study 2) was further explored and consolidated using data from the HABC study: this represents a sort of "mirror analysis", since the predictor and the outcome were reverted compared to study 2. In particular, we examined the role of gait speed in predicting a decline in attention and psychomotor speed, assessed using the performance at the Digit Symbol Substitution Test (DSST). Over 5 years, 389 (17.1%) participants had declined at least 1 SD (9 points) in the DSST score. The prevalence of DSST decline linearly decreased across increasing quartiles of baseline gait speed. The risk of DSST decline was greater across quartiles of gait speed after adjusting for age, baseline DSST and for other covariates (Figure 4). Further adjustment for 3MS 5-year change did not modify the results (OR 1.74, 95% CI 1.21–2.51, for the lowest versus the highest quartile of gait speed). The association was confirmed in linear regression models, in which a decreasing baseline gait speed was associated with an increasing decline in DSST over time (p=0.001).

Table 2 Effect of cognitive status, expressed as individual test score quartiles, on the risk of physical performance decline in the ILSA study

Quartiles	Model 1			Model 2		
	OR	95% CI	p-value	OR	95% CI	p-value
MMSE (global cognition)						
4	1					
3	0.61	0.36-1.01	0.054	0.62	0.37-1.05	0.073
2	0.66	0.36-1.21	0.180	0.66	0.36-1.21	0.177
1	1.12	0.61-2.04	0.715	1.09	0.59-2.01	0.778
Trend			0.026			0.051
Babcock Recall Story Test (episodic memory)						
4	1					
3	0.82	0.50-1.34	0.437	0.84	0.51-1.38	0.645
2	0.68	0.41-1.13	0.140	0.70	0.42-1.18	0.109
1	1.09	0.66-1.81	0.739	1.12	0.67-1.87	0.180
Trend			0.242			0.274
Digit Cancellation Test (attention)						
4	1					
3	1.33	0.74-2.37	0.343	1.31	0.72-2.37	0.376
2	1.81	0.98-3.36	0.058	1.76	0.94-3.29	0.078
1	2.71	1.43-5.11	0.002	2.47	1.29-4.74	0.006
Trend			0.011			0.003

Logistic regression, adjusted for age, gender and education (Model 1), and marital status, comorbidities (parkinsonism, distal symmetrical neuropathy, cognitive impairment non dementia, dementia, depression, anemia, heart failure), BADL and IADL, and the two other cognitive tests, with backward deletion of redundant variables (Model 2).
MMSE: Mini Mental State Examination; BSRT: Babcock Story Recall Test; DCT: Digit Cancellation Test

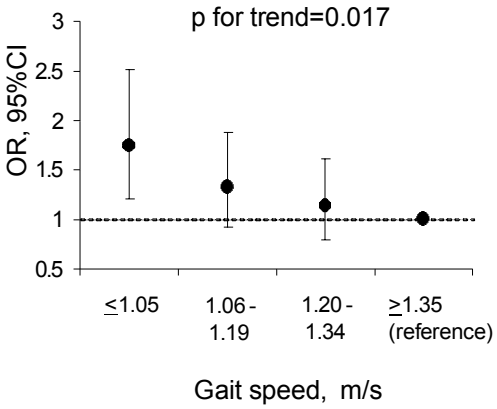

Figure 4 Risk of decline of Digit Symbol Substitution Test (>1 SD [9 points] from mean change) over 5 years, across quartiles of usual pace gait speed (m/s). Logistic regression model, adjusted for age, gender, race, education, weight, physical activity, cardiovascular comorbidity, high blood pressure, diabetes, COPD, depressive symptoms, baseline Digit Symbol Substitution Test (DSST), baseline Modified Mini-Mental Status Exam (3MS), and change in 3MS over time.

Study 4

Of 506 ICARe Dicomano participants free of neurological diseases (mean [SEM] age, 71.9[0.3] years; 42% were men), 59% had an 1 or more neurological signs at a standard neurological exam (mean [SEM], 1.1[0.06]; range, 0-8). At baseline, the number of neurological signs increased with age and with declining cognitive and physical performance, depressive symptoms, and disability, after adjusting for several covariates, but did not increase with falls and urinary incontinence. The number of neurological signs prospectively predicted worsening cognitive status and difficulty in performing basic and instrumental activities of daily living, adjusting for demographics, comorbidity and cognitive and physical performance at baseline (**Figure 5**). The mortality rates were 22.6, 23.3, 23.9, 58.6, and 91.9 per 1000 person-years in participants with 0, 1, 2, 3, and 4 or more neurological signs, respectively. Compared with a number of signs of less than 3, having an 3 or more signs was associated with an increased adjusted risk of death (hazard ratio, 1.77; 95% confidence interval [CI], 1.25-2.74) and of cerebrovascular events (hazard ratio, 1.94; 95% CI, 1.07-3.54) over 8 years.

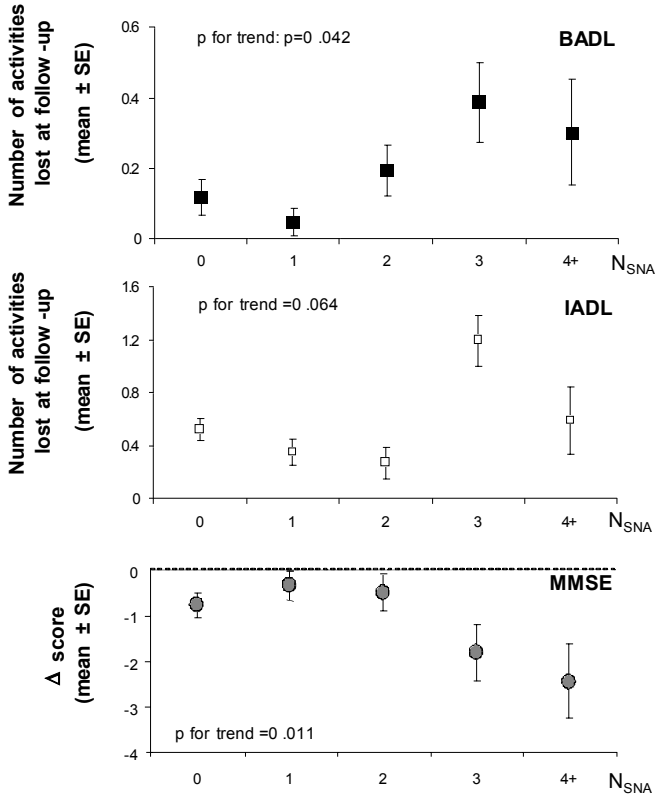

Figure 5 Prediction of functional and cognitive decline over 4 years in 420 older community-dwellers free of overt neurological diseases at baseline. All analyses adjusted for age, sex, baseline comorbidity, physical performance, cognitive functioning, and basic and instrumental activities of daily living. N_{SNA}: number of subtle neurological abnormalities.

Study 5

Among the CHS participants at the Pittsburgh study site, 387 older adults (65.1% women, 21.7% African American) without a history of cardiovascular disease underwent an electron beam tomography (EBT) for the detection of coronary artery calcium (CAC) and an assessment of physical performance in 1992-93. Mean age was 78.7 ± 3.8 (SD) years (range 71–96), and did not differ between genders. CAC scores ranged from 0 to 4151. Compared with women, more men had higher CAC scores. Considering the whole sample, none of the three performance-based measures of physical function (gait speed, chair stand, and standing balance) varied significantly across quartiles of CAC. The interaction term between gender and gait speed proved significantly associated with CAC (p=0.005). Gender-stratified analyses showed a significant trend toward lower values of gait speed and time holding tandem stand with higher CAC among women, but not among men. Women had progressively lower gait speed across CAC quartiles: those with CAC > 220 walked more than 0.1 m/s slower than those with CAC < 35 (age-adjusted p for trend=0.017) (**Figure 6**). In multivariable models adjusted for several covariates, including demographics, traditional cardiovascular risk factors and factors potentially contributing to gait dysfunction (e.g., osteoarthritis), the association remained statistically significant for women in both linear (gait speed as a continuous outcome) and logistic models (dichotomous outcome of an abnormally low gait speed): each of the top three CAC quartiles had a more than twofold higher odds of walking slower than 1 m/s, compared to the lowest CAC quartile (p=0.021). Consistent with the differences by gender described above, in multivariable models the association between CAC and gait speed remained nonsignificant in men. In women, the association between CAC and gait speed continued to be statistically significant after adjustment for other indicators of vascular disease, such as baseline ankle-arm index, brain MRI variables (white matter grade, ventricular enlargement grade, brain infarcts), and cardiac left ventricular mass.

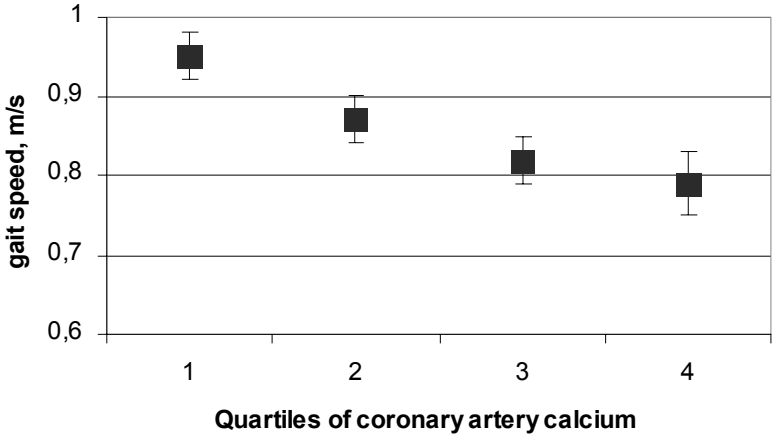

Figure 6 Association between quartiles of coronary artery calcium and physical performance in older women from the Cardiovascular Health Study, after adjustment for age.

Study 6

Among the 1846 CHS participants included in this analysis (mean age 73.7+4.4, 41% men, 15.6% African-Americans) mean hemoglobin + SD was 13.7+1.3 g/dl. Compared to baseline, 1325 of the 1846 participants (72%) showed no change and 4 a white matter hyperintensities (WMH) grade reduction on follow-up MRIs. WMH increased (worsened) 1, 2, 3 and 4 grades in 440, 67, 9 and 1 participants, respectively. Comparing these

Table 3 Risk of worsening white matter hyperintensities (WMH) >1 grade in anemic participants with and without high blood pressure (measured blood pressure >140/90), compared to non-anemic ones. Multivariable logistic regression models

	Model Adjustment Factors*	OR (95%CI) for WMH change >1 grade
		BP > 140/90 N=678
A	Demographics	1.69 (1.03-2.82)
B	A + Baseline WMH grade and time between scans	1.74 (1.04-1.92)
C	B + Vascular risk factors and comorbidities	1.83 (1.07-3.15)
D	B + Measures of vascular disease	1.84 (1.08-3.06)
E	B + History of stroke	1.70 (1.02-3.29)
F	B + Cystatin C	1.60 (1.01-2.70)
G	B + Inflammation	1.59 (1.01-2.83)
H	B + Medications	1.69 (1.01-2.82)
I	B + Incident stroke	1.68 (1.02-2.83)
	Fully adjusted	1.79 (1.03-2.98)

*Models are adjusted for the following variables:
Age, gender and race.
Model A + baseline WMH grade and time between the scans.
Model B + body mass index, diabetes, smoking status (current/past Vs. never), LDL, HDL, dizziness, factor VII and prevalent cardiovascular diseases.
Model B + ankle-arm index, left ventricular hypertrophy by ECG
Model B + history of stroke
Model B + Cystatin C
Model B + inflammation (at least two of: low albumin, high CRP, white blood cells, fibrinogen)
Model B + lowering-lipid medications, antihypertensive medications and aspirin use.
Model B + strokes between the two MRI scans.
Fully adjusted: adjusted for all the above mentioned covariates.

517 (28%) participants with a WMH worsening >1 grade with the 1329 (72%) with no worsening, mean hemoglobin (13.2+1.2 vs 13.3+1.1, p=0.987) and the prevalence of anemia (11.2% vs 10.9%, p=0.845) were similar. Mean hemoglobin and anemia were also comparable after stratification by gender and race. In univariate logistic regression models, anemia did not significantly predict the WMH worsening. We tested the interaction between hemoglobin or anemia and baseline characteristics (high BP, renal function, diabetes, race, and baseline WMH). The interaction between anemia and high BP was statistically significant (p=0.013). Hypertension was present in 678 participants, of whom 373 (55%) were treated. In this group, those in whom WMH worsened were more frequently anemic at baseline than those in whom WMH remained stable (14% versus 9%, age-adjusted p-value=0.041). In the group with normal baseline BP, neither the prevalence of anemia nor mean hemoglobin concentration were different comparing participants with or without worsening WMH. Using multivariable logistic regression, the risk of worsening WMH >1 grade was higher for participant with high BP and anemia, compared to those without anemia, after adjustment for demographics and other covariates (**Table 3**). Overall, renal function and inflammation determined the greatest reduction (around 20% of the OR) of the risk of worsening WMH for anemic participants with high BP. Adjustment for incident or recurrent cerebrovascular events did not substantially modify the results. Separate linear regression models with continuous WMH change over 5 years as an outcome yielded similar results.

Discussion

1. Summary of the results

An overview of the results of the 6 studies is provided in **Figure 7**.

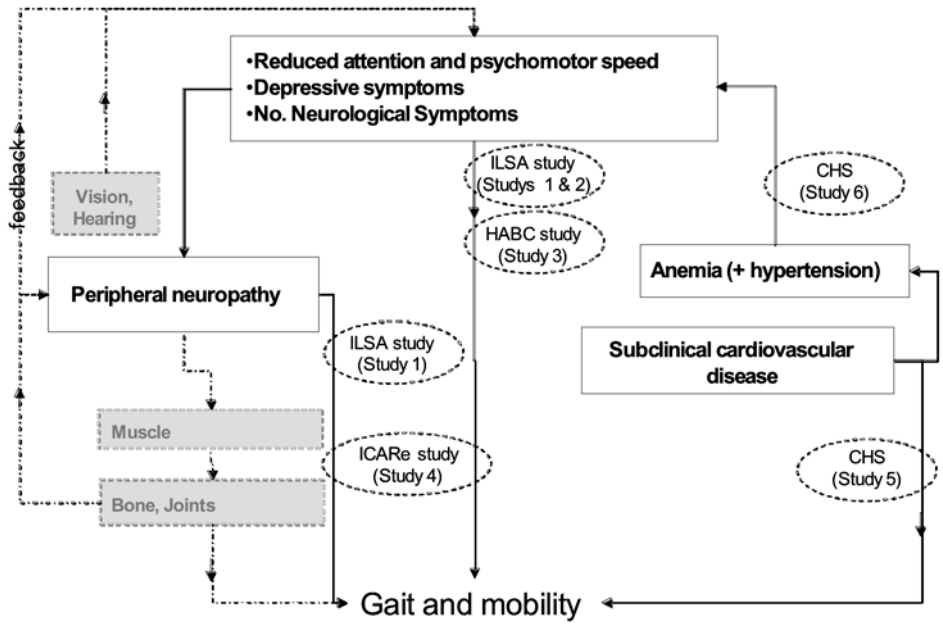

Figure 7. Physiologic domains impairments predicting mobility and gait dysfunction according to the model presented in figure 3. Solid lines indicate the associations investigated in the present work. Dashed lines indicate the physiologic domains included in the model but not explored in this work.

In the diagram, the physiologic domains listed in the model described above (**Figure 3**) and the associations with the outcome are indicated. In the ILSA study, about 16% of the 1052 participants with initially optimal physical performance experienced some decline in physical performance over 3 years. As the results of study 1 show, depressive symptoms and distal symmetrical neuropathy were independent predictors of this decline. Surprisingly, the hypotheses that cognitive impair-

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ment no dementia (CIND) could predict the decline of physical performance, was rejected. The more detailed analysis of the association between specific cognitive domains dysfunctions and physical performance decline provided in study 2 revealed an independent role of cognition in this decline, but only and very specifically for the domain of attention and psychomotor speed. Memory seemed not involved in this process. Interestingly, cognitive dysfunction in the quoted domains was associated with a subsequent impairment in almost all the individual physical sub-tests, either those more demanding on attention (e.g. walking in tandem), or even routine tasks, such as the simple walking speed at preferred pace, which is traditionally considered as a semi-automatic activity. The relationship between cognitive and physical function was confirmed and consolidated in the cohort of the HABC study, where we explored the opposite direction (study 3): gait speed at preferred pace over a short course predicted a decline in attention and psychomotor speed over 5 years. The findings reported in studies 2 and 3, taken together, might suggest that cognitive and physical functioning decline in parallel, possibly being the expression of a common underlying pathophysiologic substrate, whereas at a first glance it might be hypothesized that cognitive decline influences physical performance and gait. In effects, in a cohort without a history of overt neurological diseases a measure of the nervous system damage load, such as the number of subtle neurological abnormalities, was associated with both cognitive and physical dysfunctions at baseline and predicted decline in cognitive function and increased difficulty in performing the activities of daily living, which generally require the integration of both cognitive and physical functions (study 4). This index of nervous system damage load probably accounts for both central (upper extremities strength asymmetry, Babinski reflex, extrapyramidal signs, etc.) and peripheral (Achilles reflexes) nervous systems abnormalities: an involvement of the peripheral nervous system in the decline of physical performance seem consistent with results of study 1, in which distal symmetric neuropathy was a strong and independent predictor of physical performance decline. Study 5 demonstrated an association between subclinical vascular disease, in particular at the coronary location, and physical performance in women only: even if this association was independent of systemic vascular disease as measured with the ankle-arm index, and vascular brain disease in particular (brain MRI), the cross-sectional nature of the study does not allow to discard any potential mediation pathways linking coronary calcium and physical performance decline, including cognitive decline, peripheral arterial disease (and perhaps peripheral nerves dysfunction), and subclinical cardiac dysfunction. In a longitudinal perspective, energy transportation defects (anemia, in hypertensive older adults) might perhaps contribute to the onset of geriatric syndromes through the association with chronic and subtle cerebrovascular disease we demonstrated in study 6. An association between anemia and declining physical performance had also emerged for the univariate analysis performed with the ILSA study database (study 1) but was not confirmed in the multivariable models.

Noteworthy, the markers of the different physiologic domains which in our analyses resulted predictors of mobility and gait decline were independent of age and many other potential confounders we adjusted for. However, age remained as a substantial, independent predictor of physical decline in all the analyses, thus suggesting that the variables identified as predictors can capture only partially the complexity of age-related decline.

2. Comparison with previous studies and possible pathophysiologic pathways

2.1 Central nervous system

Recent studies are questioning the classical notion that gait is a semi-automatic activity: increasing evidence suggest that balance and walking are rather complex tasks, that depend considerably on cognitive control (105). Preserved cognitive functions are thought to be pivotal to correctly plan motor strategies, and to control for interferences from the environment (106), and are particularly stressed in challenging situations (107). Most studies examining the relationship between cognitive functions and gait in aging have focused on attention and executive functions (108). The focus on attention makes intuitive sense, and is also consistent with a large corpus of research indicating that attention resources decline with aging. Studies examining associations between attention and gait have used analytic approaches that can be broadly divided into two general classes. Dual-task methods require the participants to walk and perform a second task, usually a cognitive one, which would provide interference with motor control (109-113). The advantage of using the dual-task approach is that attention resources are experimentally manipulated. Hence, it is possible to make inferences about causality. Allocation of attention to competing tasks represents executive processes (114) that are sensitive to aging (115-117). However, dual-task methodology can be challenging in terms of both implementation and interpretation (118). With specific respect to gait, the validity and generalizability of such studies are difficult to establish because the paradigms used are not standardized in terms of the individual tasks, administration instructions, and whether analysis concentrates on outcomes pertaining to motor or cognitive task, or some combination of both (119). The second class of studies correlated gait performance with independent measures of attention and executive function. This approach presents an advantage in that examining the cognitive correlates of gait is not limited to attention only. These studies are particularly valuable in a longitudinal design. Our study 2 on the ILSA cohort belongs to this second group, together with few other studies with similar design which have been conducted and published concurrently (Ble et al., 2005; Atkinson et al., 2007). Compared to these other studies, we had the advantage of specific tests for different cognitive domains, including memory, whose measure did not simply rely on global cognitive performance, as assessed with the MMSE; this helped to tease out the specific role of attention and psychomotor speed. As a further strength, the ILSA study included a very large battery of motor tests repeated after three years. The strong relationship between cognition and gait was confirmed by the finding of a significant "reverse" association, i.e. between decreasing baseline gait speed and increasing risk of decline in attention and psychomotor speed as an outcome (study 3). This observation is consistent with other studies, which demonstrated that motor performance is longitudinally associated with the development of dementia (39;40;120) and persistent cognitive impairment (121;122). These findings suggest that motor performance can decline before cognitive impairment is detected and that objective measures of motor performance might be a very sensitive tool to predict cognitive decline in clinical settings. Study 1 also showed a longitudinal association between depressive symptoms and physical performance decline over time. The prevalence of subsyndromal depression, defined as the prevalence of significant depressive symptoms in the absence of DSM defined major depression, is very common in late life: indeed, there appears to be a shift from major depression as the pre-

dominant form of depressive disorder in late life to that of subsyndromal depression (123;124). In the CHS, 20% of the sample had depressive symptoms according to the Center for Epidemiological Studies-Depression scale (CES-D) (125). While formal DSM diagnoses were not available in the ILSA study, as well in CHS and other major epidemiological studies, it is reasonable to assume that some of the participants with high depressive symptoms likely suffered with major depression. However, given the estimates that only 1-3% of the general older population have major depression, the majority of these older people were likely affected by depressive symptoms. Our findings are in line with previous studies, demonstrating an association between depressive symptoms and an increased risk of functional disability (126), and more specifically of decline in physical performance in older adults (127).

Impairments in the three domains of cognition, mood and mobility at old ages are highly prevalent concerns in older adults, often tend to cluster in the same subject (128;129) and all seem characterized by reduced psychomotor speed. They might represent sub-threshold manifestations, in a continuum whose overt expression is major depression, dementia, and major movement disorders linked to underlying clinical neurological diseases. Besides being each a risk factor for the appearance of major clinical manifestations in their specific domain (cognitive impairment for dementia, gait dysfunction for falls and depressive symptoms for major depression), they also predict dramatic health outcomes in the elderly, including loss of autonomy, institutionalization and death (23;130-132). A rapidly emerging literature suggests that impairments in these three domains might share underlying pathophysiologic substrates, such as structural and functional brain abnormalities. The presence of neurological abnormalities at the neurological exam, in older adults without the evidence of clinical neurological disease, could represent a proxy for chronic abnormalities in the nervous system, which might represent this common substrate. In our study, we demonstrated a longitudinal association of subtle neurological abnormalities with cognitive decline and increased difficulty in the ADLs, and a cross-sectional association with physical dysfunction, whereas the longitudinal association with increasing depressive symptoms could not be confirmed in the multivariable analysis. Previous studies documented the relationship between specific subtle neurological abnormalities and diffuse brain white matter lesions at a CT scan in non-demented older adults (133). Similarly, in CHS participants without a history of stroke, the number of neurological findings was independently associated with silent infarctions at brain MRI (134). We speculate that the presence of subtle neurological abnormalities at the neurological exam reflect the presence of diffuse white matter lesions or brain infarcts. These lesions, also termed age-related white matter changes (WMH), are likely caused by hypertensive damage in the small arteries of the brain, which may appear as a signal alteration of the white matter at neuroimaging (hypodenisities at CT and hyperintensities at MRI scans). We discussed the evidence about risk factors, pathophysiology and consequences of WMH, including cognitive and physical dysfunction, in a review paper (135). More recent studies have confirmed that WMH, detected using either classical brain MRI visual readings (136), or more sophisticated and specific techniques to track abnormalities of white matter fibers (137), could be implicated in physical performance dysfunction in older adults. Brain small vessels disease is also a well established risk factor for depressive symptoms (138). As detailed in our review article (135), it has been hypothesized that WMH could disrupt the frontal-subcortical neural circuits connecting prefrontal and frontal areas to basal ganglia and the thalamus. These circuits are cardinal to integrate, process, gener-

ate, and sequence complex tasks, and are in general related to the executive cognitive functions (129). More recent studies have suggested that not only brain small vessels disease causing WMH, but also cortical brain abnormalities, could be responsible for geriatric syndromes affecting the "thinking, moving and feeling" domains. Interestingly, the affected cortical areas would be mainly located in the same prefrontal regions which belong to the frontal-subcortical circuits, even if they are supported by a more extended network of complementary and redundant functions, which are placed in different cortical areas. Focal gray matter abnormalities in prefrontal (particularly important seems the role of the dorsolateral prefrontal cortex), premotor, inferior frontal and parietal association cortex have been associated with abnormal gait in community-dwelling older adults (139;140). These cortical areas are also involved in the regulation of executive functions, with the dorsolateral prefrontal cortex playing a crucial role, and the parietal cortex providing compensation when the former area is damaged (141). Balance difficulties are rather associated with low grey matter volumes in putamen, cerebellum and posterior parietal regions (139).

Studies of physical activity and exercise confirm the hypothesis of a shared common substrate for the cognitive, mood and physical impairments. Descriptive studies have shown that older adults who exercise are less likely to develop dementia or other cognitive functional impairments, compared to those who do not exercise (142-144). It has been proposed that positive brain changes might result from the effect of an overall cardiovascular conditioning that improves cerebrovascular blood flow and neuronal oxygenation, and thus prevents age-related neurodegenerative processes and delays brain structural and functional decline. This point might perhaps be consistent with the association between subclinical vascular disease and physical dysfunction in older women, reported in study 5, even if we were not able to demonstrate a role of brain small vessels disease in that analysis. Animal studies have also confirmed that increased physical activity is associated with the development of new neurons (145). On the other side, exercise intervention studies in previously sedentary older adults have also shown beneficial short term gains in cognition (146;147), as well as overall functional activation and structural changes in the fronto-parietal lobes (148;149).

2.2 Peripheral nervous system

In the ILSA cohort, the prevalence of distal symmetric neuropathy was about 7%, and the incidence 7.9 per 1000 person-years (150). In our study, distal symmetric polineuropathy predicted the decline in mobility over time, independent of diabetes and other potential confounders. Studies on functional consequences of peripheral nerves dysfunction have been so far very scarce. Peripheral neuropathy is reported as associated with falls in the elderly (151). In one cross-sectional study (152) peripheral nerve dysfunction, as determined by vibration perception threshold measurement, contributed to lower extremity impairment independent of diabetes and other possible confounders. A clinical-pathological picture called "Chronic Idiopathic Axonal Polineuropathy (CIAP)" has been recently re-evaluated as a condition frequent in older ages (153;154). In CIAP, symptoms are distal and symmetric, and predominantly sensory, therefore symptoms on which our definition of distal symmetric polineuropathy is based are just those reported to characterize CIAP. In CIAP, impairments are thought to progress slowly over time without a substantial impact on disability (155;156). Our findings may contrast the view that peripheral nerve dys-

function in the elderly is irrelevant in terms of disability, as also recently confirmed by the Health ABC investigators in diabetic and non-diabetic older adults (157). Our index of subtle neurological abnormalities, reported in study 4, also included neurological signs (e.g. Achilles reflex etc.) which are likely the expression of a peripheral damage, more than a central nervous system dysfunction. An association between physical performance impairment and subtle findings (vibration sense, deep tendon reflexes abnormality) indicating peripheral nerve dysfunction, in the absence of a definite diagnosis of neuropathy, was demonstrated also in a previous research (158). Recent population based studies have been focusing on peripheral nerves function in community-dwelling older adults, independent of the clinical appearance of neuropathy, and the pathophysiologic mechanisms linking neuropathy to physical dysfunction have been an object of speculation. For example, axonal degeneration is associated with a reduction in muscle density (159) and also with reduced bone health and structure (160). Regarding the etiology of peripheral neuropathy, which represents a relevant condition also in non-diabetic elders (150), many hypotheses have been proposed. For example, clinical and subclinical vascular disease could be implicated (161), and this would be consistent with the association we found in study 5, between vascular disease and physical dysfunction. Systemic inflammation and the concurrent reduction of antioxidant molecules (162) have been also associated with a reduction in peripheral nerves function. An alternative, intriguing possible contribution might derive from lower erythropoietin values, which also have been associated with reduced peripheral nerves function measured with electroneurography, and with a higher risk of clinically detected polineurophaty (163). If confirmed, these findings could provide a complementary explanation to the association between anemia and physical dysfunction (164), besides the one we suggest in study 6 (i.e. the role of WMH).

2.3 Subclinical vascular disease

In relatively healthy older populations, physical performance decline is associated with vascular risk factors (165;166), which are also associated with CAC in middle-aged and older people (167;168). Only a few studies have investigated the relationship between quantitative noninvasive measures of atherosclerosis, which are considered an intermediate phenotype linking risk factors to disease, and physical performance. In community-dwelling elders free of overt cardiovascular and neurological disease, carotid plaques and common carotid artery intima-media thickness were associated with slower gait speed (98), and in older adults without clinical intermittent claudication, the ankle-arm index proved to be associated with abnormal walking performance (169). In our study, we failed to demonstrate any effect of subclinical heart, brain, or lower extremity vascular abnormalities upon the association between CAC and impaired gait. However, the cross-sectional nature of the study and the limited size of the sample, which included relatively healthy people, suggests cautions about a definitive exclusion of such a possibility. Finally, looking back at this whole work (studies 1 to 4) in a broader vision, vascular disease, either clinical or subclinical, seems to be a constant negative factor, with documented chronic adverse consequences at the level of the brain and potentially at the peripheral nervous system, which lead to functional decline, particularly in the mobility domain. Although CAC is strongly associated with other measures of subclinical atherosclerosis, it represents a more sensitive measure to detect low levels of vascular disease

in older adults (96). In facts, we were able to show that also very low levels of disease are associated with physical dysfunction. These findings might contribute to reaffirm the importance of preventive strategies to control vascular risk factors, also in older adults.

2.4 Anemia and cerebrovascular disease

Recent investigations have examined the relationship between anemia, defined according to the WHO criteria, and cognitive/affective status at old ages. In a cross-sectional evaluation from the Women's Health and Aging Study II, participants with anemia had worse executive function (measured with the Trail Making Test), compared to those without anemia (170) and in the InCHIANTI study anemia was associated with depressive symptoms (171). In an acute care setting, older adults with anemia had significantly lower global cognitive performance, compared to those with normal hemoglobin (172). Finally, anemia is also associated with a decline in physical performance in older adults living in the community (164). Our findings suggest that, in participants with high blood pressure, the association of anemia with cognitive and mood disorders might be mediated by white matter disease, which we have seen to be a well established risk factor for cognitive / executive dysfunction and depression at old ages, and is emerging as one of the critical factors in the onset of progressive mobility disability. High blood pressure is a strong risk factor for white matter disease (173;174). Different pathophysiologic mechanisms could be suggested to explain the association between anemia and WMH in older adults with high blood pressure. First, anemia could aggravate the chronic hypoperfusion of the white matter. Age and hypertension are the most important determinants of structural changes of small penetrating arteries and arterioles of the white matter. Such changes include thickening of the vessels wall and narrowing of the vascular lumen (arteriolosclerosis) (175). Sclerotic remodeling also impairs the ability of small vessels to dilate, so that in hypertensive patients with arteriolosclerosis, a reduced blood pressure, of the type that occurs during cardiac dysrhythmias (175) or heart failure (176), could lead to a decrease in blood flow. An additional factor that may impair the white matter blood flow is the tortuosity and elongation of these vessels (175), which is related to the severity of hypertension (177). In summary, these mechanic obstacles to white matter blood flow determined by hypertension could induce an increased sensitivity to a further reduction of oxygen supply when hemoglobin concentration is low. Another possible mechanism, which has been also invoked to explain the effect of anemia in precipitating stroke in chronic kidney disease patients, is the reduced production of erythropoietin. Besides regulating red blood cell production, erythropoietin receptors in the brain seem to have a protective effect against hypoxic/ ischemic injury (178), and a small trial in humans has shown initial limited evidence towards a positive effect of treatment with erythropoietin towards an improvement in clinical outcomes 1 months after stroke (179). Although the association of anemia with WMH progression in hypertensive older adults was independent of renal function, the possible role of erythropoietin deficiency can not be excluded, since the adjustment for renal function reduced the strength of the association between anemia and worsening WMH. The systemic effects of erythropoietin are gaining increasing attention in the study of the aging process, as we have seen regarding the quoted intriguing suggested association between low values of this molecule and peripheral nerve dysfunction.

3. Main strengths and limitations

Even though the studies presented here differed in terms of populations and predictors, they were broadly homogeneous in terms of study design, within their overarching epidemiological approach, and predictors.,The samples examined were large, population-based, and characterized by ethnic, geographic, cultural, and socio-economic diversity. These factors increase the external validity of our findings. On the other hand, we also took advantage of the difference and peculiarities of the different studies, which allowed to test different hypotheses using specific, sensitive and sophisticated markers of the different physiologic domains contributing to mobility and gait.

However, methodological differences across the studies also represented a limitation of our work: the lack of availability of certain measures prevented, for example, evaluation of changes in physical performances in the ICARe Dicomano. Also, there is a certain degree of heterogeneity in study designs, for example in the fact that the CHS analysis on vascular disease and physical function (study 5) was only cross-sectional, and the analysis on the association between anemia and white matter disease (study 6) did not include the possible impact on geriatric syndromes.

Conclusions

In conclusion, this work suggests that progressive mobility and gait dysfunction in older adults from the community has a multifactorial origin, which is complicated by reciprocal interrelations of different physiologic domains. This represents a challenge for researchers, who need to test new analytic strategies to account for these multiple influences and redundant pathways, which moreover vary over time. But this aspect represents a challenge also for clinicians, who have to embrace a multidisciplinary vision of the progressive disablement process of older adults. Our findings, supported by additional evidence from other authors and studies, could have implications also for treatment: on one hand, the relevance that our results give to sub-threshold disease, which should probably not defined as "subclincal" because of its measurable impact on function, urges to maximize preventive strategies when these are likely to be effective (e.g., on cardiovascular risk factors and anemia). On the other hand, the multifactorial origin of mobility and gait dysfunction might probably need the development of multifactorial interventions to treat geriatric syndromes.

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