Motoric Cognitive Risk Syndrome: What we should know?

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ABSTRACT

Background: Motoric Cognitive Risk syndrome (MCR), which combines slow walking speed with subjective cognitive impairment (SCI), is a new pre-dementia syndrome. MCR has the potential to rapidly screen individuals who are at risk for dementia but more information to better understand this association is required. The following four aims have been selected for this thesis: 1) To systematically review the association of MCR with incident cognitive impairment, cognitive performance and brain structures; 2) To explore an updated definition of MCR by comparing the characteristics of older individuals with MCR defined with slow walking speed and increased Five Times Sit to Stand test (FTSS) time; 3) To examine the association between depression as well as depressive symptomology and MCR in the participants of the Canadian Longitudinal Study on Aging (CLSA); and 4) To examine the association between MCR and cardiovascular disease and risk factors (CVDRF) in the Canadian population.

Methods: In the first study, a systematic review of the literature was completed for the subject headings “Walking” and “Cognition disorders” combined with “Subjective cognitive impairment”, “Subjective cognitive decline” and “Motoric cognitive risk”. A total of 11 studies were included after the application of the inclusion criteria. For the other part of this thesis, two databases from previous studies with information on MCR were identified and selected. For the second study, a total of 633 individuals without mild or major neurocognitive disorders were included from the Gait and Alzheimer Interactions Tracking study (GAIT). Individuals were grouped based on MCR definition, using either or both slow walking speed and time to complete FTSS. For the third and fourth studies,

a total of 29,569 individuals that met the inclusion criteria were selected from the CLSA. Participants were grouped based on MCR criteria and age groups.

Results: The systematic review reported a significant association between MCR and incident cognitive impairment (polled Hazard Ratio (HR)=1.70, 95% Confidence Interval (CI), 1.46-1.98 with P-value <0.001) as well as MCR and dementia (pooled HR=2.50, 95% CI, 1.75-2.39 with P- value < 0.001). When comparing FTSS and slow walking speed for the definition of MCR, it was found that there was only a small overlap between identified individuals (2.4%). Moreover, a significantly larger proportion of individuals were identified when using slow walking speed, as compared to FTSS in the definition of MCR (12% versus 6.2% with P≤0.001). When considering the association between MCR and depression, significant findings were reported for between group comparisons for sex, Indigenous identity, independent place of living, living alone, low household income, high education level, number of medications, mean BMI, high BMI (overweight/obese), at least 1 depressive symptomology, at least 2 depressive symptomologies, 3 depressive symptomologies, and depression. Though some variation was reported depending on age group mood disorder, number of depressive symptoms (at least one, at least two or three) and the total population were found to be positively associated with MCR. Lastly, when studying the association between MCR and CVDRF, it was reported that cardiovascular diseases (CVD) are more prevalent in individuals with MCR, compared to individuals without MCR. Moreover, younger individuals have more cardiovascular risk factors (CVRF) than their older counterparts.

Conclusion: Systematic review and meta-analysis confirmed that MCR is associated with incident cognitive impairment, though its pathophysiology remains unclear. The original studies showed that slow walking speed cannot be replaced by the FTSS for the definition of MCR and that MCR is associated with CVDRF as well as depression and depressive symptomology in the Canadian population.

French ABSTRACT

Contexte: Le syndrome de risque cognitif moteur (MCR), qui combine une vitesse de marche lente et une plainte cognitive subjective (SCI), est un état pre-dementiel. Le MCR a le potentiel de repérer rapidement les personnes qui sont à risque de démence mais une meilleure compréhension de l'association entre le MCR et la survenue d'une démence est requise. Les quatre objectifs suivants ont été retenus pour cette thèse: 1) Faire une revue systématique de l'association entre le MCR et le déclin cognitive incident, les performances cognitives et les structures cérébrales; 2) Comparer les caractéristiques des personnes avec un MCR, définies par une vitesse de marche lente et/ou un score plus long au Five times sit-to-stand test (FTSS); 3) Examiner s'il existe une association entre la dépression et le MCR et 4) Examiner le lien entre le MCR et les facteurs et les maladies cardio-vasculaires (CVDRF) dans la population canadienne.

Méthodes: La revue systématique de la littérature a été réalisée avec les mots-clés "Marche" et "Troubles cognitifs" combinés avec "Troubles cognitifs subjectifs", "Déclin cognitif subjectif" et "Risque cognitif moteur". 11 études ont été sélectionnées. Pour les autres études, deux bases de données contenant des informations sur le MCR ont été retenues. Pour la deuxième étude, 633 personnes sans troubles neurocognitifs légers ou majeurs ont été incluses dans l'étude GAIT (Gait and Alzheimer Interactions Tracking). Les personnes ont été regroupées en fonction de la définition du SCI, en utilisant l'une ou l'autre vitesse de marche lente ou les deux, ainsi que le temps nécessaire pour effectuer l'essai FTSS. Pour les troisièmes et quatrièmes études, un total de 29 569 personnes répondant aux critères d'inclusion ont été sélectionnées à

partir de CLSA. Les participants ont été regroupés en fonction des critères de la RCM et des groupes d'âge.

Résultats: La revue systématique montre une association significative entre le MCR et le déclin cognitif incident (rapport de risque (HR) = 1,70, IC à 95%, 1,46-1,98 avec valeur P < 0,001) ainsi qu'entre le MCR et la démence (HR regroupé = 2,50, IC à 95%, 1,75-2,39 avec valeur P < 0,001). En comparant le FTSS et la vitesse de marche lente pour la définition du MCR, on constate qu'il n'y avait qu'un faible chevauchement entre les personnes identifiées (2,4%). De plus, une grande part des personnes ont été identifiées lorsqu'elles marchaient lentement, comparativement au FTSS dans la définition de du MCR (12% contre 6,2% avec P≤0.001). En examinant l'association entre le MCR et la dépression, des résultats significatifs ont été rapportés pour les comparaisons entre les groupes pour le sexe, l'identité autochtone, le lieu de vie autonome, le fait de vivre seul, le faible revenu du ménage, le niveau de scolarité élevé, le nombre de médicaments, l'IMC moyen, l'IMC (surpoids/obésité), au moins une symptomatologie dépressive, au moins deux symptômes de dépression, trois symptômes de dépression et la dépression. Bien qu'une variation ait été signalée selon le groupe d'âge, le nombre de symptômes dépressifs et la population totale ont été associés de façon positive au MCR. Enfin, lors de l'étude de l'association entre le MCR et les CVDRF, les maladies cardio-vasculaires (CVD) sont plus fréquentes chez les personnes ayant un MCR que chez les autres. De plus, les personnes plus jeunes présentaient plus de facteurs de risque cardiovasculaire (CVRF) que les sujets plus âgés.

Conclusion: La revue systématique et la méta-analyse ont confirmé que le MCR est associé à un déclin cognitif incident, bien que sa pathophysiologie demeure incertaine. Les études initiales ont montré qu'une vitesse de marche lente ne peut pas être remplacé par le FTSS pour le diagnostic du MCR et que le MCR est associé aux CVDRF ainsi qu'à la dépression et à la symptomatologie dépressive dans la population canadienne.

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PREFACE- Contributions of Authors and Contribution to Original Knowledge

This thesis has been completed by Harmehr Sekhon under the expert guidance of Dr. Olivier Beauchet. Manuscript 1, 2, 3 and 4 of this thesis are original scholarship. For the four studies below Harmehr Sekhon and Dr. Olivier Beauchet completed study conceptualization, study design, data analysis, data interpretation, as well as the manuscript draft. All other co-authors completed critical revisions.

Study 1, has been published in the journal of Frontiers in Aging Neuroscience. Study 2, has been published in the Maturitas journal. Study 3 has been submitted for publication in the Journal of the American Aging Association. Study 4 has been accepted for publication in the Archives of Gerontology and Geriatrics Journal.

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Chapter 1 Introduction- Overview

1.1 What do we know about Motoric Cognitive Risk Syndrome?

Motoric Cognitive Risk Syndrome (MCR) is a new syndrome reported by Dr. Joe Verghese in 2012 for the first time (1). This syndrome is defined as a combination of subjective cognitive impairment (SCI) and objective slow gait (1-4). MCR is associated with the occurrence of dementia (1-4). Additionally, it has also been found to be a good predictor of falls and mortality in older adults (5, 6). Currently, there is a need for early detection of adverse health events like dementia, to allow patients to plan ahead and manage their risks. Early detection will also potentially slow down the brain pathophysiological process with the aim to delay the occurrence of dementia and related adverse health events. Most patients at-risk for dementia are primary care patients and thus are seen in a short duration of time and with limited resources, which explains the under-diagnosis of dementia, estimated to be around 50% in individuals over 65 years of age (7). Thus, a simple and easy-to-use screening tool for the general public is required. MCR has the potential to rapidly screen individuals who are at risk for dementia in a primary care setting.

There is a higher proportion of individuals affected by dementia in lower and middle-income countries as compared to high-income countries (8). Moreover, resources can be scarce in low and middle-income countries, such that a screening tool that is usable in all healthcare settings, including primary and tertiary, is required. MCR has various strengths such as 1) not being resource rich or costly; 2) not requiring specialized

equipment or staff; and 3) being accessible: can be used in all healthcare settings. Thus, screening for MCR could prove useful in the early identification of older adults at-risk for dementia.

1.2 What do we not know about MCR?

Seven years after its first description, MCR's utility and its value for the prediction of dementia have yet to be determined. A recent non-systematic review underscored the possibility of MCR ambiguity by asking whether this syndrome is "a condition to treat or a mere matter for research purposes" (9). Data accumulated since its first description seem to disagree with this proposition, but no systematic review and meta-analysis has been performed on the association of MCR with dementia and incident cognitive impairment. In addition, to better understand the association of MCR with cognitive impairment, there is also a need for a review of its association with various brain structures and their abnormalities. As such, the first focus of this thesis was to complete a systematic review and meta-analysis to examine the association of MCR with dementia, incident cognitive impairment and brain morphology abnormalities.
Walking speed, a component of MCR, may be difficult to assess during a primary care visit because of space constraints (10). Gait speed must be recorded at usual steady state pace rhythm over a distance of at least 3 meters (11). Few consultation rooms in primary care possess the features required for the assessment of gait speed, which complexifies the process of consultation and increases physician workload (12). The

use of another test that is already being completed by the physician in lieu of walking speed would simplify the diagnosis even further. Thus, the second manuscript of this thesis analyzed whether the five-times-sit-to-stand test (FTSS) could be used to define MCR instead of slow walking speed, to further simplify MCR assessment.

Slow walking speed and SCI are the two fundamental components of the definition of MCR. However, there is also overlap with depression and depressive symptomatology, which can also result in slow walking speed and subjective cognitive complaint (5, 13). The association between MCR and depression/depressive symptoms has not been previously studied in the Canadian population. This was concerning as many previous MCR papers have used various items from depression scales to identify subjective cognitive complaints. Thus, if there is indeed an overlap between MCR and depression/depressive symptoms, the predictive value of MCR may be drastically affected. The third manuscript aims to better understand the association between MCR and depression/depressive symptoms in the Canadian population.

The physiopathology of MCR is still a matter of debate (1-4). MCR has been associated with the occurrence of both Alzheimer Disease (AD) and Vascular Dementia (VD) (1-4). However, MCR is a stronger predictor of VD compared to AD (2). In a few previous international studies the association between cardiovascular disease and risk factors (CVDRF) and MCR has been studied in older individuals (1, 14, 15). More specifically, this association has been studied in America, France, India and Japan, however, it has not been studied in the Canadian population till date (1, 14-16). The Canadian population must be considered as it is unique, as compared to previous international

studies due to an increase in the aging population, diverse lifestyles and genetics (16). Additionally, CVDRF are the second leading cause of death in Canadians (17). Thus, it is essential to understand the association between MCR and CVDRF in the Canadian population, which is the focus of the fourth manuscript.

1.3 Research Question

MCR is a relatively newly defined syndrome. There is currently a knowledge gap regarding the pathophysiology of MCR and its prediction of dementia. As such, a systematic review and meta-analysis was completed. The research question for the first manuscript is: What is the association between MCR and dementia, incident cognitive impairment and brain structures?

MCR is highlighted for its usability in various clinical settings, which is an opportunity due to the current under-diagnosis of dementia. Currently, physician workload and time constraints are highlighted as limitations. Thus, to increase the utility of MCR diagnosis in the clinical setting, barriers such as space and time must be addressed. The usability of the FTSS is considered in lieu of walking speed as the FTSS only requires a chair and stopwatch, and can be completed rapidly in any small setting. The research question for the second manuscript is: Can the FTSS be used instead of slow walking speed for defining MCR?

Depression and depressive symptomology are very prevalent in the Canadian population (13, 18). Individuals with depression/depressive symptomology as well as MCR can

exhibit symptoms such as slow gait speed and cognitive complaint. This overlap can impact the predictive value of MCR. Previous literature on this potential association has reported mixed findings. The research question for the third manuscript is: what is the association between MCR and depression as well as depressive symptomology in the Canadian population?

CVDRF and MCR have been found to be significantly associated in a recent meta-analysis (16). However, this meta-analysis had a few limitations. The participants are limited to a few countries, not including Canada, and were primarily recruited from memory clinics and hospitals. The Canadian population reports CVDRF to be the second leading cause of death (19). As such, there is a need to better understand this association in Canada in a representative population. The research question for the fourth manuscript is: What is the association between MCR and CVDRF in the Canadian population?

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Chapter 2 Literature Review

Section 1 Dementia

Dementia is a clinical syndrome characterized by cognitive impairment and their consequences on function (i.e. everyday activities which is considered using the activities of daily living (ADL) and instrumental activities of daily living (IADL)) (1). Recently, the term major neurocognitive disorder was used instead of dementia due to the negative stigma surrounding the term dementia (1). The Diagnostic and Statistical Manual of Mental Disorder (DSM) 5 diagnoses major neurocognitive disorder using four criteria (1). The first criterion of major neurocognitive disorder is cognitive impairment in one or more cognitive domains (1). Cognitive impairment is noted based on a combination of 1) cognitive impairment reported by the patient, family/friends or clinician and 2) cognitive decline as compared to previous neuropsychological testing or other quantified clinical assessment (1). The second criterion is that the cognitive impairment(s) results in ADL being affected (1). The third criterion is that the cognitive impairment(s) is observed in the absence of delirium (1). The fourth criterion is that the cognitive impairment(s) is not due to major depressive disorder, schizophrenia or other mental disorders (1).

Additionally, the DSM 5 notes that an individual can have three levels of severity: mild, moderate and severe (1). Mild refers to some IADL being affected (1). Moderate refers to basic ADL being affected (1). Severe refers to difficulties with ADL such that an individual is completely dependent (1).

1.1 Epidemiology

Dementia affects 564,000 Canadians, with 25% of Canadians aged 85 and older and more than 50 million individuals in the world living with dementia, which is predicted to triple to 152 million in 50 years (2-4). Dementia will be most prevalent in lower and middle-income countries as compared to high-income countries (2). The implication of this is that a screening tool that can be used in lower and middle-income countries effectively is required (2). It is estimated that up to 90% of individuals in lower and middle-income countries are not aware that they are living with dementia (2). Under-diagnosis is a phenomenon that not only affects lower and middle-income countries but also 50-80% of individuals living with dementia in higher-income countries are also not aware of their diagnosis (5).

A high cost of care is also associated with dementia due to the healthcare and caregiving support required, which is estimated to be 818 billion US dollars (2). The adverse consequences of this is that this large cost is unexpected and typically presented after an individual retires and has limited sources of income. Though some economic support and bursaries are available from the government, they are very limited and the burden largely falls on the individual and their family (6). The cost of dementia has been found to exceed the cost of other illnesses such as cancer and heart disease (6). In the US, it is predicted that individuals pay over $60, 000 (US dollars) or 80% more for dementia than the cost for cancer and heart disease out of pocket, in addition to medical insurance and bursaries (6).

1.2 Caregiver Burden

Dementia greatly impacts the Canadian population due to the large number of individuals diagnosed and the burden on caregivers (7, 8). Caregivers are often informal caregivers (i.e. individuals that are not paid and are typically family) (8). The cost of the approximate 18 billion hours that informal caregivers provide unpaid care is estimated to be 232 billion in 2017 in the United States alone (8). In Canada, 85% of individuals with dementia received care. Specifically, 43% received both informal and formal care, while 41% were dependant on only informal care (7). Another consideration is that 2 of 3 caregivers, are women as compared to men. These caregivers are often overburdened, though there is some financial support and services available, as they typically have limitations and do not meet all the needs of individuals with dementia, especially individuals with advanced dementia (8). Thus, due to the burden on caregivers, it is reported that they may be impacted by an increase in the following health concerns: depression, anxiety, stress, health care utilization, incidence of chronic conditions and decreased self-reported health (9).

1.3 Subtypes

There are many types of dementia; the two most common subtypes of dementia are: AD and VD, which are 60-90% and 10% of all dementia diagnosis, respectively (1, 10). Other types of dementia include: Lewy Body (DLB) (1.7-30.5%) and Frontal/Temporal (5%) (1). Moreover, there are various substance/medication-induced dementia and

dementias due to: Traumatic Brain Injury, HIV Infection, Prion Disease, Parkinson's Disease, Huntington's Disease and Another Medical Condition. An individual can have more than one type of dementia, which is called mixed dementia or major neurocognitive disorder due to multiple etiologies (1). The DSM 5 defines major neurocognitive disorder due to multiple etiologies as: 1) meeting the criteria for major neurocognitive disorder; 2) evidence from the clinical and laboratory findings that the neurocognitive disorder is due to more than one etiological process (except for substances); and 3) the cognitive decline is not due to another mental disorder and is observed in the absence of delirium (1). An individual's risk of being diagnosed with dementia is thought to be due to both genetics and environmental factors (which are modifiable) (11). Though dementia is typically synonymous with aging and impacts individuals over 65 years of age, young or early onset dementia can affect individuals' decades younger than 65 (1).

AD is defined by the DSM 5 as a combination of the criteria of major neurocognitive disorder and if the criteria for probable AD or possible AD is met (1). Probable AD is defined by the criteria: 1) AD genetic mutation, in combination with, 2) decline in memory, learning and one or more other cognitive domains, 3) progressive decline in cognition, 4) no mixed etiology and 5) the changes cannot be explained by another disease or disorder (1). Possible AD is defined by the criteria: 1) decline in memory and learning, 2) progressive decline in cognition, 3) no mixed etiology and 4) the changes cannot be explained by another disease or disorder (1).

VD (or neurocognitive disorder) is defined by four criteria; 1) meeting the major

neurocognitive disorder criteria; 2) vascular etiology, specifically, cognitive decline is related to cerebrovascular events and decline in complex attention and frontal-executive function; 3) neurocognitive decline is due to cerebrovascular disease; and 4) the changes cannot be explained by another disease or disorder (1). Probable vascular neurocognitive disorder is defined if three criteria are met: 1) neuroimaging supports clinical criteria of parenchymal injury due to cerebrovascular disease; 2) neurocognitive syndrome is related to cerebrovascular events; and 3) evidence of cerebrovascular disease (i.e. clinical and genetic) (1). If the criteria for probable vascular neurocognitive disorder is not met, specifically, if neuroimaging is not available or the relationship between cerebrovascular events and neurocognitive syndrome is not confirmed, but the clinical criteria is met, then possible vascular neurocognitive disorder diagnosis is made (1).

1.4 Treatments and Risks

The current treatment of dementia is through the use of pharmacology to aid in slowing the progression of cognitive decline and managing the symptoms (12). Some examples of medications used are: antidepressants, anxiolytics, antipsychotic medications and acetylcholinesterase inhibitors/memantine to manage low mood, irritability, anxiety, restlessness, verbally disruptive behavior, hallucinations, delusions, aggression, agitation, hostility, uncooperativeness and stopping the breakdown of acetylcholine/the effect of glutamate (i.e. increasing nerve cell communication) (12, 13). Additionally, it has been recommended that individuals partake in a healthy lifestyle, with a focus on

nutrition, exercise and preventing cardiovascular risk factors(CVRF) (11, 14). Moreover, recent studies have greatly stressed the importance of social interaction as well as other therapies and approaches such as: modifying the environment, music therapy, art therapy, massage therapy, pet therapy, etc. (14). Lastly, an early diagnosis greatly improves the management of dementia (5).

1.5 Early Diagnosis

Currently, a large barrier that exists is the lack of accurate diagnosis of dementia, specifically early diagnosis (5). An early diagnosis of dementia saves, on average, $10,000 (US dollars) per individual (5). Moreover, improved treatment, support management and slowing the progression of dementia can be better completed with an earlier diagnosis (5). There has been a great focus on biomarkers as an avenue for early detection and diagnosis, however, there are also various limitations such as resources, cost, accessibility and usability (15-18). This is especially a concern as most patients must be screened in a primary care setting, for individuals living in lower and middle-income countries another considering factor is that resources may be scarce. Thus, a simple, economic and easy to use screening tool, which can be used in any healthcare setting globally is required.

Overall, the early identification of individuals at risk for dementia is beneficial for three reasons. Firstly, it allows the focus to switch to prevention, such as managing CVDRF, which are known risk factors for dementia, especially VD (11, 14). Secondly, it identifies the subset of the population that should be monitored closely and have timely follow ups

to assess their risks and management. Thirdly, it allows individuals with dementia and their family/friends to plan ahead, with respect to care and finances (5, 19-21).

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Section 2 Gait Disorders in Patients with Cognitive Impairment

The main clinical hallmark of dementia is cognitive decline (1). Although not as prominent, motor disorders are commonly described in later stages of dementia and include gait apraxia, bradykinesia, extrapyramidal rigidity, resting tremor and various gait disorders, such as cautious gait or gait slowing (2-6). Recently, a few studies have shown that motor disorders, and specifically gait disorders, may be present at an early stage of dementia (2-4, 7-9). There is an increased interest in the study of these dementia-related gait changes (DRGC) since they could be used to improve early diagnosis and better understand risk of falling in subjects with dementia or even at a pre-dementia stage (10).

Gait disorders/abnormalities are found to affect a large proportion of elderly individuals (11). Specifically, 35% of community dwelling elderly individuals over the age of 70 are diagnosed with gait disorders/abnormalities (11). Gait abnormalities have been found to increase with age and has a prevalence of 35% with a CI of 28.6-42.1 (11). The incidence for gait abnormalities is reported to be 168.6 per 1,000 person-years, with a CI of 117.4-242.0 (11). Gait abnormalities do not affect all individuals equally (12). Rather, it was found that gait abnormalities affect individuals with cognitive impairment more than their cognitively healthy counterparts (12). Specifically, 46-53% of cognitively impaired individuals were seen to be affected by gait abnormalities, compared to only 30-35% of cognitively healthy individuals (CHI) (12). In addition to the association

between gait abnormalities and cognition, gait has also been found to be associated with rate of institutionalization as well as mortality with a HR of 2.2 and CI of 1.5-3.2 (11). This risk was also found to be linked to the severity of gait abnormalities (11). The individuals with mild gait abnormalities were found to be at a lower risk than individuals with moderate or severe gait abnormalities, with a HR of 1.8 with a CI of 1.0-2.8 and a HR of 3.2 with a CI of 1.9-5.2, respectively (11).

2.1 Gait Changes in Demented Patients: Evidence for a Relationship

Dementia and gait disorders represent a major public health issue because of their high prevalence, their related adverse outcomes leading to loss of autonomy/independence, high costs for public health and social services (13-15). It has been shown that demented older adults present with greater gait impairments than those expected as a result of the normal aging process (13-16). Different DRGC have been described, mostly when comparing subjects with AD versus healthy control subjects. The walking speed decreases in AD and further parallels severity of the disease (13, 16-18). This change in velocity has been related to a decrease in stride length and an increase in support time (18). Furthermore, subjects with VD and dementia with DLB walked more slowly and presented a reduced step length than AD subjects (13, 19). DRGC are not specific to any type of dementia as similar changes in gait pattern have been reported with advanced age (15, 16).

Both mobility impairment as well as cognitive decline are independently associated with dementia. Cognitive decline has been found to be a predictor of dementia (20). Previous

literature has also reported that slow gait is a predictor of dementia (7, 21). Most studies exploring gait DRGC have focused on mean values of stride parameters (16, 18). Recently, it has been found that an increase in stride-to-stride variability while walking and dual-tasking has been shown to be most specific in patients with dementia (5, 9, 24-27). This stride-to-stride variability is a fine marker of gait control and, thus, highlights that gait should not be considered as a simple automatic motor behavior but rather associated with complex and higher level cognitive functioning (25-27). Exploring stride-to-stride variability in demented subjects represents a new way to access gait disorders related to higher levels of gait control impairment.

2.2. Early Diagnosis of Dementia: Gait Analysis as a New Method of Expertise?

Whatever its etiology, treatments of dementia are not curative, although its evolution may be slowed down (28). Available treatments such as acetylcholinesterase inhibitors (AchEIns) or memantine are efficient in their effect on cognitive symptoms and on global evolution for a limited period of time (28, 29), and their efficiency depends on early administration (29).

AD is seen to be the main type of dementia (30, 31). Although operational criteria do exist, it has been shown that within subjects with AD-related cognitive decline, only 50% are diagnosed with the disease, and only 30% are diagnosed at an early stage (31, 32). This may principally be explained by unclear boundaries between early dementia syndrome and normal aging. Neuropsychological deficits including memory, attention and executive functions are frequently affected first (30-32), but heavily rely on

psychometrics, are time consuming and lack specificity in terms of predicting the occurrence of dementia. Defining pathological cognitive aging seems quite straightforward in the presence of dementia according to DMS 5 criteria. However, it becomes much more complex for intermediate cognitive impairment such as the concept of age related cognitive decline or mild cognitive impairment (MCI), that is a risk factor for AD but not specific to it and hence cannot be used for early diagnosis (31, 32, 33, 34) .

The question is, then, to determine whether the specificity of cognitive expertise in the early diagnosis of AD may be improved. Over the past five years, a few studies demonstrated that cortical gait control impairment and certain motor deficits were one of the early signs of AD and non-Alzheimer's dementia (2-4, 7-9). Rhythmic motor tasks such as "finger tapping" and walking were performed more slowly in subjects developing cognitive impairment than in those with no cognitive impairment. A one-second increase compared to the mean score of healthy subjects was associated with a risk of cognitive decline increased by a factor of 1.26 (CI 1.01-1.60) (2). In the same study, a motor coordination impairment, i.e. the capacity to alternately repeat movements of the lower limbs, was associated with a high risk of developing cognitive decline (Odd Ratio(OR) 6.10, CI 1.40-26.30). In a longitudinal cohort of 630 community-dwelling participants aged 75 or over at recruitment, subjects with cognitive impairment associated with gait and motor slowing were the most likely to develop dementia (OR 5.6, CI 2.5-12.6) (3). Recently, Verghese et al. (9) presented similar findings in 427 subjects aged 70 and older, and concluded that quantitative gait measures might predict future risk of

cognitive decline and dementia in initially non-demented older adults. These recent data suggest that an early diagnosis of dementia and/or related syndromes in the elderly should include DRGC analysis.

2.3. Dual Tasking Condition

The 1997 seminal paper "`Stops walking when talking' as a predictor of falls in elderly people" focused on dual tasking and emphasized the link between cognition and gait (35). Dual tasking is defined as completing two tasks at the same time; typically, the participant is asked to walk while performing a cognitive task (36). There is an overlap between impairments in cognition and motricity (37). Dual tasking emphasizes the connect between motricity and cognition, and is related to executive function, whereby, when performing both tasks simultaneously, motor or cognitive impairments become more apparent (38, 39). Following the publications on dual tasking it was considered whether dual tasking could be utilized as a prognostic tool for occurrence of falls in the elderly.

2.3.1 Concept of Dual Tasking

Walking is classically described as an automatic, rhythmic and regular motor activity characterized by alternate, coordinated movements of crossed flexion-extension of the lower limbs while in a steady-state of walking (40). It is considered as a simple motor activity in healthy subjects because of its predominant automatic character acquired during the simultaneous maturation of the locomotor and nervous systems. From a

neurological viewpoint, the acquisition of such automatisms relies on motor procedural memory, allowing for the gradual appearance of motor processes enabling the automation of walking in healthy adults. Motor procedural memory handles information based on action rules (41, 42). Its expression is implicit, and cannot be dissociated from action.

In experimental psychology, the Adaptative Control of Thought (ACT) by Anderson is considered as a reference (43). It distinguishes three successive phases during which the subject generates, combines and improves a specific procedure for a given task. The first phase is the declarative phase, corresponding to the selection of relevant information for the requested task, and relies on intellectual abilities, as well as on important attentional resources. In the case of a motor action, it may be assimilated to the motor plan elaboration step. The second phase, called the knowledge compilation phase, corresponds to the transformation of declarative information into procedures, and may be assimilated to the elaboration of the motor program. Finally, the third and final phase is the procedural phase, corresponding to the adjustment and automation of the procedure.

The procedural learning of walking enables the automatic, unconscious triggering of underlying motor programs in healthy adults. Such an implicit character is predominant in walking and implies that walking only requires limited attentional resources in healthy subjects (25, 44-46). Although this assumption has been confirmed in young subjects (46), several studies proved it was not the case in older adults and demented subjects, in which cortical gait control is involved while walking (25, 44-46). Furthermore, the most

ordinary walking conditions demonstrate that the implicit character of walking is not univocal: stride-to-stride time modifications, the presence of obstacles or directional changes constitute intentional parameters requiring explicit cognitive function.

The clinical test used to highlight cortical involvement in gait control is based on a dual-task paradigm, the principle of which is to have the subject perform an attention-demanding task while walking and to observe any walking modification compared to the reference task, i.e. usual walking (47, 48). Dual-task paradigms are based on the hypothesis that two simultaneously-performed tasks interfere if relying on identical functional and/or cerebral subsystems (47, 48). In the case of a paradigm including walking and an attention-demanding task, the interference is based on the hypothesis of a joint involvement of attention (47). The primary task therefore is the “attention-demanding” task, while the secondary task is represented by walking. The interferences observed are modifications of the performance in one or both tasks, which are measured by comparing the performances under single- and dual-task conditions (47-49). Gait modifications are then interpreted as the involvement of attention while walking, and therefore attest of a level of cortical control ensuring the functionality of walking, while making it frailer.

Attention is a complex and multidimensional cognitive function that overlaps with executive functions and is one dimension in which participates improve the processing of information (50). Attention is a limited resource in cognitive processing that may be overloaded by two competing tasks when performed simultaneously, or dual-tasking (47-49), then consecutively leading to a decline of performance in one or both tasks.

Two categories of interferences have been defined (47-49). The first one is called capacity interference and is the result of a central overload due to involvement of different information processes requiring attention. In contrast with capacity interference, structural interference is defined as a peripheral overload due to an inability to perform two tasks involving the same category of information, simultaneously. The bottleneck and cross-talk models are based on this theoretical approach. Although similar tasks performed simultaneously provoke a decline in performance in the bottleneck model, the cross-talk model assumes that task similarity reduces interferences, thus leading to better performance.

Dual-task related gait changes reflect the capacity to appropriately allocate attention between two tasks performed simultaneously and, therefore, are related to executive function efficiency (5, 26, 49). Alzheimer's subjects with moderate dementia and executive dysfunction presented with high gait variability suggesting that this gait parameter could be a sensitive and specific marker of frontal cortical control of walking (5). In another sample, the degree of efficiency of the executive function was correlated to the degree of cycle time variability (51). Recently, the disruption of stride-to-stride variability was shown to be the most significant gait parameter while dual-tasking in a sample of older subjects with a dysexecutive syndrome (26).

2.3.2. The Neuronal Basis for Dementia-Related Changes in Gait

The automatic, implicit character is predominant in walking. It essentially relies on sub-cortical and spinal control, with a neuronal network localized in the lumbar area (40, 52).

These spinal neuronal networks that include motor neurons and interneurons are called central pattern generator (CPG) for locomotion (52-54). They allow the generation of automatic and rhythmic motor activity patterns, corresponding to alternate, coordinated movements of crossed flexion-extension of the upper limbs, even in the absence of sensory afferences or control by supraspinal structures (52). In humans, several clinical observations corroborate the existence of CPG, such as spontaneous locomotor activity in infants, or persistent rhythmic, coordinated movements of the lower limbs in paraplegic subjects after a medullar section in the dorsal region (53, 54). At the supramedullary level, a particularly important locomotor zone is the pediculopontine nucleus (PPN), localized at the mesencephalic level that is considered to be a site of termination for basal ganglia output, and hence probably plays a key role in the modulation of walking (55).

At the cortical level, there is increased evidence that dysfunction of temporal and frontal lobes may explain motor impairment among demented subjects. It has been shown that temporal atrophy, and specifically the hippocampus, is not only related to memory but also to motor dysfunction (16). Furthermore, both clinical studies based on dual-tasking and brain imaging studies have shown that frontal lobe dysfunction may be related to gait disorders in demented subjects. Nakamura et al. (56) demonstrated that increased oscillations of the body in a static position, a reduced stride length and increased stride variability in subjects with AD could be related to a decreased cerebral perfusion in the frontal lobe.

2.3.3. Limitations of Dual Tasking

Yet, limitations to the utilization of dual tasking as a prognostic tool must be considered, such as the lack of evidence in support of dual tasking as a prognostic tool and the fact that it cannot be easily used in a clinical setting (57-59). Previous systematic reviews have concluded that further research is needed prior to establishing dual tasking as a prognostic tool. Although there is an indication regarding the predictive value of dual tasking, the findings are inconclusive and insufficient (57-59). Dual tasking's applicability to clinical settings is difficult as there are resource constraints, such as lack of space and time. Thus, a new simple approach is required.

2.5. Mobility Tests

Due to the limitations outlined above for dual tasking a simple solution is required. Two avenues have been considered in this respect. First, the use of cognitive impairment, as is the case with MCI as it is a predictor of dementia. This strategy is limited as MCI diagnosis is a lengthy process that cannot be administered easily in all healthcare settings. The second strategy is to use gait speed and SCI. SCI, unlike MCI is simpler and easier to assess. Moreover, in respect to gait, speed walking tests have been considered, but tests such as the FTSS test, which can be easier to administer even in settings with space constrictions, have not been considered.

2.5.1. Five time Sit to Stand Test

The FTSS test measures stability and lower limb strength (60). This is done by asking the patient to sit and stand five times without moving forward, rotating their shoulders, or any other movements during the test (61). The participants are asked to sit on an armless chair and to get up and sit down on the chair without touching the sides (62). During the FTSS the participants are asked to fold their arms at their chest (62). Moreover, the participants are also asked not to bounce off their chair.

The average time for completion of the FTSS is based on age, they have been reported as 11.4 s, 12.6 s and 14.8 s, for age group 60-69, 70-79 and 80-89, respectively (63). Generally, the less time that an individual takes to complete the test the better their performance. The strength of the FTSS is that, it is a valid modality of measurement in numerous papers considering mobility and risk of falls in geriatric adults (61). In older adults taking longer to complete the test is associated with an increased risk of recurrent falls (64). Moreover, the FTSS can easily and rapidly be administered in the clinic.

2.5.2. Time Up and Go Test

The Time Up and Go test (TUG) is comprised of instructing the individual to 1) begin seated on a chair, 2) after saying go (and starting the timer) the individual gets up and walks three meters to the line, 3) turns around, 4) walks back to the chair and 5) sits back down (and stop the timer) (65). The longer the individual takes to complete the test, the worse the outcome/score (65). Individuals who take less than 20 seconds have

better mobility and are reported to be more independent (65). Comparatively, individuals that take 20-30 seconds may have some mobility concerns and those that take 30 seconds or longer have severe impairments (65). Moreover, individuals who take more than 14 seconds are at higher risk for falls (66).

2.5.3. Walking Speed

2.5.3.1. Four-Meter Test

The four-meter test is a screening test for mobility (67, 68). It measures walking ability and is widely used in the clinical setting (67, 68). It has also been previously used among geriatric populations (67, 68). The four-meter test consists of the measurement of walking speed during a four-metre span, which is timed from the first step taken until the first foot crosses the finish line (68). The cut-off typically considered is walking speed slower than 0.6 m/s (68).

2.5.3.2. Six-Meter Test

The six-meter test is a valid mode to measure mobility (69). It has been used in geriatric populations previously, and is a reliable mode of testing (69). The strength is that the six-metre test is reliable and replicable in the clinical setting (69). It is also a good alternative to the 10-metre walking test (69).

2.5.4 Conclusions

Gait disorders and dementia are frequently associated. There is increase evidence that gait impairment due to cognitive impairment are not only attributable to usual motor disorders (i.e., extrapyramidal disorders), but also associated to problems with the cortical processing of information what may be present at the early stage of dementia. Dysfunction of temporal and frontal lobes may in part explain gait disorders among demented subjects. The main clinical implications are that cortically related changes in gait characteristics could be used to improve the early diagnosis of dementia.

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Section 3 Cognitive Performance and Status

The ever-increasing aging population has brought with it a concern of cognition. More specifically, a concern regarding what is normal and what is abnormal in cognitive decline. A better understanding of cognition and age has elucidated that dementia and forgetfulness is not a normal part of aging. Moreover, a decline in cognition, even early on (i.e. SCI), has been linked with dementia. Thus, a need for a screening tool has been identified. Early screening is necessary as pharmaceutical trials for individuals with MCI have failed (1). Rather, it has been suggested that therapy is best directed at individuals with SCI (1).

Cognitive health is categorized on a spectrum from cognitively healthy to SCI, then MCI and finally major neurocognitive disorders. It is important to note that not all individuals will follow this trajectory. Specifically, not all individuals with subjective SCI will progress to MCI. The same is true for individuals with MCI not progressing to major neurocognitive disorders.

3.1 Cognitively Healthy Individuals

Individuals who do not present with cognitive impairments, subjective or objective, are categorized as CHI. The myth that dementia is a normal part of aging has long been debunked (2). It is true, however, that as individuals age there will be changes in cognition and cognitive ability (2). This is seen both ways as some cognitive ability

improves with age, such as vocabulary (2). Comparatively, most individuals will notice a gradual decline in aspects such as reasoning, memory and multitasking with age (2). CHI are defined as individuals who do not present with subjective memory complaint and do not have a diagnosis of dementia. The mini mental state examination (MMSE) is the most widely used test and, on average, only takes about 8 minutes to administer (3). The cut-off score is considered 25 (or lower) out of 30, which signifies significant impairment (4). Since level of education can have an impact, the cut-off was decreased to 23 or lower for individuals with less than 12 years of education. (4).These assessments are used in combination with the interactions that the physician has with the individual and the concerns reported by the individual and/or their family/friends to select the appropriate test(s) and make a diagnosis.

3.2 Subjective Cognitive Impairment

3.2.1 Definition

Individuals who report cognitive impairment without an objective measure of cognitive impairment are categorized as individuals with SCI (6). SCI is the first in the scope of cognitive impairment. It is important to note that not all individuals with SCI will translate to MCI (6). Individuals with SCI are those that are considered under the definition of MCR.

3.2.2. Statistics

SCI, similar to MCI, has been found to be a predictor of dementia (7). Moreover, SCI has also been found to be a predictor of MCI, which it often precedes (7). A recent meta-analysis completed in 2014 found that the annual percentage of individuals with subjective memory complaints who progressed to dementia was 2.3% (7). This number was reported to be almost 3 times higher for the annual percentage of individuals with subjective memory complaints who progressed to MCI (7). These statistics for individuals with subjective memory complaints that are later diagnosed with dementia and MCI over four years are 10.9% and 24.4%, respectively (7). Comparatively, only 4.6% of individuals without subjective memory complaints are diagnosed within the four-year mark (7).

3.3 Mild Cognitive Impairment

3.3.1. Definition

MCI or mild neurocognitive disorder, as used by the DSM 5 is defined by four criteria. The first criterion is a decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, and/or social cognition) (8). The mild cognitive decline can be observed by the individual, family/friends or a clinician and must be observed in combination with objective cognitive performance (i.e. neuropsychological testing) (8). The second criterion is that the cognitive impairment does not affect an individuals' ability to independently complete activities, including complex ones such as paying bills and taking medications

(8). The third criterion is that the cognitive impairment is also observed during the absence of delirium (8). Lastly, the fourth criterion is that no other mental disorder can be the reason for the cognitive impairment (8).

3.3.2. Subtypes

There are four subtypes of MCI (9). Specifically, the subtype amnestic and non-amnestic, which further separate based on single and multiple domain cognitive impairment (9). The first subtype, amnestic MCI single domain subtype, refers to impairment only in the memory domain (9). The second subtype, amnestic MCI multiple domain subtype also called combined MCI, refers to impairment in at least 2 domains, including the memory domain (9). The third subtype, non-amnestic MCI single domain subtype, refers to impairment only in one domain (cannot be the memory domain) (9). The fourth subtype, non-amnestic MCI multiple domain subtype, refers to impairment in at least 2 domains (cannot include the memory domain) (9).

3.3.3. Statistics

The rate of conversion from MCI to dementia is reported to be at 10-15% a year (10, 11). This is higher than the conversion to AD or VaD, which are 8.1% and 1.9%, respectively (10). The incidence of MCI for individuals 65 and over was reported to be 12-15 per 1000 person-years (11). This increased to 54 per 1000 person-years when considering individuals 75 and over (11). The prevalence of MCI is reported to be 2-

10% in individuals 65 and over (12). This is predicted to increase to 5-25% for individuals 85 and over (12).

The incidence for amnestic MCI subtypes was reported to be 9.9-40.6 per 1000 person-years (9). Comparatively, the incidence for non-amnestic MCI subtypes was reported to be 28-36.3 per 1000 person-years (9). Cognitive impairment is found to be more prevalent in older individuals (13). Amnestic MCI multiple domain subtype is found to be the most prevalent (33.9%), followed by non-amnestic MCI single domain subtype (28.9%), amnestic MCI single domain subtype (21.9), and lastly non-amnestic MCI multiple domain subtype (8.6%) (13).

3.4 Neuropsychological and Bedside Assessments

Bedside assessments are those that can be completed in any setting with a limited amount of training required. The strengths of bedside assessments are that they can be completed rapidly and do not require specialized staff. The concerns with bedside assessments are the facts that they are less sensitive to identifying individuals with milder cognitive decline (14). Furthermore, when assessing certain domains, such as executive function, bedside assessments are considered inadequate (14). Moreover, there is also the concern that when using bedside assessments, individuals with fewer years of education, limited English proficiency and poor/high lifelong cognitive function can be incorrectly diagnosed (14). Neuropsychological testing is completed by a trained neuropsychologist. The strengths of neuropsychological assessments are that they are

more sensitive tests and can provide an earlier diagnosis (14). The weakness of neuropsychological assessments is that they are more time and resource consuming.

3.4.1 Mini Mental State Examination

The MMSE is used for assessing global cognitive function (15). The MMSE is composed of 11 questions and scored out of 30 points (16). This is a widely used test that was created in 1975; typically, 23 or 25 points is the cut-off score (15, 16). Below, or at 23 or 25 points, is representative of possible cognitive impairment (16). The test takes about 5-10 minutes to be administered and is a bedside examination (15). It is important to consider an individual's education (ability to read, write and speak), eyesight, hearing and English language speaking proficiency, as these factors can affect this score (16, 17).

3.4.2 Free and Cued Selective Reminding Test-Total Recall

The Free and Cued Selective Reminding Test-Total Recall (FCSRT-TR) is used for assessing memory (18). The FCSRT-TR is composed of 2 sections, the free and cued recall (19). The free recall entails that the individual is shown a word and later asked to remember the word (18). This is repeated with a total of 16 words (18). The cued recall is the second component, which takes place after the aforementioned section. In this section individuals are given prompts/hints to help remember the words they forgot. The FCSRT-TR is found to better aid in diagnosing AD dementia than other dementias (19, 20).

3.4.3 Trail Making Test

The Trail Making Test (TMT) is composed of 2 parts: A and B. The two parts, A and B, assess visuospatial abilities and executive function (i.e. visual search and scanning, sequencing and shifting, attention, ability to adapt/change a plan, thinking of two things simultaneously, etc), respectively (21, 22). This is a widely used test that was created in 1938 (21). The individual is presented with a sheet of paper with numbers on it and is asked to connect the numbers in increasing order (i.e. connect 1 to 2, 2 to 3, etc.). Part 2 is more complex and entails presenting the individual with a sheet of paper with both numbers and letters on it and asking the individual to connect the numbers and letters alternatively in ascending order (i.e. connect 1 to A, A to 2, 2 to B, B to 3, etc.) (21). It is important to consider an individual's education (ability to read, write and speak), eyesight, hearing and English language speaking proficiency, as these factors can all affect the score. Age has also been found to be an important factor (22).

3.4.4 Stroop test

The Stroop test is used for assessing an individual's ability to inhibit cognitive interference (23). The Stroop test is composed of different sections. The individual is presented with a sheet of paper with words used to describe colours (e.g. blue, yellow, etc.). With the words printed in black or in the colour they are spelling (i.e. the word blue is printed in the colour blue). The participant is asked to identify the word that they are shown. Then the individual is presented with a sheet of paper with words that describe

colours (e.g. blue, yellow, etc.). In this section, the words are printed in colour. The complexity lies in the fact that the words are printed in colour that do not correspond to the colour the word means (e.g. the word green is written in the colour orange, etc.).

3.4.5 Instrumental Activities of Daily Living

The IADL is used for assessing independence in daily activities. The IADL is composed of 8 questions (24). The IADL was established in 1969 to identify individuals who were self-sufficient and those who required assistance with their daily activities. In the 8 questions, the IADL tests the individuals' comfort and independence in their ability to: use the telephone, go shopping, prepare food, complete housekeeping tasks, laundry, transportation, independently manage medication and the ability to handle finances (24). It is an 8-point scale for women and 5-point scale for men (24). The 8-questions are not simply yes or no; they have a range of answers which corresponds to an individual's comfort and independence in performing the task (24). All questions are scored out of 1, with multiple possible answers for each question the answers can have either 1 or 0 points awarded (24). The individual can only receive a maximum score of 1 per question (24). The test takes about 10-15 minutes to be administered. The target population for the aforementioned test is older adults (24, 25).

3.4.7 Pfeiffer's Short Portable Mental State

The Pfeiffer's Short Portable Mental State exam is used for assessing intellectual functioning, specifically short-term memory, long-term memory and orientation to

surroundings, to name a few (26). The Pfeiffer's Short Portable Mental State is composed of 10 questions (26). It is scored out of 10 (26). The test was established in 1975 and the target population is older adults (26). When used to screen individuals for dementia it was found to be a good screening tool to identify individuals, both in community dwellers and individuals in the hospital, with moderate to severe dementia (27). Specifically, in community dwellers the sensitivity was found to be 66.7% and the specificity 100% (27). Comparatively, the sensitivity was found to be 86.2% and the specificity 99.0% among patients (27).

3.5 Conclusions

The spectrum of cognitive health is large and goes from cognitively healthy to dementia. Over the past 5 years, two clinical characteristics have been reported as predictors of dementia and thus are identified as characteristics of the pre-dementia stage. First, individuals with perceived changes in memory and/or cognition in the absence of objective evidence are commonly given a 'diagnosis' of SCI. SCI has been defined as a pre-MCI stage and, thus, is considered the earliest clinical stage of AD. Second, low gait performance, such as slow walking speed, has also been associated with the occurrence of dementia. Recently, a syndrome combining subjective cognitive complaint (i.e.; memory complaint) and slow gait speed, called **MCR syndrome**, has been associated with the occurrence of dementia. Indeed, in elderly cohorts mainly based in the United States and Europe, MCR has been associated with increased risks of developing major cognitive decline and dementia, including both AD and VD. It must

be noted that not all individual will follow this trajectory linearly or even at all. It has been previously considered that identifying individuals at the MCI or even early in the SCI stage will allow for better screening and resource management. Identifying individuals at this earlier stage is discussed further in Section 4.

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Section 4 Motoric Cognitive Risk Syndrome

MCR is an important syndrome for the prediction of dementia. Currently, early dementia diagnosis, especially in lower and middle-income countries has been identified as a barrier (1). The unique requirements for a screening tool that is accessible in all healthcare settings globally is highlighted with the current prevalence of under diagnosis and lack of early diagnosis of individuals with dementia (1, 2). Thus, a simple and usable screening tool, which is quick to administer is required. A screening tool that is usable for rapid screening at the population level would enable better resource management and timely follow up.

Both cognition and mobility impairment/decline, independently are associated with dementia. Cognitive decline has been found to be a predictor of dementia (3). Previous literature has also reported that slow gait is a predictor of dementia (4, 5). A recent meta-analysis confirmed that, slow gait is a predictor of dementia (6). It was found that gait, specifically slowing of gait, was an earlier indicator of dementia, compared to cognitive impairment (7). Moreover, slowing of gait has also been found to be an early predictor of cognitive impairment. This emerging data on the predictive value of gait has resulted in a boom and a recent shift in thinking, from simply considering cognitive impairment as a predictor of dementia to instead considering gait in combination with cognitive impairment. This is evident from the shift in research interest and publications, as

depicted by the number of annual number of published studies with the keywords in pubmed, as depicted in figure 1 (page 94).

The increasing number of publications with findings on the association between gait and cognition led the way to MCR being conceived (see figure 1 on page 94). The first article by Dr. Joe Vergese in 2012 attempted to combine impairments in cognition and motricity to consider if together they are better predictors of dementia than individually (8). As such, MCR is defined as the combination of slow gait and cognitive complaint, and is found to be a stronger predictor of dementia than either risk factors individually (3, 6, 9).

4.1. Subjective Cognitive Impairment

SCI is defined as a cognitive complaint by an individual concerned about their cognition, but without any objective measure of cognitive impairment. SCI is considered a precursor to MCI. SCI is based on an independent question or an item selected from a scale, such as a depression assessment (i.e. geriatric depression scale (GDS)).

Over the years, studies on MCR have used a variety of different questionnaires, tests and questions (i.e. GDS) to identify individuals with SCI, table 1 (page 90) summarizes the questionnaires/tests/questions used by publications. One limitation of previous studies is the heterogeneity in how SCI is tested. Previous publications have used depression scales, IADL, independent question, etc. Depression scales like the GDS have been used, or components/questions from the scale have been extracted. Independent questions such as “How would you rate your memory?”, “Compared to 1 year ago, would you say your memory is better now, about the same, or worse now than it was then?” and

“In the last month, how often did memory problems interfere with your daily activities? Would you say every day, most days, some days, rarely, or never?” have also been used. Many previous publications are also limited as they recruited individuals from geriatric or memory clinics. Thus, all participants had some form of memory complaint. Lastly, as SCI is often taken from a depression scale and there is overlap in the symptoms of depression/depressive symptoms and dementia, the association between depression/depressive symptoms and MCR must be further explored (10, 11).

4.2. Slow Gait

Slow gait is defined as walking speed at least 1 standard deviation (SD) below the age and sex norm (8, 12, 13). Walking speed is a unique opportunity as, though more advanced data collection tools can be used, all that is essentially required is space (3-meters) needed to walk and a stop watch (14). Moreover, slow walking speed is a predictor of cognitive decline (15, 16). Thus, making this (walking speed) a very accessible tool that can be administered rapidly and in any setting.

A study by Rosso et al. has found that slower gait can predict cognitive impairment at year 14, with an OR (per 0.1 s/y slowing) of 1.47 and CI of 1.04–2.07 (16). Slow gait speed has also been identified as an independent factor for predicting rapid cognitive decline, with an OR of 4.58 and CI of 1.22-17.2 (17). Slower gait speed is associated with dementia, with a HR of 1.59 and CI of 1.39-1.81 (15). This association has also been found at the 4 and 7-year mark, with a HR of 1.46 and CI of 1.26-1.68 and a HR of 1.30 and CI of 1.00-1.70 (15). Furthermore, it has been reported that those with both cognitive

impairment and a decline in gait speed had the highest risk of later being diagnosed with dementia, with an OR of 5.6 and CI of 2.5-12.6) (18). Individuals with both cognitive impairment and a decline in gait speed also had the highest risk of dying, with an OR of 3.3 and CI of 1.6-6.9) (18).

An association between walking speed and mortality has been established in previous publications (19). Individuals whose walking speed falls within the slowest third of participants were found to have a mortality of 19.2 per 1000 person years, compared to the mortality rate of 9.5 per 1000 person years for individuals who walk faster (19). Moreover, individuals with slow walking speed within the slowest third of participants, which is walking speed below 1.5 m/s for men and below 1.35 m/s in women in the study, were found to have an increased risk of mortality due to cardiovascular causes ($p=0.002$) (19). This subgroup of individuals with slow walking speed are also found to have a significant association with all-cause mortality ($p=0.02$) (19).

Previous studies have also found that older individuals with walking speed below 0.8 m/s are at a high risk of frailty (20). A study comparing hemodialysis patients and healthy adults has found a significant association between walking speed and cardiac disease, as well as fractures, leg strength, and standing balance (21). The authors found that slow walking speed was found to be significantly ($p<0.05$) associated with all variables (cardiac disease, as well as history of fractures, decreased leg strength, and poor standing balance) (21).

4.3. Prevalence, Incidence and Definition

The prevalence of MCR is 9.7% (12). As explained previously, MCR is composed of two components, slow gait and SCI, in the absence of a dementia diagnosis (6, 8, 12, 13). MCR is a good predictor of dementia (6, 8, 13, 22). Individuals diagnosed with MCR were more than 3 times likely to develop dementia, with a CI of 1.55–6.90 (8). Furthermore, MCR has been found to be an even better predictor of VD (8). Individuals diagnosed with MCR were 13 times more likely to develop VD, with a CI of 4.98–32.97 (8).

Incidence of MCR, similar to incidence of dementia, increases with age. Specifically, an article, which compiles data from four studies, reported that MCR incidence was 54.9/ 1,000 person-years for the 60-69 age group, 56.6/1,000 person-years for the 70-79 age group and 94.2/1,000 person-years for the 80 and above age group (22). The overall age and sex incidence of MCR was found to be 65.2/1,000 person-years, with a CI of 53.3–77.1 (22). Additionally, MCR is also a good predictor of falls and mortality (10, 23). The opportunity with MCR is that it is simple and easy to use. Thus, MCR can be used in all healthcare settings worldwide.

4.4. Risk Factors

The physiopathology of MCR is still under question (6, 8, 12, 13). Although MCR may predict both AD and VD, it is a stronger predictor of VD (6, 8, 12, 13). There are various factors which increase an individual's risk for MCR (13). After adjusting for age, sex and education it was found that stroke, Parkinson's disease, depressive symptoms, sedentariness and obesity were significantly associated with MCR (13). Specifically,

individuals with strokes were almost 1.5 times more likely to be diagnosed with MCR, with a CI of 1.14–1.77 (12). Individuals with Parkinson's disease were 2.5 times more likely to be diagnosed with MCR, with a CI of 1.68–3.76 (13). Individuals with depression were 1.65 times more likely to be diagnosed with MCR, with a CI of 1.28–2.13 (13). Individuals with sedentariness were 1.76 times more likely to be diagnosed with MCR, with a CI of 1.44–2.17 (13). Obese individuals were 1.39 times more likely to be diagnosed with MCR, with a CI of 1.17–1.65 (13). There is a need for further research as no systematic review and meta-analysis has been completed to confirm the predictive value of MCR. This knowledge gap will be addressed by the first manuscript of this thesis.

The association between CVDRF and MCR has been explored in 8 studies (8, 12, 23-28). After pooling all studies, cardiovascular diseases (CVD), hypertension, diabetes, stroke and obesity were found to be significantly associated with MCR (27). Specifically, individuals with CVD were 1.4 times more likely to be diagnosed with MCR, with a CI of 1.29-1.53 (27). Individuals with hypertension were 1.21 times more likely to be diagnosed with MCR, with a CI of 1.12-1.30 (27). Individuals with diabetes were 1.44 times more likely to be diagnosed with MCR, with a CI of 1.31-1.58 (27). Individuals with stroke were 2.05 times more likely to be diagnosed with MCR, with a CI of 1.78-2.36 (27). Obese individuals were 1.34 times more likely to be diagnosed with MCR, with a CI of 1.20-1.50 (27). When considering all CVDRF an individual is 1.38 times more likely to be diagnosed with MCR, with a CI of 1.33-1.45 (27). Moreover, though few studies have focused on the association between MCR and CVDRF, there are no studies with a focus on the Canadian

population (27). This knowledge gap will be addressed by the fourth manuscript of this thesis.

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Table 1. Summary of Motoric Cognitive Risk Syndrome criteria.

Article	MCR criteria	
	Subjective cognitive complaint	Walking speed
Verghese, 2012 (8)	– 15-item CERAD questionnaire	– Electronic walkway – Walk 4.60 m and 6.10 m
Verghese, 2014 (13)	– LonGenity, MAP, ROS and EAS: self-reported	– LonGenity and EAS: Electronic walkway – MAP and ROS: Stopwatch
Verghese, 2014 (12)	– H-EPESE: IADL scale – MAP: self-report ROS: self-report – InCHIANTI: Disability scale	– H-EPESE: Walk 2.74 m – MAP and ROS: Walk 2.44 m – InCHIANTI: Walk 4 m
Doi, 2015 (24)	– Response yes to the question “Do you feel you more memory problem with memory than most?” of the 15-item GDS	– 6.4 m
Kumai, 2016 (32)	– Score 15-item GDS ≥1	– Walk 6 m – Stopwatch

Beauchet, 2016 (25)	– Self-cognitive complaint	– Electronic walkway – Walk 9.7 m
Mergeche, 2016 (28)	– Score 15-item GDS ≥1	– Electronic walkway – Walk 4.9 m
Wang 2016 (26)	– Score 15-item GDS ≥1	– Electronic walkway – Walk 4.9 m
Allali, 2015 (33)	– CDR score ≥0.5; and/or a yes response on the15-item GDS; and/or AD8-dementia screener score ≥1	– Electronic walkway – Walk 6.10 m

Ayers, 2016 (23)	– Health and Retirement Study: response to the questions (1) “How would you rate your memory at the present time? Would you say it is excellent, very good, good, fair, or poor?” (responses: fair or poor). (2) “Compared to (the last 2 years/2 years ago], would you say your memory is better now, about the same, or worse now than it was then?” (response: worse). – National Health and Aging Trends Study: response to the questions (1) “How would you rate your memory at the present time? Would you say it is excellent, very good, good, fair, or poor?” (response: fair or poor). (2) “Compared to 1 year ago, would you say your memory is better now, about the same, or worse now than it was then?” (response: worse). (3) “In the last month, how often did memory problems interfere with your daily activities? Would you say	– Health and Retirement Study: 2.5 m – National Health and Aging Trends Study: 3m – The Survey of Health, Ageing and Retirement in Europe: 2.5 m

	every day, most days, some days, rarely, or never?" (response: every day, most days, or some days). – The Survey of Health, Ageing and Retirement in Europe: IADL scale	
Sathyan, 2017 (34)	– Score 15-item GDS ≥1	– Electronic walkway – 8.5 m
Doi, 2017 (35)	– Response yes to the question "Do you feel you have more problems with memory than most?" of the 15-item GDS	– Walk 2.4 m – Stopwatch
Sekhon, 2017 (36)	– Self-cognitive complaint	– Electronic walkway – Walk 9.7 m
Blumen, 2018 (37)	– GAIT study: Self-cognitive complaint – CCAM study: CDR score ≥0.5 and/or response yes on the15-item GDS and/or AD8-dementia screener score ≥1 – EAS: 15-item CERAD questionnaire	– Electronic walkway – GAIT study: Walk 9.7 m – CCAM study: Walk 6.10 m – EAS: Walk 4.60 m and 6.10 m
Maguire, 2018 (38)	– How would you rate your memory?" (responses: fair or poor, rather than excellent, very good, or good).	– Electronic walkway – 4.88 m

Beauchet, 2018 (39)	– One or two wrong answers on the Short Portable Mental Status Questionnaire	– 6 m – Stop watch

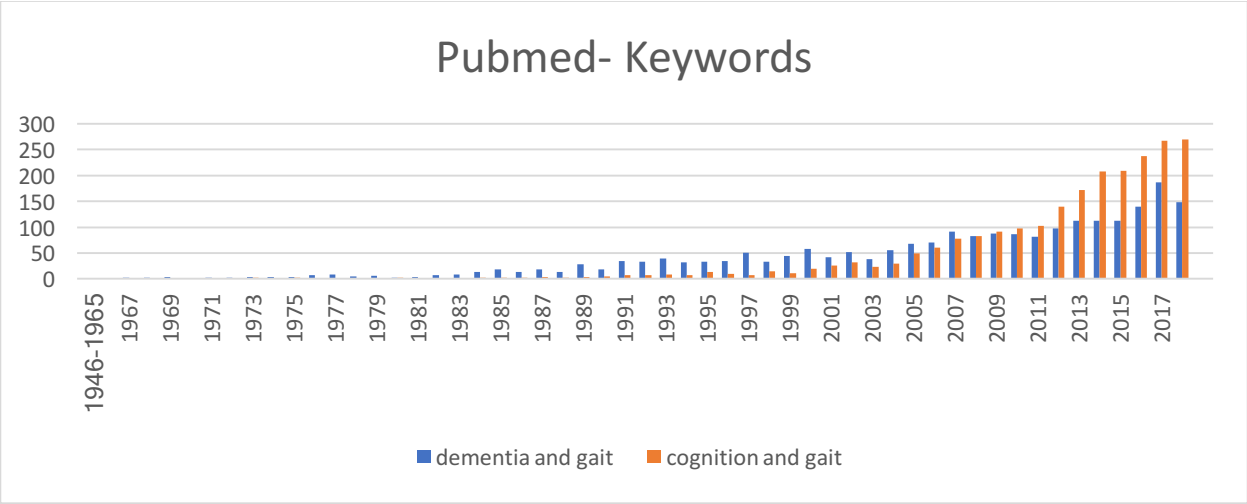

Figure 1. Number of yearly Pubmed publications based on key words.

Chapter 3 Methodology

No new data was collected for the studies below as there were databases which had various strengths and were well suited to answer the research questions. The two databases that were used are the Gait and Alzheimer Interactions Tracking (GAIT) study in manuscript two and the Canadian Longitudinal Study on Aging (CLSA) in manuscript three and four. The GAIT study, is a cross sectional data set (1, 2). Comparatively, the CLSA is a based on a longitudinal design. Both databases collected data on cognition and gait as well as other variables such as CVD, CVRF, depression and depressive symptomology.

3.1 Gait and Alzheimer Interactions Tracking Study

Participants in the GAIT study were recruited in France (Angers University Hospital) from 2009-2016 (2). The aim of the GAIT study was to compare the gait of individuals with different cognitive profiles. Data collection included questionnaires that were standardized, interviews, physical examination, blood tests, MRI, hand strength, vision test, and gait assessments using the GAITRite walkway, which is an electronic carpet (1).

Gait assessments were completed in a well-lit room, in comfortable footwear (1). The participants were asked to walk starting 2 meters from the GAITRite walkway and continue till 2 meters after the walkway (1). The gait assessments included instructions for walking at a normal steady pace and walking in a fast pace (without running or

jogging) (1). Moreover, participants also completed the FTSS test. The total time from seated position and returning to seated position at the end of the five-subsequent sit to stand positions were recorded.

Age, sex, education level, number of medications taken daily, number of psychoactive medications taken, hypertension, diabetes medications, height, weight and number of falls were recorded (1). The ADL, GDS (4 items), in addition to other cognitive assessments (i.e. MMSE, Frontal Assessment Battery, French version of the Free and Cued Selective Reminding Test-Total Recall, the Trail Making Test parts A and B and Stroop test) were completed (1). Using these cognitive assessments and multidisciplinary meetings, individuals were categorized based on cognitive impairment (Dementia, AD, CHI, MCI- amnestic and non-amnestic) (1). Moreover, severity of dementia was also determined (if applicable), MMSE score > 19 and MMSE score = 10-19 in addition to impairments in ADL, indicates mild and moderate dementia, respectively (1).

The selected GAIT participants also had blood tests including Vitamin B12, thyroid stimulating hormone (TSH), calcemia and other serum electrolytes, creatinine and urea. Hand strength on each side was also measured using a computerized hydraulic dynamometer to measure the maximal isometric voluntary contraction (MVC) (Martin Vigorimeter, Medizin Tecnik, Tutlingen, Germany). A vision test was also completed for binocular distance vision using a standard Monoyer letter chart at 5 m and corrective lenses if needed. The vision test was scored from 0-10, with 0 being the worst and 10 the best.

It is comprised of 912 participants (2). The participants are individuals age 60 and over at the time of recruitment (2). The participants were community dwelling older adults (1, 2). All participants were patients at the Angers University Hospital (1, 2). The participants were recruited from the hospital's memory clinic (1, 2).

The GAIT study inclusion criteria were: 1) written, informed consent to participate in the study, 2) age ≥ 60 years, 3) ability to walk 15 meters unassisted and without a walking aid, 4) completed MMSE, 5) absence of depression (based on GDS), 6) community dweller, 7) proficiency in French, 8) absence of extrapyramidal rigidity of the upper limbs, 9) no acute medical illness in the past month (1, 2). For manuscript two, only participants from the GAIT study that had information on gait speed, FTSS time, did not have dementia, vascular brain abnormalities, and did not use walking aid were included. Furthermore, age, sex, educational level, number of drugs taken daily, Body Mass Index (BMI), handgrip strength and distance vision acuity were covariables.

3.2 The Canadian Longitudinal Study on Aging

The CLSA is a population-based prospective and observational study (3). The CLSA aims to fulfill the knowledge gap on how Canadians age in the community (4). The Canadian population is rapidly aging and there is now a proportionately higher number of older adults compared to children. The focus of the CLSA is to better understand what variables are associated with the development and progression of cognitive

impairment in Canadians (4). Answering this knowledge gap will help in future research and policies (4).

The strength of the CLSA is that it is a longitudinal study that will continue to follow participants as they go through different life phases (4). The participants are individuals between the age of 45 and 85 at the time of recruitment (3). The large age range of the participants is another asset as it provides a different perspective in following younger adults as compared to older adults through different life phases (4).

Data is collected in various provinces and hospitals/research centers (3). A total of 11 cities have data collection sites, including Calgary, Halifax, Hamilton, Montréal, Ottawa, Surrey, Sherbrooke, St. John's, Vancouver, Victoria and Winnipeg (4). Two types of data collection were completed, a phone interview and a home interview along with data collection site visits (3). A total of 51, 388 individual participants were recruited, of which 21, 241 completed the phone interview and the remaining 30, 097 completed both the home interview along with data collection site visits (3).

The CLSA excluded individuals living in the three territories, federal First Nations reserves and settlements, institutions (i.e. long-term care institutions) and full-time members of the Canadian Armed Forces due to the sampling frame (4). Individuals who had temporary visas, transitional healthcare, not proficient in English or French and individuals who could not understand the purpose of the survey or answer questions accurately were also excluded (4).

The CLSA was built on the understanding that an individual is impacted by their combined physical, social, psychological and biological environments, which change

throughout their life (4). As such, the CLSA collected extensive data on participants social functioning, psychological health, biological health and physical well-being (4). Which makes the CLSA an appropriate fit for the research question and objectives regarding CVD, CVRF, depression and depressive symptomology.

For manuscript three and four, individuals were excluded if they did not have walking speed available or were diagnosed with dementia. As such, only the subset of CLSA participants who had completed the in-home interviews and data collection site visits were considered, as compared to individuals who only completed the phone interview. Furthermore, age, sex, Indigenous identity, country of birth, place of living, marital status, low household income, education level, total number of medications daily taken and BMI were considered.

3.3 Depression and Depressive Symptomology

3.3.1 Depression

Depression in the CLSA is defined by the question “Has a doctor ever told you that you suffer from clinical depression?” (3). The term clinical depression is synonymous with major depression and major depressive disorder (2). The diagnostic criteria for major depressive disorder is three-fold (5). Firstly, an individual must exhibit some change in at least five of the nine symptoms, depressed mood and decreased interest/pleasure especially must be observed (5). The nine symptoms include 1) depressed mood, 2) decreased interest/pleasure, 3) unexpected weight loss/gain, 4) insomnia/hypersomnia,

5) agitation, 6) low energy, 7) feeling worthless, 8) lower concentration and 9) suicidal ideation (5). The symptoms should be present for most days over a 2-week period (5). Most of the nine symptoms, except weight loss and suicidal ideation, should be observed daily (5). Secondly, these symptoms are found to negatively affect some areas of the individual's life and functioning (5). Thirdly, the symptoms cannot be better explained by another medical condition or side effect (5).

There is prevalence of 7% for major depressive disorder in the US (6). It must be noted that a proportionately higher proportion of women (1.5-3 folds higher, as compared to men) are affected by the same (6). Moreover, individuals with major depressive disorder also had a higher rate of mortality (5). This was even noted in individuals with major depressive disorder admitted to nursing homes (5). The onset of major depressive disorder is highest in the 20s, though it can occur both before and after that, even in later life (6).

3.3.2 Mood Disorder

Mood disorder in the CLSA is defined by the question "Has a doctor ever told you that you have a mood disorder such as depression (including manic depression), bipolar disorder, mania, or dysthymia?" (3). Manic depression is also known as bipolar disorder (2, 5). Bipolar disorder is subcategorized into bipolar disorder I and II (5). To be diagnosed with bipolar I disorder an individual must be diagnosed with a manic episode (5). Though hypomanic episodes can occur with bipolar I disorder, they are not required for a bipolar I disorder diagnosis (5). Comparatively, in bipolar II disorder the criteria for

both (at least one) hypomanic episode and (one) major depressive episode must be met, in addition to never being diagnosed with a manic episode (5). Moreover, the hypomanic episode(s), depression symptoms and behaviors should not be better explained by another medical condition or side effect (5).

Bipolar I disorder (manic episode) is defined by 4 criteria (5). Firstly, mood disturbances (i.e. abnormal mood, activity and energy) must be exhibited regularly for at least 1 week (5). Secondly, during the first criteria, three or more symptoms should be exhibited (5). The symptoms include increased self-esteem, less sleep required than normal, more conversational, racing thoughts, increased level of distractedness, more goal directed activity and increased risk taking/lack of concern of the consequences (5). Thirdly, the exhibited behaviors are found to negatively affect areas of the individual's life and functioning, even to the extent of potentially causing harm to themselves or others (5). Fourthly, the symptoms cannot be better explained by another medical condition or side effect (5).

Dysthymia or persistent depressive disorder is defined by 8 criteria (5). First, depressed mood is experienced for most days over a 2-year period (5). Second, 2 or more of the following symptoms are exhibiting: a) unexpected weight loss/gain, b) insomnia/hypersomnia, c) low energy, d) feeling worthless, e) lower concentration and f) hopelessness (5). Third, both criteria 1 and 2 have occurred during the 2 years, excluding times of 2 months (at a time) maximum (5). Fourth, major depressive disorder can be present for the 2 years (5). Fifth, no manic episode, hypomanic episode or cyclothymic disorder is exhibited (5). Sixth, the symptoms cannot be better explained by

another medical condition (5). Seventh, the symptoms cannot be better explained by the side effect of any substance (5). Eighth, the exhibited behaviors are found to negatively affect areas of the individual's life and functioning (5). The prevalence of persistent depressive disorder is reported to be 0.5% in the US in 12 months (7). Comparatively, the prevalence of chronic major depressive disorder is reported to be 1.5% in the US in 12 months (7).

3.3.3. Anxiety Disorder

Anxiety disorder in the CLSA is defined by the question "Has a doctor ever told you that you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?" (3). Obsessive-compulsive disorder is defined by four criteria (5). First, there must be the presence of either/both obsession and compulsions (5). Where obsession is defined as repetitive unpleasant thoughts/urges that usually cause anxiety/distress and attempting to subdue the thoughts by a compulsive action (5). Compulsion is defined as repetitive behaviors that are done in response to unpleasant thoughts/urges (obsessions) and these behaviors are done to try to alleviate the anxiety/distress, though they are not connected in any manner and are excessive in nature (5). Second, the obsessions/compulsions cause distress and are a waste of time (5). Third, the obsessions/compulsions cannot be better explained by the side effect of any substance (5). Fourth, the obsessions/compulsions cannot be better explained by another medical condition (5).

Panic disorder is defined by four criteria (5). First, the individual experiences repeated and unforeseen panic attacks, during which four or more of the follow symptoms are experienced: increased heart rate, perspiration, trembling, perceived shortness of breath, perceived chocking, chest pain, nausea, dizziness, chills/heat, tingling, depersonalization, fear of losing control or dying (5). Second, for 1 month or more after experiencing the symptoms above, the individual is worried about another attack occurring and/or changed behavior to try to avoid another attack (5). Third, the obsessions/compulsions cannot be better explained by the side effect of any substance (5). Fourth, the obsessions/compulsions cannot be better explained by another medical condition (5).

Phobia is defined by seven criteria (5). The criteria must: 1) persist (≥6 months), 2) cause avoidance of a situation and/or object and 3) consistent of un-proportional fear/anxiety. Moreover, the exhibited behaviors significantly, negatively affect areas of the individual's life and functioning. Lastly, the symptoms cannot be better explained by another medical condition (5). The average person has three phobias (8). Moreover, 75% of individuals have more than one phobia (8).

3.3.4. Depression Assessments

3.3.4.1. Center for Epidemiologic Studies Depression Scale

The center for epidemiologic studies depression scale (CESD) was first published in 1977 by Radloff as a 20-item scale (9). The higher the score that the individual has the more serious their symptoms (9). A shorter 10 item scale of the CESD has also been

created and been shown to be accurate, similar to the 20-item version (9, 10). The cut-off scores for the questionnaires are 16 for the 20-item scale and 10 for the 10-item scale (10). Some of the items in the CESD have been previously used in other scales and were incorporated based on their association with depression (9).

The purpose of the CESD is to identify an individual's current level of depressive symptomatology (9). Specifically, the CESD is used to assess factors such as depressed mood, feelings of worthlessness, helplessness and hopelessness, loss of appetite and sleep, etc. (9). Efforts have been taken to validate the scale in different countries (i.e. Canada, France, etc.) and populations, such as the adolescent and elderly population (9, 11-15). Moreover, it has also been validated in different groups such as individuals with HIV and individuals with a lower socioeconomic status (11, 12). One limitation of the use of the CESD scale is that it was created for use in the general public and is not specific to the geriatric population.

3.3.4.2. Geriatric Depression Scale

The GDS was first published in 1983 by Yesavage et al. as a 30-item scale (16). Shorter versions of the GDS have also been considered (17). The test was later shortened to 15 items in 1986 (18). The 15, 10 and 4 item GDS have all been validated (17). Moreover, the GDS 15 has also been validated in primary care settings (19). The assessment is typically completed within 5-10 minutes (20).

The 15-item version is scored out of 15 (18). The scale of scores can be from 0-15, with the categories 0-4. 5-8. 9-11 and 12-15 representing a normal score, mild depression,

moderate depression and severe depression, respectively (18). The strength of the GDS is that it is a dedicated geriatric scale.

3.4 Cardiovascular Diseases and Risk Factors

3.4.1. Cardiovascular Risk Factors

3.4.1.1. Body Mass Index

BMI is defined as the ratio of an individual's weight (in kg) to the square of their height (in meters squared) (21). The corresponding value is then placed into a category based on the following cut-off values, <18.5, 18.50-24.99, 25.00-29.99, 30.00-34.99, 35.00-39.99 and ≥40, which are classified as underweight, average weight, preobese, obese class I, moderate obese class II and severe obese class III, respectively (21).

It has been reported that individuals with a BMI ≥25 have a higher lifetime risk of CVD incidence than individuals with a BMI between 18.5-24.9 (22). Moreover, individuals with a higher BMI were affected by CVD for longer and lived with the disease for more years (22). A higher BMI was also found to be associated with heart failure (22). One limitation to BMI is that it does not take into consideration where the fat is stored or the age of the individuals. This is important to consider as high BMI is often generalized to be associated with CVD. However, this is not always the case, as with CVD mortality, individuals that are 60 and above do not have a significant association between increased BMI and CVD mortality (23).

3.4.1.2. Waist to Hip Ratio

Waist to hip ratio (WHR) is defined as the circumference of the waist divided by the circumference of the hip (24). WHR has been found to be a better predictor of CVD, due to the association between CVD and abdominal fat (24). Moreover, as identified by the World Health Organization (WHO) a major limitation currently is the generic cut-offs used for both BMI and WHR (24). Rather, cut-offs should be based on sex, age and ethnicity (24).

3.4.1.3. Smoking

Smoking is the most preventable risk factor that greatly impacts CVD (25). Smoking alone is responsible for 10% of CVD, which in turn are preventable (26). Smoking is most prevalent in lower- and middle-income countries (2). The reported risk of coronary heart disease increases 2-4 folds by smoking (25). Moreover, smoking has also been linked to a 70% higher risk of death from coronary heart disease (25). There is still a lack of awareness regarding the negative implications of smoking on CVD (2). Better knowledge dissemination of research and information is needed along with support programs (2).

3.4.1.4. Hypertension

Hypertension is a chronic disease which affects 2-25% of the adult Canadian population (27). Hypertension is associated with obesity, CVD and death, to name a few (27). It has been deemed that the most important CVRF is hypertension, even when

considering smoking (28). Elevated blood pressure (above 115/75 mmHg) has been associated with an increased risk for coronary disease and stroke (28). Hypertension and diabetes are also associated (29). It has been reported that individual with diabetes have hypertension two times more than individuals without diabetes (29). Moreover, individuals with hypertension are more likely to develop diabetes, as compared to individuals without hypertension (29).

Hypertension is the strongest CVD risk factor (30). Lower blood pressure has been associated with a reduced risk of CVD mortality (29). The strength of the association between blood pressure and stroke varies based on ethnicity (30). Blood pressure below 140/90 mm Hg is also seen to decrease the risk of developing end-stage renal disease in individuals with type 2 diabetes (29).

3.4.2. Cardiovascular Diseases

3.4.2.1. Diabetes

Diabetes is diagnosed when one of the following three criteria are met (31). Either 1) casual plasma glucose 200 mg/dl (11.1 mmol/l) is reported, irrespective of time since last meal, 2) a plasma glucose of 126 mg/dl (7.0 mmol/l) after fasting for at least 8 hours, or 3) when completing an Oral Glucose Tolerance Test the 2 hour plasma glucose is reported to be 200 mg/dl (11.1 mmol/l) (31). CVD are the primary cause of death in individuals with diabetes (29). The association between diabetes and CVD is found to be sex specific. Women have been found to be a greater risk, than men (29).

Individuals with type 2 diabetes can control their risk for CVD by glycemic control (31). Physical exercise has been reported to increase glycemic control (31). Specifically, it is recommended that an individual participate in aerobic exercise with moderate intensity for a minimum of 150 minutes a week spread over 3 days, with a maximum break of 2 days between physical activity (31). Additional vigorous aerobic activity in addition to or in lieu of moderate intensity exercise is also recommended (31). Individuals with hypertension are two times more likely to develop diabetes (29). It has been reported that 75% of CVD in individuals with diabetes is due to hypertension (29). It is thus recommended that individuals with diabetes and hypertension reduce their blood pressure to below 130/85 mm Hg (29). Individuals with diabetes that also have systolic hypertension, increased cholesterol and smoke are found to have an even higher risk of death due to CVD (29).

3.4.2.2. Angina

Angina presents as a pain/heaviness that is felt in the chest, jaw and left arm which typically subdues in 5-10 minutes (32, 33). The discomfort is often experienced after laborious activity or stress and lessens upon rest (32, 33). However, other symptoms can also present, notably among individuals with diabetes (32). The discomfort has also been reported to be worsened by increased stress, colder weather and heavy meals (33). 50% of individuals with coronary artery disease will present with angina (34). Individuals with angina are 2 times more likely to have a major cardiovascular event (34).

Angina is associated with higher BMI (33). It is recommended that a BMI below 25 be targeted (33). In addition to the same, increased consumption of oily fish and decreased saturated fats and sugar intake is suggested along with smoking cessation (33, 34). More older women are reported to have angina (35). Angina is also associated with heart failure and polyvascular disease, cardiovascular hospitalizations, and coronary revascularization (35).

3.4.2.3. Peripheral Vascular Disease

Peripheral vascular disease (PVD) or peripheral arterial disease affects 5-10 million adults in America alone (36). It is a global vascular disease that affects lower limbs, it is due to plaque accumulation, typically in the leg arteries, which impedes blood flow (36). It is associated with age, worth 1 in 20 Americans over the age of 50 being affected (36). Claudication or cramping in the lower limbs which causes a limp while walking is a common symptom (37). The muscle cramping is most commonly seen in the calves (37). 15-40% of individuals present with claudication (36).

Age and sex are both reported to be associated with PVD (37). Moreover, increasing age is associated with claudication (37). Additionally smoking, hypertension, diabetes, cholesterol levels, CVD, hypertension and physical inactivity are all risk factors for PVD (36, 38). Individuals who smoke, especially men who smoke are most at risk (36). A third of individuals over 50 years of age with diabetes will develop PVD (36). The accumulation of risk factors is found to further increase an individual's risk of developing PVD (37, 38). The association between PVD as well as older age, renal dysfunction,

heart failure, hypercholesterolemia, diabetes, cerebrovascular disease, and pulmonary disease have been found to be associated with 10-year mortality (39). It is recommended that individuals with PVD partake in regular exercise (36). Walking/physical activity provides benefits such as the ability to walk further, longer and fast for individuals with PVD (36). Claudication is also reported to decrease with physical activity (36).

3.4.2.4. Stroke

Stroke affects over 400, 000 Canadians (40). Stroke is the third leading cause of death in Canada (40). Moreover, in adults it is also the leading case of neurological disability (40). Individuals who have experienced one stroke and have many risk factors are at high risk for additional strokes (41). The risk of death due to stroke is highest in countries in Asia (42). This trend is seen to be decreasing in Japan and some areas in China (42).

Diabetes, hypertension, smoking, increased weight, lack of exercise and high sodium intake have all been found to be associated with risk of stroke (42). It is recommended that individuals who are at risk for stroke or have had a stroke eat fewer processed foods and have a diet higher in vegetables and fruit (42). Typically, it is recommended that the Mediterranean diet, which consists of more whole grains, fish, fruits, vegetables, olive oil and decreased red meat intake be followed (42). It is further recommended to limit sugar and sodium intake and maintain/achieve a heathy BMI or waist circumference based on sex, 18.5 to 24.9 kg/m2, circumference less than 88 cm

(women) and circumference less than 102 cm (men) (42). Alcohol consumption is recommended to be a maximum of 2 drinks a day or a maximum of 3 drinks on an occasion, with the week limit being 10 drinks for women (42). Comparatively, for men it is recommended that consumption be limited to a maximum of 3 drinks a day or a maximum of 4 drinks on an occasion, with the week limit being 15 drinks (42).

3.5. Statistical Analysis

Statistics were performed by the software program WINPEPI Computer Programs for Epidemiologists (version 11.48) in study one and SPSS (version 23.0; SPSS, Inc., Chicago, IL) in all other (two, three and four) studies. The systematic review and meta-analysis completed in manuscript 1 selected articles based on an inclusion criteria described above. Upon selection of the studies, adjusted HR were used to determine if MCR was associated with the incidence of dementia, using adjusted baseline characteristics of participants. Furthermore, adjusted ORs were used for the coefficient of regression for dementia, incident cognitive impairment, brain structures and cognitive performance, also using adjusted baseline characteristics of participants. As presented in the forest plots fixed effects meta-analyses were completed. Cochrane's Chi-squared test for homogeneity (Chi^2) and I^2 calculations were used to evaluate heterogeneity and the amount of variation between studies.

In manuscript two, three and four, means and SD or frequencies and percentages were used as appropriate to summarize participants characteristics. A Kruskal-Wallis Mann-

Whitney, t-test or Chi square test was used for between group comparisons. In manuscript two participants were grouped based on MCR status as well as walking speed vs FTSS. In manuscript three and four participants were grouped based on age group (1. 45-54, 2. 55-65, 3. 65-74 and 4. 75+) or MCR status (1. No MCR and 2. MCR). In study two findings were considered statistically significant for a p-value of 0.05 or less. The association between MCR and MCI were completed using uni and multiple logistic regressions and adjusting for participants characteristics. In study three and four multiple logistic regressions were also performed to examine the association between MCR and depressive symptomology as well as between MCR and CVDRF. Separate models were used individually with no adjustment, adjustment for clinical characteristics and adjustment on clinical characteristics and CVDRF (only for study four). Due to the multiple comparisons in studies three and four the p-value was derived accordingly.

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Chapter 4 Motoric cognitive risk syndrome, incident cognitive impairment and morphological brain abnormalities: Systematic review and meta-analysis

This systematic review and meta-analysis examines the association between motoric cognitive risk syndrome (MCR) as well as incident cognitive impairment, incident of dementia and morphological brain abnormalities.

This systematic review was essential as no systematic review has been completed on MCR since the time of its conception.

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ABSTRACT

Background: Motoric cognitive risk syndrome (MCR) is a pre-dementia stage, which associates slow walking speed with subjective cognitive impairment (SCI). MCR's clinical utility for the prediction of dementia and its pathophysiology are unclear. The aim of this systematic review and meta-analysis is to examine the association of MCR with incident cognitive impairment, cognitive performance and brain structures.

Methods: A systematic search was conducted using the Medical Subject Heading terms "Walking" and "Cognition disorders" combined with the terms "Subjective cognitive impairment", "Subjective cognitive decline" and "Motoric cognitive risk". A total of 11 studies were included in the systematic review and meta-analysis: 3 studies had dementia as the outcome, 3 studies had cognitive performance as the outcome, 4 studies had brain structures as the outcome and one study examined the incidence of both major neurocognitive disorders and cognitive impairment.

Results: MCR was found to be associated with incident cognitive impairment (pooled hazard ratio (HR) = 1.70, 95% CI, 1.46–1.98 with P-value<0.001) and dementia (pooled HR=2.50, 95% CI, 1.75–2.39 with P- value < 0.001). MCR was also found to be associated with low grey matter volume involving the premotor and the prefrontal cortex, and lacunar lesions in the frontal lobe. No significant association was found with white matter abnormalities.

Conclusion: MCR predicts cognitive impairment and dementia, suggesting that it may be used as a screening syndrome for dementia in a primary care setting. Its significant

association with both low grey matter volume and lacunar lesions makes its pathophysiology unclear and suggests multiple pathways.

Introduction

Dementia is a significant health issue because of its high prevalence and incidence (in which it's estimated to affect up to 20% of the older population), and because of the adverse consequences for patients (e.g., disability, institutionalization) and the health care system (e.g., increased expenditures) (1–3). Predicting individuals at risk for dementia provides an opportunity to intervene early on potent risk factors with the aim to reduce the incidence rate of dementia (4,5). Characterization of risk for dementia at the population level is still a challenge because it must be performed in a primary care setting where there are multiple constraints limiting its utilization (5,6). For instance, in Canada only 24% of primary care physicians routinely screen for dementia, regardless of the type of screening tests (7). To increase the compliance by primary care physicians, the process of screening for dementia risk must be easy, rapid, and integrated into daily practice and applicable everywhere (5–7).

Slow walking speed and subjective cognitive impairment (SCI), defined as perceived changes in cognition in the absence of objective impairment, are both clinical characteristics that have been independently associated with an increased risk for dementia (8,9). In 2013, Verghese et al. defined a syndrome known as "Motoric Cognitive Risk" syndrome (MCR), which combines slow walking speed and SCI in individuals free of dementia and mobility disability (10). This clinical syndrome, which has a high prevalence and incidence rate, estimated around 10% and 65.2/1,000 person-years respectively, is associated with an increased risk for dementia (11,12). This risk is higher than the risk of slow walking speed and SCI alone (10–12). MCR has

all the characteristics required for a clinical screening assessment for dementia risk in primary care populations. However, five years after its first description, MCR's utility and its value for the prediction of dementia have yet to be determined. For instance, a recent non-systematic review underscored the possibility of MCR ambiguity by asking whether this syndrome is "a condition to treat or a mere matter for research purposes" (13). Data accumulated since its first description seem to disagree with this proposition, but no systematic review and meta-analysis has been performed on the association of MCR with dementia and incident cognitive impairment. In addition, to better understand the association of MCR with cognitive impairment, there is also a need for a review of its association with various brain structures and their abnormalities. Therefore, the aim of this systematic review and meta-analysis is to examine the association of MCR with dementia, incident cognitive impairment and brain morphology abnormalities.

Methods

Search strategy and data extraction

A systematic search was conducted in October 2018 and updated in January 2019 with a time period that ranged between January 1, 2013, which was the year of first publication by Verghese et al. on MCR [10], and December 31, 2018, for all English articles in Medline (Pubmed) and EMBASE (Ovid, EMBASE). Medical Subject Heading (MeSH) terms such as "Walking" and "Cognition disorders", combined with the terms "Subjective cognitive impairment", "Subjective cognitive decline" and "Motoric cognitive

risk", were used. We did not use other databases for the search strategy, because it increased the number of non-selected studies, and did not increase the number of selected studies. This singularity may be explained by the recent description of MCR (i.e., first publication in 2013) and, thus, the low number of studies on MCR. Two authors (HS and OB) conducted independent data extraction. A consensus procedure was developed but was not implemented due to concordance.

Study selection

To be included in the primary analysis, the following preliminary selection criteria were applied: the study had to be 1) a human study, 2) published in English, 3) about MCR and 4) an original study. If a study met the initial selection criteria or its eligibility could not be determined from the title and abstract (or the abstract was not provided), the full text was retrieved. Two reviewers (HS and OB) then independently assessed the full text for inclusion status. Full articles were screened using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and Consolidated Standards of Reporting Trials (CONSORT) checklists (14,15). Furthermore, the quality of each study included in the meta-analysis was assessed using the PRISMA checklist (16). The final selection of criteria was, therefore, applied when the subjects of publication were: 1) prediction of dementia, 2) association of MCR with cognitive performance and 3) association of MCR with brain morphology. The study selection procedure is presented in the PRISMA flow diagram (Fig. 1).

Qualitative analysis

Of the 609 identified abstracts, 16 (2.6%) met the initial inclusion criteria (10–12,17–28). After examination, 5 were excluded (31.3%) because the outcomes were not incident dementia, cognitive impairment, cognitive performance or brain morphology outcomes (12,13,19,20,22). As a result, 11 studies were included in the systematic review and meta-analysis: 3 studies with dementia as the outcome (11,17,18), 3 studies with cognitive performance as the outcome (23–25), 4 studies with brain structures as the outcome (21,26–28) and one study that examined the incidences of major neurocognitive disorders and cognitive impairment together (10). Articles selected for the full review had the following information extracted: authors' last name and date of publication, country of origin, name and design of the study, participants' generic information (i.e., setting, number of participants and proportion of women), age, cognitive status and walking measures at baseline assessment, length of follow-up period, incident cases of dementia as appropriate, and main results.

Meta-analysis

The association of MCR with incident dementia and cognitive impairment was determined using the adjusted Hazard Ratio (HR), the adjusted Odds Ratio (OR) and the adjusted coefficient of regression with a 95% Confidence Interval (CI). The association between MCR and brain morphology was not examined because of the few number of studies. In all cases, only adjusted values on the participants baseline characteristics were used. Fixed effects meta-analyses were performed on the

estimates to generate summary values. Results are presented as forest plots. Heterogeneity between studies was assessed using Cochrane's Chi-squared test for homogeneity (Chi (2)), and the amount of variation due to heterogeneity was estimated by calculating the I2 (29). Statistical analyses were performed using WINPEPI, which is a free software program for epidemiologists (version 11.48) (30).

Results

Characteristics of studies

Table 1 summarizes the 11 studies included in the systematic review (10,11,17,18,21,23–28). All studies were published within the last 5 years. Nine studies were conducted in the older population living in the United States (10,23,28), Japan (17,18), France (24,26), and India (21,27) and analyzed separately data from each country. Two studies pooled data from different countries (11,28). The number of participants ranged from 139 (21,27) to 4555 (11). All participants were older adults at baseline with the mean age ranging from 66.6 (27) to 79.9 (11) years. Data collection was based on observational studies, in which 6 studies (10,11,17,18,23,25) used a longitudinal prospective cohort design with a follow-up period ranging from 2.4 (18) to 9.3 years (11), and 4 studies (24,26,24–28) used a cross-sectional design. SCI was assessed using different standardized questionnaires by extracting one item focusing on cognitive complaint or using a threshold value based on a range of scores for questionnaires (15-item Consortium to Establish a registry for Alzheimer's Disease

questionnaire, instrumental activity daily living scale, 15-item Geriatric Depression scale, Assessment Dementia eight-item informant interview, Clinical Dementia Rating scale) or using an answer for a single question in a closed end format (yes versus no) (10,17,18,23–28). Walking speed was assessed using a stopwatch or a computerized walkway with embedded pressure sensors (10,17,18,23–28). The distance used to measure walking speed ranged from 2.4 m (18) to 9.7 m (24,26,28).

MCR and incident cognitive impairment

The prevalence of MCR syndrome ranged from 6.0% (10) to 18.2% (24). The majority of cohort studies demonstrated a significant association between MCR and dementia with a Hazard ratio (HR) that ranged from 1.7 (11) to 4.3 (10), as well as an association with cognitive decline with lowest HR = 1.6 (11) and a negative association with cognitive performance with coefficient of regression beta ranging from −8.05 to −9.75 (23). Two studies reported a non-significant association with dementia: the Kurihara project in Japan (17) and Verghese et al. (10) that explored MCR in participants without MCI. Slow walking speed alone was significantly associated with the incidence of cognitive impairment in one study (11) but not with the occurrence of dementia in two studies (10,18). In these three studies, the HR of walking speed was lowest compared to the HR of MCR. Cognitive complaint was not associated with incident cognitive impairment (11), but was associated with dementia with the lowest HR compared to MCR (18).

MCR and cognitive performance

The association of MCR and cognitive performance was heterogeneous and varied across studies. MCR was negatively associated with global cognitive performance (13) and executive function (13,24), but this last significant association was dependent on the MCI status of the MCR participants (24). In addition, one study did not show any association with executive function (25). One study reported a significant negative association with memory (25) while two other studies did not (23,24).

MCR and brain structures

The association between MCR and brain structures also varied across studies. Two studies found no association with vascular lesions (26,27), while one study showed that the frontal lacunar infarcts were significantly associated with MCR (21). Two studies reported a significant negative association between MCR and gray matter in the premotor (26) and prefrontal cortex (28).

Meta-analysis

The meta-analysis was performed on 3 studies, which reported results from 6 different studies with a total of 9156 participants when examining the association with dementia (Fig. 2), and 4936 participants when examining the association with cognitive impairment (Fig. 3). Fig. 2 shows the forest plot of the pooled HRs and OR for one study (17) that showed an association between MCR syndrome and incident dementia, which were computed with meta-analysis techniques. All pooled Ratios were significant,

except the OR for the Kurihara project (17). The pooled ratio was 2.50 (95% CI, 1.75–2.39) with a P- value < 0.001. Fig. 3 shows the forest plot of the pooled HRs for the association between MCR syndrome and incident cognitive impairment. All pooled HRs were significant, and the pooled HR was 1.70 (95% CI, 1.46–1.98) with a P-value < 0.001.

Discussion

The primary finding of this study is that MCR is significantly associated with incident dementia and cognitive impairment. These associations were greater compared to slow walking speed and SCI alone and depend on the cognitive status of the individuals. Mild cognitive impairment (MCI) syndrome may increase or decrease the strength of the association. In addition, lower global cognitive performance was reported in individuals with MCR compared to those without MCR. In contrast, the association of MCR with cognitive performance in subdomains like memory and executive function was inconsistent; some studies showed a significant association while others did not. Finally, MCR status was associated with lower grey matter volume involving the premotor cortex and the prefrontal cortex. No significant association was found with white matter abnormalities, however there was an association with frontal lacunar infarcts.

MCR and incident cognitive impairment

This meta-analysis confirms that MCR is a significant and stronger predictor of cognitive impairment and dementia, than slow walking speed and SCI alone. This result highlights that MCR has a clinical interest for the screening of dementia risk in primary care populations and, therefore, is not only a research concept as was recently suggested (13). MCR is a pre-dementia syndrome like MCI but, compared to MCI, MCR is easy to diagnose. Measuring walking speed can be performed anywhere with a simple stopwatch and SCI can be recorded during the time of usual consultation in primary care. Early identification of individuals at risk of dementia is a key step in the efficient care of cognitive impairment [5–7]. Indeed, undetected cognitive impairment like dementia places individuals (i.e., patients and their caregivers) at risk for psychosocial issues, financial issues and adverse health events (4,5,9,31,32). Early identification of individuals at risk provides an opportunity to adjust to the diagnosis and to participate actively in planning for the future, which can reduce the heavy personal and societal costs (4,5). The past decade has been characterized by an increased interest in identifying and validating biomarkers for early diagnosis and identification of individuals at risk for dementia. However, the use of biomarkers has limitations in many settings (31,32). For instance, access to neuropsychological testing or neuroimaging may be difficult and expensive. Compliance to lumbar puncture for an early diagnosis of dementia is low (9,31,32). The large expense of biomarkers limits their use and they are not accessible in primary care. Finally, the highest incidence of dementia is observed in low and intermediate income countries, where the accessibility of biomarkers is very

limited (2,3). Hence, there is a need to optimize and increase the accessibility of clinical risk assessment for dementia in community-dwelling older populations (4,5). Using a syndrome like MCR based on a simple and “low tech” motor test like walking speed, combined with a cognitive complaint to predict early risk of dementia, may be a preferential solution. The next step for researchers on this topic is to examine the performance criteria for MCR (i.e., sensitivity, specificity, positive and negative predictive value) for the prediction of dementia.

MCR and cognitive performance

The association of MCR and incident cognitive impairment including dementia underscores that MCR is a useful syndrome, which is a clinical application of recent advances to provide a better understanding of interactions between cognitive processes and walking control and their impairments (8). There is increasing evidence of a strong association between cognitive impairment and walking performance, but the nature of this association is still a matter of debate (8,11). Cognition and locomotion are two human abilities that demand significant attentional resources (8,24). The impairment of cognition and locomotor performance with dementia is greater than the simple sum of their respective prevalence, suggesting a complex interplay that leads to walking instability (8,11,12,23,24). Walking instability in individuals with dementia is caused by impairments in the highest levels of walking control (i.e., sub-cortical and cortical levels), secondary to brain lesions and disturbed brain networks (8). The temporality of the sequence of impairment occurrence (i.e., motor versus cognitive or cognitive versus

motor) and their nature (i.e., caused directly by brain lesions, cognitive impairment or both) remains to be determined. Recently, a meta-analysis of prospective cohort studies assessed the association of walking speed with the risk of cognitive decline and dementia in elderly populations (33). This study confirmed that slowly walking older adults free of dementia had a higher risk of both cognitive decline and dementia, suggesting that slow walking speed is the first symptom leading to dementia. However, the contribution of cognitive impairment to the mechanism of slow walking speed is still an open question. It has been demonstrated that executive functions have a key role in walking control in healthy young and older adults (8,23,24). This involvement suggests that early impairment in cognitive performance at the stage of MCI may cause or increase walking impairment, and thus will affect walking speed. One study examined the association of MCR and cognitive performance in older individuals with respect to their cognitive status (i.e., MCI versus non-MCI) (24). This study highlighted that the combination of MCR and MCI was associated with lower cognitive performance compared to individuals with MCR but without MCI. In addition, the first publication of Verghese et al. (10) demonstrated that individuals with MCR and amnestic MCI have a greater risk of converting to dementia compared to those with MCR only (HR = 4.3 versus HR = 2.91). These results suggest that the combination of MCR with MCI may be the last stage before dementia in the spectrum of dementia (please see Fig. 4). For the association of MCR and cognitive performance, our systematic review showed more inconsistent results. Indeed, some studies showed a significant association between low performance in memory and executive function, while others did not. This result may be

explained by the fact that most studies classified participants free of dementia but provided no information on the MCI diagnosis.

MCR and brain structure

Our study showed that individuals with MCR had lower gray matter volume mainly in the premotor cortex and the prefrontal cortex, but had no significant association with white matter abnormalities. Only one study reported that individuals with MCR had significantly more lacunar frontal lesions compared to those without MCR (21). This result suggests that neurodegenerative lesions are, in large part compared to ischemic lesions, involves in the pathophysiology of MCR. This result is counterintuitive as MCR seems to be a greater predictor of vascular dementia compared to Alzheimer disease (10–12). For instance, the risk of developing dementia reported in the first publication involved a hazard ratio [HR] of 3.3 (95% Confidence interval (CI): 1.55–6.90), which increased to 12.8 (95% CI: 4.98–32.97) for vascular dementia (10). One explanation could be related to the fact that MCR detects individuals at an early stage of the process leading to dementia, whereas the consequences of the vascular component may not be detected and/or be the trigger of neurodegenerative lesions. For instance, since the first report by Hatazawa et al. (1) in 1984, a growing number of epidemiological studies have shown that high blood pressure (BP) levels are associated with a lower volume of regional brain tissue (34–41).

Limitations

Some limitations of this systematic review and meta-analysis need to be acknowledged. First, a limited number of studies have been selected due to the fact that MCR is a recently described syndrome. In particular, the meta-analysis was performed on 3 studies, which represents the minimum number of studies for a meta-analysis. However, these 3 studies reported the results of 6 different studies which have been used for the meta-analysis. Second, the criteria used to define subjective SCI and walking speed varied across the selected studies. Third, we found that different approaches have been used to define SCI but none of them used a specific and validated questionnaire, which is the gold standard assessment (42). Indeed, SCI was diagnosed from an item of questionnaires designed to screen other syndrome, like depressive symptomology, or a single question. Fourth, even if the way to assess walking speed was standardized, two types of evaluation were used: a stopwatch versus a computerized walkway with embedded pressure sensors. This last solution is more objective and accurate compared to a stopwatch. However, the clinical interest of MCR is its ability to be used in primary care setting, where there is a need for a simpler mobility test, which can be completed rapidly. Thus, the best approach is probably to find a good balance between an objective measure with a more accurate sensor assessing walking speed compared to stopwatch and it usability in primary care setting. Fifth, the different lengths of the respective follow-ups, the inclusion of older adults only from developed countries, and the various proportions of women may limit the generalization of the present findings.

Conclusion

This systematic review and meta-analysis confirms that MCR successfully predicts cognitive impairment including dementia, suggesting that it may be used as a screening syndrome for dementia in a primary care setting. However, its significant association with both low grey matter brain volume and lacunar lesions makes MCR pathophysiology unclear and suggests multiple pathways.

Author Contributions

Harmehr Sekhon contributed to study concept and design, data acquisition, analysis and interpretation, and drafting of the manuscript. Gilles Allali contributed to data acquisition, analysis and interpretation, and critical revision of the manuscript for important intellectual content. Cyrille P Launay contributed to critical revision of the manuscript for important intellectual content. John Barden contributed to critical revision of the manuscript for important intellectual content. Tony Szturm contributed to critical revision of the manuscript for important intellectual content. Teresa Liu-Ambrose contributed to critical revision of the manuscript for important intellectual content. Victoria L Chester contributed to critical revision of the manuscript for important intellectual content. Chek Hooi Wong contributed to critical revision of the manuscript for important intellectual content. Olivier Beauchet contributed to study concept and design, data acquisition, analysis and interpretation, and drafting of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Summary of the main characteristics of selected studies (n=11) included in the qualitative systematic review.

References	Country / Name and design of study/ Participants (Age, years, setting; number, women%)	MCR criteria		Outcomes (cognitive impairment / Brain structures)	Follow-up period in years	Incidence cases of cognitive impairment or major neurocognitive disorders	Main results*
		Subjective cognitive complaint	Walking speed				

Verghese, 2013 (10)	– US – EAS – Observational longitudinal prospective cohort – Participants: Community-dwelling N=767, mean age 79.8, 60% women; MCR, n=52 (6.0%); MCI, n=148 (19.3%) with n=69 (9.0%) amnestic MCI and n=79	– Standardized – 15-item CERAD questionnaire	– Walk 4.60 m and 6.10 m – Usual pace – Computerized walkway with embedded pressure sensors	– Major neurocognitive disorder: DSM 5	– 3.1	– Major neurocognitive disorders: Total population: N=70 (9.1%) MCR: N=8 (15.4%) Non-MCR: N=62 (8.7%)	– MCR: All MCR, HR=2.72 [1.24;5.97] MCR without non-amnestic MCI, HR=4.33 [1.96;9.58] MCR without amnestic MCI, HR=1.47 [0.46;4.70] MCR without any MCI, HR=2.91 [0.69;12.68] – Slow walking speed: HR=1.70 [0.80;3.20]

	(10.3%) non-amnestic MCI						

Verghese, 2014 (11)	– 3 studies in the US: H-EPESE, MAP and ROS – One study in Italy: InCHIANTI – Observational longitudinal prospective cohort – Participants: Community-dwelling Total population: N=4,555 H-EPESE: N=1,562, mean age 72.3 years, 56% women MAP: N=1,280, mean age 79.9 years, 74% women ROS: N=1,013, mean age 75.1 years, 69% women	– H-EPESE: Standardized IADL scale – MAP: Unstandardized self-report ROS: Unstandardized self-report – InCHIANTI: Standardized Disability scale	– H-EPESE: Walk 2.74 m Usual pace – MAP and ROS: Walk 2.44 m Usual pace – InCHIANTI: Walk 4 m Usual pace	– Cognitive impairment: Decline in score of MMSE ≥4 during follow-up period – Major neurocognitive disorders: H-EPESE, Clinical; MAP, DSM-III-R; ROS, DSM-III-R; InCHIANTI, DSM-IV	– 5.1 to 9.3	– Cognitive impairment: Total population, n= 1,757 (38.6%); H-EPESE, n=826 (52.9%); MAP, n=377 (29.5%); ROS, n=374 (36.9%); InCHIANTI, n=180 (25.7%) – Major neurocognitive	– Incident cognitive impairment: Pooled sample: All MCR, HR=1.71[1.31;2.24] MCR without MCI (71%), HR=1.63[1.39;1.89] MCI, HR=1.36[1.19;1.1.89 Slow walking speed alone, HR=1.40 [1.20;1.65] Cognitive complaint alone, HR=1.09 [0.94;1.27] Each study and all MCR: H-EPESE, HR=1.48 [1.16;1.88] MAP, HR=1.49 [1.08;2.07] ROS, HR=1.90 [1.44;2.51] InCHIANTI: HR=2.74 [1.54;4.86] – Major neurocognitive disorders and all MCR: Pooled sample,

	InCHIANTI: N=700, mean age 74.1 years, 55% women MCR: H-EPESE, n=141 (9%); MAP, n=166 (13%); ROS, n=132 (13%); InCHIANTI, n=56 (8%)					disorders: Total population, n=70 (9.1%); H-EPESE, n=417 (26.7%); MAP, n=212 (16.6%); ROS, n=265 (26.2%)	HR=1.93[1.59;2.35] H-EPESE, HR=1.79[1.31;2.44] MAP, HR=2.10[1.43;2.39] ROS, HR=1.98[1.44;2.74] – Major neurocognitive disorders and slow walking speed alone in pooled sample: HR=1.77 [1.38;2.27] – Major neurocognitive disorders and cognitive complaint alone in pooled sample: HR=1.27 [0.99;1.63]

Kumai, 2016 (17)	– Japan – Kurihara project – Observational longitudinal prospective cohort – Participants: Community-dwelling N=299, age ≥ 75 years; MCR, n=35 (11.7%); MCI, n=57 (19.1%)	– Standardized – Score 15-item GDS ≥1	– Standardized – Walk 6 m – Usual pace – Stopwatch	– MCI: CRD=0.5 – Major neurocognitive disorder: CDR≥1	– 3 to 5	– Major neurocognitive disorders: Total population, n=103 (34.4%) MCR, n=15 (42.9%) Non-MCR, n=88 (33.3%)	– Major neurocognitive disorders: MCR, OR=1.50 [0.73;3.07]

Doi, 2017 (18)	– Japan – OSHPE – Observational longitudinal prospective cohort – Participants: Community-dwelling N=4,235, mean age 72.0 years, 50% women; MCR, n=265 (6.3%); MCI, n=57 (19.1%)	– Standardized – Response yes to the question “Do you feel you have more problems with memory than most?” of the 15-item GDS	– Standardized – Walk 2.4 m – Usual pace – Stopwatch	– Major neurocognitive disorder: Diagnosis by a medical doctor according to ICD-10	– 2.4	– Major neurocognitive disorders: Total population, n=138 (3.3%); MCR, n=25 (9.4%); non-MCR, n=113 (2.8%)	– Major neurocognitive disorders: MCR, HR=3.18 [1.83;5.54] Slow walking speed alone, HR=1.19 [0.58;2.45] Cognitive complaint alone HR=1.58 [1.03;2.42]

Allali, 2016 (23)	- US - Observational longitudinal prospective cohort - CCMA study - Community-dwelling N=314, mean age 76.9 years, 56% women; MCR, n=25 (8.0%)	– Standardized – CDR score ≥0.5; and/or a yes response on the15-item GDS; and/or AD8-dementia screener score ≥1	- Standardized – Computerized walkway with embedded pressure sensors – Walk 6.10 m – Usual pace	– Cognitive performance – Standardized assessment using RBANS exploring different domains with global cognition, Memory, executive functions – Cognitive impairment: Score 1Sd or below the mean baseline RBANS index score at a follow-up visit	– N/A	– Information on the number of participants with incident cognitive impairment not applicable	– Cognitive performance: Global cognition, ß=-8.05 [-12.90;-3.20] Memory, ß=-3.62 [-7.90;0.60] Executive function (Attention), ß=-9.75 [-15.90;-3.60] – Indecent cognitive impairment (global cognition): OR=3.59 [1.30;10.10]

Sekhon, 2017 (24)	– France – Cross-section study – GAIT study – Community-dwelling N=291, mean age 70.8 years, 35% women; MCR, n= 53 (18.2%); MCI; n=119 (40.9%)	– Unstandardized – Self-cognitive complaint	– Computerized walkway with embedded pressure sensors – Walk 9.7 m – Usual pace	– Cognitive performance – Standardized assessment exploring different domains with global cognition (MMSE), memory (FCRST-TR) and Executive functions (FAB)	– N/A	– N/A	– Global cognition: Non-MCI and MCR, ß=-0.15 [-0.69;0.39] MCI and MCR, ß=-1.36 [-1.95;-0.77] – Memory: Non-MCI and MCR, ß=-0.74 [-0.80;2.38] MCI and MCR, ß=-3.07 [-4.77;-1.38] – Executive functions: Non-MCI and MCR, ß=-0.05 [-0.65;0.55] MCI and MCR, ß=-1.67 [-2.34;-1.01]

Maguire, 2018 (25)	– Ireland – Observational longitudinal prospective cohort – TILDA study – Community-dwelling N=2,151, mean age 67.8 years, 54.3% women; MCR, n=52 (2.4%)	– Standardized – Response “fair” or “poor” to the question “how would you rate your memory?”	– Computerized walkway with embedded pressure sensors – Walk 4.9 m – Usual pace	– Cognitive performance – Standardized assessment exploring different domains with global cognition (MMSE), memory (10-word recall task) and executive functions (word fluency)	– N/A	– N/A	– Global cognition: ß=-0.42 [-0.67;-0.17] – Memory: ß=-0.58 [-0.96;-0.20] – Executive function: ß=-0.31 [-0.68;0.06]

Beauchet, 2016 (26)	– France – Cross-section study – GAIT study – Community-dwelling N=171, mean age 70.2 years, 36.8% women; MCR, n= 28 (16.4%)	– Unstandardized – Self-cognitive complaint	– Computerized walkway with embedded pressure sensors – Walk 9.7 m – Usual pace	– MRI of the Brain – Total white matter abnormality (T1 hypointensities) – Gray matter (total and different brain regions)	– N/A	– N/A	– Total white matter abnormality: OR=1.08 [0.91;1.28] – Total gray matter: OR=0.98 [0.97;0.99] Premotor cortex: OR=0.84 [0.73;0.97] – Prefrontal cortex: OR=0.88 [0.78;0.98] – Motor cortex: OR=0.64 [0.39;1.06] – Hippocampus: OR=0.77 [0.46;1.26]
Mergeche, 2016 (27)	– India – Cross-section study – KES – Community-dwelling N=139, mean age 66.6 years, 33.1% women; MCR, n= 38 (16.4%)	– Standardized – Score 15-item GDS ≥1	– Computerized walkway with embedded pressure sensors – Walk 4.9 m – Usual pace	– MRI of the Brain – Lacunar infarcts – Total white matter abnormality (ARWMC scale)	– N/A	– N/A	– Global Lacunar infarcts: OR=2.43 [0.88;6.68] – Total white matter abnormality: OR=0.80 [0.29;-2.16]

Wang 2016 (21)	– India – Cross-section study – KES – Community-dwelling – N=139, mean age 66.6 years, 33.1% women; MCR, n= 38 (16.4%)	– Standardized – Score 15-item GDS ≥1	– Computerized walkway with embedded pressure sensors – Walk 4.9 m – Usual pace	– MRI of the Brain – Lacunar infarcts – Total white matter abnormality (ARWMC scale)	– N/A	– N/A	– Lacunar infarcts in the frontal lobe: OR= 4.67, [1.69 ;12.94]
Blumen, 2018 (28)	– 2 studies in the US: CCMA and EAS – One French study: GAIT study – Community-dwelling N=267, mean age 75.6 years, 50.6% women; MCR, n= 38(14.2%)	– GAIT study: Unstandardized Self-cognitive complaint – CCAM study: Standardized CDR score ≥0.5 and/or response yes on the15-item GDS and/or AD8-dementia screener score ≥1 – EAS: Standardized 15-item CERAD questionnaire	– Computerized walkway with embedded pressure sensors – Usual pace – GAIT study: Walk 9.7 m – CCAM study: Walk 6.10 m – EAS: Walk 4.60 m and 6.10 m	– MRI of the Brain – Gray matter volume	– N/A	– N/A	– Significant gray matter atrophy with covariance network involving supplementary motor, insular and the prefrontal cortex regions

m: meter; EAS: Einstein Ageing study; CERAD: Consortium to Establish a registry for Alzheimer's Disease; MCR: Motoric cognitive risk syndrome; MCI: mild cognitive impairment

DSM-IV: Diagnostic and statistical manual of mental disorders, fourth edition; HR: hazard ratio; OR: Odds ratio; [95%, confidence interval]; US: united states; SD: standard deviation; H-EPESE: Hispanic Established Population for Epidemiologic studies of the Elderly; MAP: Memory and Aging Project; ROS: Religious Orders Study; InCHAINTI: Invecchiare in Chianti; IADL: instrumental activity daily living; MMSE: Mini mental state examination; ICD-10: International Classification of Diseases-10; CRD: Clinical Dementia Rating; OSHPE: Obu Study of Health Promotion for the Elderly; CCMA: Central Control of Mobility in Aging; RBANS: Repeatable Battery for the Assessment of Neuropsychological status; AD8: Assessment Dementia eight-item informant interview; GAIT: Gait and Alzheimer Interactions tracking; FAB: Frontal assessment battery; TILDA: The Irish Longitudinal Study on Aging

KES: Kerala-Einstein study; ARWMC: Age-related white matter changes; *: All HR, OR and coefficient of regression β are adjusted on participant's clinical characteristic (adjustment changed between study

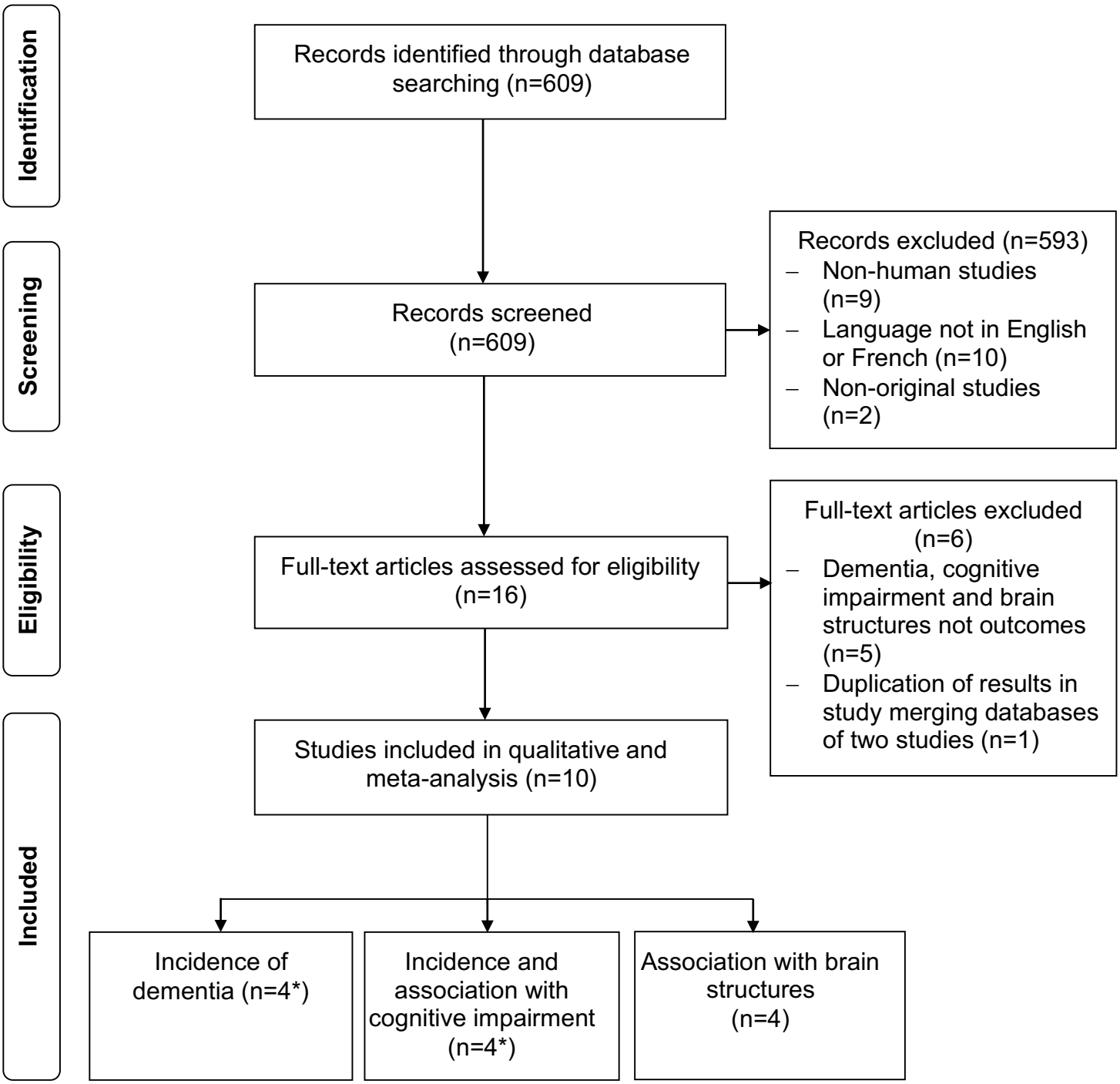

Figure 1. Flow diagram of selection of studies

*: Study of Verghese et al. 2014 examined both incidences of major neurocognitive disorders and cognitive impairment

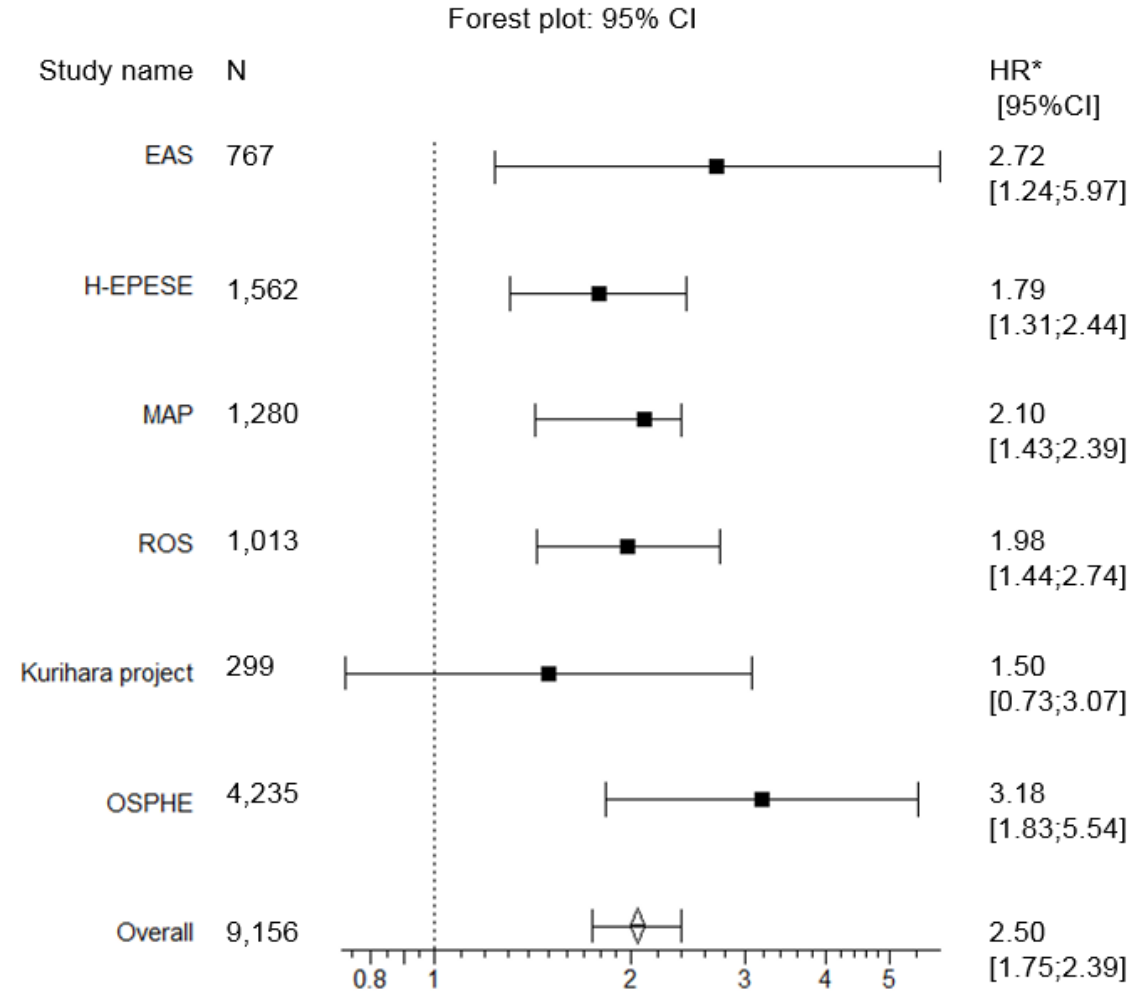

Figure 2. Forest plot of the pooled estimated ratio for risk of incident dementia in participants with motoric cognitive risk syndrome at baseline compared to those without motoric cognitive risk syndrome

Square box area proportional to the sample size of each study; horizontal lines corresponding to the 95% confidence interval; diamond representing the summary value; vertical line corresponding to a ratio combined with the relative risk of 1.00, equivalent to no difference HR: Hazard ratio; *: Hazard ratio for all studies, except for Kurihara project (odd ratio); EPESE: Hispanic Established Population for Epidemiologic studies of the Elderly; MAP: Memory and Aging Project; ROS: Religious Orders Study; OSHPE: Obu Study of Health Promotion for the Elderly

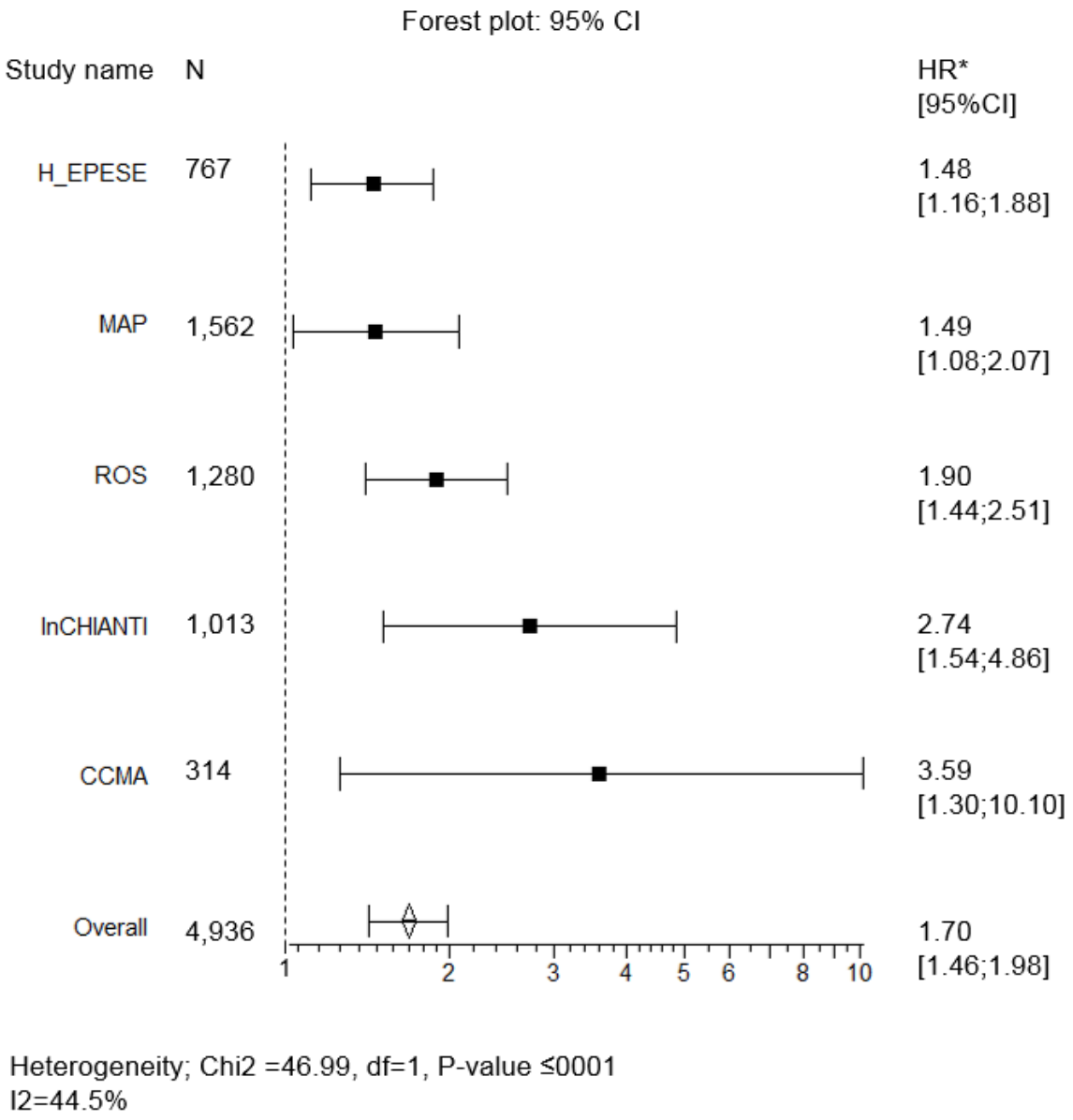

Figure 3. Forest plot of the pooled estimated ratio for risk of cognitive impairment in participants with motoric cognitive risk syndrome at baseline compared to those without motoric cognitive risk syndrome

Square box area proportional to the sample size of each study; horizontal lines corresponding to the 95% confidence interval; diamond representing the summary value; vertical line corresponding to a ratio combined with the relative risk of 1.00, equivalent to no difference HR: Hazard ratio; *: Hazard ratio for all studies, except for CCMA study (odd ratio); EPESE: Hispanic Established Population for Epidemiologic studies of the Elderly; MAP: Memory and Aging Project; ROS: Religious Orders Study; InCHAINTI: Invecchiare in Chianti; CCMA: Central Control of Mobility in Aging

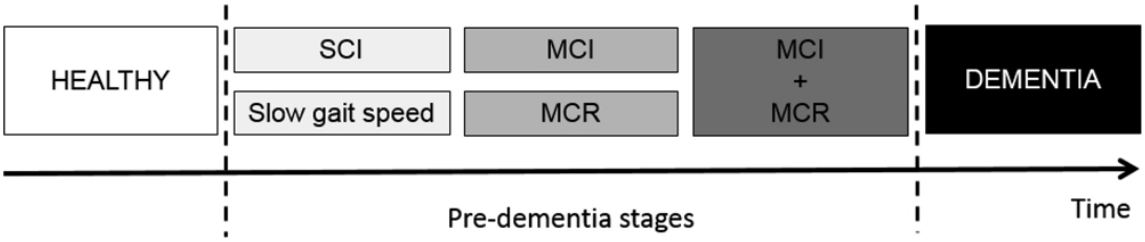

Figure 4. Suggested spectrum of pre-dementia stages.

Chapter 5 Motoric cognitive risk syndrome: Could increased five-times-sit-to-stand test time be used instead of slow walking speed for the definition?

The second manuscript examines whether the five times sit to stand test can be used in lieu of walking speed for the definition of motoric cognitive risk syndrome (MCR).

As previously discussed MCR has the potential to be a global screening tool to identify community dwelling older individuals at risk for dementia. The strength of early MCR identification or diagnosis include its economic cost, usability in any healthcare setting and simplicity. The second manuscript considered whether the usability of MCR could be further simplified. The five times sit to stand test was considered as it is simple and quick to complete, requiring only a chair and stopwatch. Moreover, it is similar to slow walking speed in its association with cognitive impairment in older community dwelling adults without dementia. This is the first time that the five times sit to stand test was considered in lieu of walking speed for the definition of MCR.

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Running title: Motoric Cognitive risk syndrome and Five-Times-Sit-to-Stand test

Key words: Older inpatients; Epidemiology; Screening; Cognition; Motricity

– ABSTRACT

Background: Slow walking speed, time to perform the five-times-sit-to-stand (FTSS) test and motoric cognitive risk syndrome (MCR; defined as slow gait speed combined with subjective cognitive complaint) have been separately used to screen older individuals at risk of cognitive decline. This study seeks to (1) compare the characteristics of older individuals with MCR, as defined through slow walking speed and/or increased FTSS time; and (2) examine the relationship between MCR and its motor components as well as amnestic (a-MCI) and non-amnestic (na-MCI) Mild Cognitive Impairment.

Methods: A total of 633, individuals free of dementia, were selected from the cross-sectional “Gait and Alzheimer Interactions Tracking” study. Slow gait speed and increased FTSS time were used as criteria for the definition of MCR. Participants were separated into five groups, according to MCR status: MCR as defined by (1) slow gait speed exclusively (MCRs); (2) increased FTSS time exclusively (MCRf); (3) slow gait speed and increased FTSS time (MCRsaf); (4) MCR; irrespective of the mobility test used (MCRsof); and (5) the absence of MCR. Cognitive status (i.e., a-MCI, na-MCI, CHI) was also determined.

Results: The prevalence of MCRs was higher, when compared to the prevalence of MCRf (12.0% versus 6.2% with $P \leq 0.001$). There existed infrequent overlap (2.4%) between individuals exhibiting MCRs and MCRf, and frequent overlap between

individuals exhibiting MCRs and na-MCI (up to 50%). a-MCI and na-MCI were negatively [odd ratios (OR) ≤ 0.17 with $P \leq 0.019$] and positively (OR ≥ 2.41 with $P \leq 0.019$) related to MCRs, respectively.

Conclusion: Individuals with MCRf are distinct from those with MCRs. MCRf status does not relate to MCI status in the same way that MCRs does. MCRs is related negatively to a-MCI and positively to na-MCI. These results suggest that FTTS cannot be used to define MCR when the goal is to predict the risk of cognitive decline, such as future dementia.

Introduction

Motoric cognitive risk syndrome (MCR) is defined as the relationship between objective slow gait speed and subjective cognitive complaint (Verghese et al., 2013). MCR is one of the stages of pre-dementia, similar to mild cognitive impairment (MCI) (Verghese et al., 2013, 2014). MCR does not require a time-consuming comprehensive neuropsychological assessment when compared to MCI, which opens new perspectives in terms of detection of individuals who are at risk of dementia in older populations (Verghese et al., 2013, 2014; Belleville et al., 2017). The past decade has been characterized by an increased interest in identifying and validating biomarkers for early diagnosis and identification of individuals who are at risk of dementia (Belleville et al., 2017). However, the use of biomarkers has limitations in many settings. For instance, access to neuroimaging is difficult and the cost of biological biomarkers limits their use (Handels et al., 2017). Additionally, the highest prevalence and incidence of dementia in the coming years will be observed in low and intermediate income countries, where the accessibility of actual biomarkers is limited (de Jager et al., 2017). Hence, there is a need to optimize and increase the accessibility to clinical risk assessment of dementia in community-dwelling older populations. Using a motor test to predict dementia in older populations may be a solution.

Motoric cognitive risk syndrome has the potential to rapidly screen individuals who are at risk of dementia in a primary care setting, where the under-diagnosis of dementia is

estimated to be around 50% in individuals over 65 (Iliffe et al., 2009). This under-diagnosis of dementia is largely related to limited resources and the time required for in-depth assessments of cognitive complaint (Iliffe et al., 2009; Villars et al., 2010). The simplicity of assessment of MCR syndrome could help overcome this issue. However, gait speed, a component of MCR, may be difficult to assess during a primary care visit because of space constraints (Abellan van Kan et al., 2009). Gait speed must be recorded at usual steady state pace rhythm over at least 3 meters (Middleton et al., 2015). Few consultation rooms in primary care possess the features required for the assessment of gait speed, which complexifies the process of consultation and increases physician workload and consult time, when gait speed must be measured. It has been reported that consult time in general practice is very short (around 6.9 min) and depends on the physician, the physician's workload and the type of visit (Petek Ster et al., 2008). There is, therefore, a need in primary care for a simpler mobility test, which can be completed rapidly and within limited space, so as to facilitate MCR diagnosis in primary settings. In addition, the chosen motor test must be proven to show a link to cognitive impairment or risk of dementia, as the objective of a redefined MCR is to identify individuals at risk of dementia.

The five-times-sit-to-stand test (FTSS) is a physical test, which measures the time taken by an individual to repeat five consecutive chair rises as quickly as possible (Whitney et al., 2005). This motor test examines the challenged balance condition, which is the

transfer from a sitting position to a stand-up position. The FTSS test possesses the necessary features for assessment of mobility performance to diagnose MCR in primary care, as it can easily and rapidly be performed in limited space and its requirements are limited to a chair and a stopwatch. In addition, this test may be performed at the time of consultation, as its duration is of fewer less than 2 min in length, including explanation and performance (Whitney et al., 2005). Thus, the FTSS test does not increase the physician's workload. The one-leg-balance (OLB) test is another simple motor test to examine the challenged balance condition. In it, the individual is asked to stand unassisted on one leg. An impaired OLB test result – defined as being unable to stand on one leg for 5 s – has been identified as a predictor of injurious falls among community-dwelling older adults and cognitive decline in patients with dementia, but not in non-demented individuals (Vellas et al., 1997). In contrast, increased FTSS time has been associated with low cognitive performance in older community dwellers free of dementia (Annweiler et al., 2011). Because non-demented individuals with poor cognitive performance like MCI are at risk of dementia, this association suggests that poor FTSS performance (i.e., increased time) may be used to identify individuals at risk of dementia and thus, that it could be used as an alternate motor test, as opposed to gait speed, to define MCR. Using FTSS performance instead of gait speed to define MCR value for the prediction of dementia requires an investigation, which will determine whether or not individuals classified as MCR through FTSS performance and gait speed

are one and the same. This line of questioning is justified, as the FTSS test explores different subdomains of mobility, when compared to gait speed (Whitney et al., 2005; Annweiler et al., 2011; Beauchet et al., 2017; Sekhon et al., 2017). The FTSS test examines the ability to transfer from a sitting position and depends largely on balance control, muscle mass, strength, and the power of lower limbs (Whitney et al., 2005). In comparison, gait speed is a surrogate measure of gait ability, which depends on different body movements and higher levels of movement control involving executive and memory functions (Abellan van Kan et al., 2009; Middleton et al., 2015; Beauchet et al., 2017). These differences between the FTSS test and gait speed, therefore, call into question the possible overlap between individuals whose MCR status was determined using either the FTSS test or gait speed, and their relative MCI.

Motoric cognitive risk syndrome and cognitive impairment are both intermediate stages between normal cognitive aging and major neurocognitive disorders (Verghese et al., 2013, 2014; Belleville et al., 2017). A knowledge gap exists regarding the relationship between MCR and MCI syndromes. Recently, we underscored that there exists overlap between MCR – defined through slow gait speed – and MCI in the population of older community dwellers (Sekhon et al., 2017). The prevalence of MCI was higher in individuals with MCR, when compared to those without MCR (47.2% versus 39.5%) (Sekhon et al., 2017). Unfortunately, the relationship between MCR subcategories of MCI syndromes such as amnestic (a-MCI) and non-amnestic (na-MCI) has not been

examined in this study. As gait is largely controlled by executive functions (Beauchet et al., 2017), we have hypothesized that MCR as defined by slow gait speed (MCRs) may be more frequently associated with na- MCI, when compared to MCR as defined by increased FTSS time (MCRf), which may be associated with a-MCI. Using the data of the cross-sectional study known as the “Gait and Alzheimer interactions tracking” (GAIT) study (Beauchet et al., 2018), we had the opportunity to explore the overlap between MCR as defined by slow gait speed and increased FTSS time, and their relationship with a-MCI and na-MCI. This study aims to (1) compare the characteristics of participants of the GAIT study with and without MCR as defined by slow gait speed and increased time of FTSS, and (2) examine the relationship between MCR, and a-MCI and na-MCI. Comparing gait speed and FTSS as a construct of MCR, as well as their relationship with MCI subtypes, may provide new insight into the interaction between motor and cognitive impairment in the aging population.

Method

Population and study design

A subgroup of older individuals recruited in the GAIT study were selected for the present study. The GAIT study is a cross- sectional design-based study, which was conducted in France between November 2009 and 2015 (Beauchet et al., 2018). All

GAIT participants were relatively healthy community-dwelling individuals, who were recruited during a visit in the memory clinic of Angers University Hospital, in France, for cognitive complaint evaluation. The GAIT study inclusion criteria were: (1) age 65 years and over, (2) living at home in the community, and (3) an adequate understanding of French. Exclusion criteria included acute medical illness (regardless of nature) in the past month; extrapyramidal rigidity of the upper limbs (regardless of etiology); neurological diseases [past history of stroke, (NPH), multiple sclerosis, Parkinson's disease, cerebellar disease, polyneuropathy, and vestibular disease]; psychiatric diseases (past history of psychosis, personality disorders or severe depression as well as active depression as defined by a 4-item geriatric depression scale (GDS) score above 1) (Shah et al., 1997) other than cognitive impairment; severe gait-affecting medical conditions which left potential participants with the inability to walk unassisted for 15 min, such as rheumatologic diseases (spine, pelvic, and joint arthritis with deformation); and ophthalmic diseases with severe vision abnormality. In addition, for the present study, we also excluded participants with NPH or presenting vascular brain abnormalities (i.e., lacunar lesions and strokes) on brain imaging [i.e., computed tomography (CT) or magnetic resonance imagery (MRI) scan] performed during the assessment, suffering from dementia, using a walking aid, and presenting no gait speed or FTSS time data. A total of 663 participants were selected, after applying these selection criteria.

Study assessments

The selected GAIT participants had a full-standardized clinical examination, a comprehensive neuropsychological assessment, brain imaging (i.e., MRI or CT) and blood tests including Vitamin B12, TSH, calcemia and other serum electrolytes, creatinine, and urea. Age, sex, educational level [evaluated by number of years of schooling and categorized by high school level (i.e., yes or no)], number of drugs taken daily and body mass index (BMI; kg/m2) were recorded. Maximal isometric voluntary contraction (MVC) strength of hand was measured with the help of a computerized hydraulic dynamometer (Martin Vigorimeter, Medizin Tecnik, Tutlingen, Germany). The test was performed once on each side. The highest MVC value recorded was used in the present data analysis. Binocular distance vision was measured at 5 m with a standard Monoyer letter chart and scored from 0 (i.e., worst performance) to 10 (i.e., best performance) (Lord et al., 1991b). Vision was assessed with corrective lenses if needed. Lower-limb proprioception was evaluated with the help of a graduated tuning fork placed on the tibial tuberosity, so as to measure vibration threshold (Buchman et al., 2009). The mean value obtained for the left and right sides ranged between 0 (i.e., worst performance) and 8 (i.e., best performance) and was used in the present data analysis. Gait speed was measured with the help of GAITRite (Gold walkway, 972 cm long, active electronic surface area 792 cm × 610 cm, total of 29,952 pressure sensors,

scanning frequency 60 Hz, CIR System, Havertown, PA, United States). Time to perform FTSS was also measured. A trained evaluator demonstrated the test procedure while giving standardized verbal instructions. Moreover, before testing, participants were allowed to practice the sit-to-stand test twice. Participants began by crossing their arms upon their chest and sitting with their back against the chair (45 cm above the floor). The chair was padded and armless. They were prompted not to bounce off the chair when returning to the standing position, and reminded to fully straighten their legs when elevating. Participants were instructed to stand up and sit down five times as quickly as possible. Performance was measured with a stopwatch in seconds, from the time at initial seated position to the time at final seated position, after completing five stands. A bedside face-to-face neuropsychological assessment was also performed using the mini-mental state examination (MMSE) (Folstein et al., 1975) and frontal assessment battery (FAB) (Dubois et al., 2000), the French version of the free and cued selective reminding test-total recall (FCSRT-TR) (Van der Linden et al., 2004), parts A and B of the trail making test (TMT) (Brown et al., 1958), the Stroop Test (Stroop, 1935), and the instrumental activities of daily living scale (IADL) (Pérès et al., 2006). The diagnosis was determined, following a standardized procedure and consensual definition, during multidisciplinary meetings involving geriatricians, neurologists, and neuropsychologists of Angers University Memory Clinic. It was based on the aforementioned neuropsychological tests, physical examination findings, blood tests,

and MRI or CT scan of the brain. First, the cognitive status was determined using the performances obtained during the neuropsychological assessment. Participants were classified within cognitively healthy individuals (CHI), a-MCI and na-MCI categories, diagnosis of MCI being in accordance with the criteria detailed by Dubois et al. (2010). CHI were individuals who exhibited normal cognitive function with all cognitive scores using the referent age-appropriate mean value. Participants with a-MCI and na- MCI were individuals, who have an objective impairment in the memory (i.e., a-MCI) or non-memory (i.e., na-MCI) domains, respectively, defined as a score >1.5 SDs beneath the age- appropriate mean, and who have not impaired daily living activities (i.e., normal IADL score). Second, the etiology of MCI (i.e., related to neurodegenerative brain lesions versus secondary to metabolic disorders) was determined using the results of blood tests and the brain MRI.

Definition of motoric cognitive risk syndrome and categorization of participants

Different definitions of MCR were used for each subgroup. First, the diagnosis of MCR was made through slow walking speed (MCRs) in accordance with the criteria described by Verghese et al. (2013): a combination of cognitive complaint and slow gait, with the absence of dementia or any mobility disability. As cognitive complaint was the reason for referral to the memory clinic for participants of the GAIT study, all of them met the criteria for cognitive complaint. Slow gait speed was defined as gait speed of one SD or

greater, beneath the age-and sex- appropriate mean values established by the present cohort, as done in previous studies (Verghese et al., 2013, 2014). Second, MCR was also defined using increased FTSS time (MCRf) defined as time one SD or greater, above the age-and sex- appropriate mean values established by the present cohort. Five subgroups of individuals were identified: (1) those with MCRs using gait speed exclusively; (2) those with MCRf using FTSS time exclusively; (3) those with MCR with abnormal scores in both gait speed and FTSS time (MCRsaf); (4) those with MCR irrespective of mobility test used (MCRsof); and (5) those without MCR.

Standard protocol approvals, registrations, and patient consents

This study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). Participants in the study were included after obtaining written informed consent for research. The local Angers Ethics Committee approved the study protocol (n◦2009-A00533-54).

Statistics

The participants' characteristics were summarized using means and SDs or frequencies and percentages, as appropriate. Between-group comparisons were performed using a Kruskal- Wallis or Chi square test, Mann-Whitney, independent t-test; unpaired t-test or Chi square test, as appropriate. Uni and multiple logistic regression analyses were

performed to examine the relationship between MCR (i.e., dependent variable) and MCI (i.e., independent variable), relative to participants' characteristics. P-values less than 0.05 were considered statistically significant. All statistics were performed using SPSS (version 23.0; SPSS, Inc., Chicago, IL, United States).

Results

Table 1 illustrates the participants' characteristics and their comparisons between the different subgroups of participants based on MCR definition. A total of 76 (12.0%) participants were classified as having MCRs, 39 (6.2%) MCRf, 15 (2.4%) MCRsaf, and 130 (20.5%) MCRsof. Individuals with MCR, irrespective of the type of MCR, had the same clinical characteristics, except for sex and level of education. Prevalence of women varied between the different subgroups of MCR (P = 0.029), the highest prevalence being observed with MCRs. Participants with MCRs displayed a lower level of education when compared to those with MCRf (P = 0.008). Participants with MCR displayed lower limb proprioception when compared to non-MCR participants (P = 0.042). The prevalence of MCI syndrome, regardless of type, was significantly different between the three subgroups of MCR (P = 0.039). The prevalence of a-MCI was lower in individuals with MCRs when compared to those with MCRf (P = 0.010) and MCRsaf (P = 0.018), whereas the prevalence of na-MCI was higher in individuals with MCRs

when compared to those with MCRf (P = 0.010) and MCRsaf (P = 0.018). Those displaying MCRf registered greater walking speeds when compared to those with MCRs (P ≤ 0.001) and MCRsaf (P ≤ 0.001). Time to perform FTSS was lower in individuals with MCRs (P ≤ 0.001) and MCRsaf (P ≤ 0.001). Comparisons between individuals with MCR, irrespective of definition, and without MCR show that all characteristics differed significantly (P < 0.05), except for age.

Multiple logistic regressions have shown a positive relationship between MCRs and a-MCI and a more marked (Table 2) negative relationship between MCRs and na-MCI (*P* ≤ 0.020). All MCR, irrespective of definition, displayed a positive relationship with MCI (all categories *P* = 0.010, a-MCI *P* = 0.040 and na-MCI *P* = 0.046). These last relationships remained insignificant when logistic regressions were adjusted for all participant characteristics.

Discussion

The study findings demonstrate that the use of gait speed and FTSS time to define MCR results in the selection of different subgroups of individuals, with infrequent overlap (2.4%). In contrast, there existed significant overlap between MCR and na- MCI participants (up to 50%). In addition, only MCRs exhibited a significant relationship with

the MCI subgroups, the na-MCI subtype, relating positively and the a-MCI relating negatively to this MCR subgroup.

There existed infrequent overlap between individuals with MCR as defined by gait speed and FTSS time. This result suggests that impaired performance in these two motor tests tracks different clinical phenotypes of individuals. But it is not consistent with a previous study, which used alternate gait parameters to define MCR and reported greater overlap (68%) (Allali et al., 2016b). Comparatively, in the previous study the definition used for the different subtypes of MCR involved low performance of gait parameters (mean and variability of stride length and swing time). In our study, even if both gait speed and FTSS examine a condition of dynamic balance in which the body's center of gravity is maintained within a narrow base of support while moving (Lord et al., 1991a; Dubost et al., 2005), they relate to different brain regions, which may explain the infrequent overlap observed (Lord et al., 1991a; Nutt et al., 1993; Dubost et al., 2005; Rosano et al., 2007; Wittenberg et al., 2017). For instance, gray matter volumes in the left frontal lobe were correlated with usual gait speed in healthy older adults, whereas reduced volumes in putamen and superior posterior parietal lobule were associated with balancing difficulty in semi-tandem stance (Rosano et al., 2007). Functional brain imagery study findings point to involvement of the premotor, supplementary motor, and parietal cortex in standing balance control, whereas the hippocampus and premotor cortex are the key region for gait control (Janssen et al., 2002; Rosano et al.,

2007; Beauchet et al., 2009, 2012, 2016; Spyropoulos et al., 2013; Wittenberg et al., 2017). Subcortical regions have also been identified as key regions for gait control including the cerebellar locomotor region, the mesencephalic locomotor region, and the subthalamic locomotor region (Bohnen et al., 2011). Gait speed is a surrogate measure of gait, which is the medical term used to globally describe the human locomotor movement of walking (Nutt et al., 1993; Beauchet et al., 2017). Gait is a complex movement in terms of biomechanics and motor control (Nutt et al., 1993; Rosano et al., 2007; Beauchet et al., 2009, 2012; Wittenberg et al., 2017). It has been highlighted that even the simplest walking condition, such as straight-line walking at a comfortable steady- state pace without any disturbances, involves cortical networks and cognitive functions (Nutt et al., 1993; Rosano et al., 2007; Beauchet et al., 2009; Wittenberg et al., 2017). This association may explain the predictive value of slow gait for the occurrence of dementia (Beauchet et al., 2016). In contrast, FTSS time explores the performance of body transfer movement from a seated position (Whitney et al., 2005). This movement is more unstable in terms of biomechanics, when compared to walking at a comfortable steady-state pace without any disturbances (Spyropoulos et al., 2013). It involves an unstable movement from a static and stable position to a quasi static position (Janssen et al., 2002; Whitney et al., 2005; Bohnen et al., 2011; Schofield et al., 2013; Spyropoulos et al., 2013; Lee et al., 2017). Thus, FTSS time is strongly related to several physiological sensory and motor subsystems which contribute to the

dynamic postural control, the most important ones identified in older adults being the muscle strength, lower-limb proprioception, vestibular, and vision subsystems (Janssen et al., 2002; Bohnen et al., 2011; Schofield et al., 2013; Spyropoulos et al., 2013). Balance control like gait control deteriorates with the progression of dementia (Lee et al., 2017). This is similar to the decline of gait control with the progression of dementia (Annweiler et al., 2011). Increased FTSS time has been associated with low cognitive performance in older adults free of dementia (Annweiler et al., 2011). This association has mainly been reported through bedside cognitive tests exploring global cognitive functioning, such as the MMSE the modified mini mental state (3MS) and Pfeiffer's Short Portable Mental State Questionnaire (Hirsch et al., 1997; Raji et al., 2002; Rosano et al., 2005; Annweiler et al., 2011).

The second main finding of our study is the significant overlap between MCI and MCR, irrespective of the criteria for MCR definition. The prevalence of MCI was significantly higher in individuals with MCR when compared to those without MCR, and ranged from 52.6% for individuals with MCRs to 66.7% for individuals with MCRsaf. In addition, the overlap between MCR and MCI was greater for na-MCI when compared to aMCI. This result concords with our previous study (Sekhon et al., 2017) and underscores the strong relationship between MCR and impaired cognitive performance, which explains the ability for both syndromes to predict dementia (Verghese et al., 2013, 2014; Beauchet et al., 2016; Sekhon et al., 2017). Cognition and locomotion are two human

abilities, which are controlled by the brain (Nutt et al., 1993; Beauchet et al., 2009, 2012, 2016). Their decline is highly prevalent with physiological and pathological aging, and is greater than the simple sum of their respective prevalence, suggesting complex age-related interplay between cognition and locomotion (Nutt et al., 1993; Rosano et al., 2007; Beauchet et al., 2009, 2012, 2016; Wittenberg et al., 2017). Recently, a systematic review and meta-analysis provided evidence that poor gait performance could predict dementia (Beauchet et al., 2016). We have previously reported that individuals who exhibited both syndromes had poorer cognitive performance in all domains when compared to participants with MCI without MCR, and to participants with isolated MCR (Sekhon et al., 2017).

Furthermore, the present study concludes that MCR related positively to na-MCI and negatively to a-MCI. This result may be related to studies that reported executive dysfunction in individuals with MCR (Kumai et al., 2016; Belleville et al., 2017; Sekhon et al., 2017). This correlation between MCRs and na-MCI (but not with a-MCI) suggests that in our cohort (i.e., memory clinic based), MCRs is associated with an underlying non-AD process, such as vascular dementia or dementia with Lewy bodies, but not with an underlying AD process. This double dissociation is supported by the observation that at disease onset, gait speed is more affected in non-AD dementia than in AD dementia (Allali et al., 2016a). The absence of relationship between FTSS time and MCI status suggests that there is no interaction with cognitive performance in cognitively impaired

individuals, such as MCI individuals. This result was not expected because of the previous positive relationship reported in CHI (Hirsch et al., 1997; Raji et al., 2002; Rosano et al., 2005; Annweiler et al., 2011), which underlines a non-linear complex relation between FTSS time and decline in cognitive performance. This relationship between MCRs and na-MCI supports that MCR appears to be a good predictor of non-Alzheimer's dementia, and in particular of vascular dementia (Verghese et al., 2013, 2014). Furthermore, the absence of any relationship with MCRf suggests that increased FTSS tracks a profile for older adults which is not relevant in identifying older adults who are at risk of dementia.

Our study has certain limitations. First, the cross-sectional design does not allow us to make any causal association. Secondly, the recruitment of participants was performed in one center. Thirdly, all participants in this study presented a cognitive complaint, preventing the generalization of study findings to all non-demented community-dwelling older adults. Indeed, the non-MCR/non-MCI participants cannot be considered as strictly cognitively intact, but as participants with subjective cognitive impairment (SCI). SCI is a prodromal state of MCI and is considered the earliest clinical stage of dementia (Jessen et al., 2014). Fourthly, we have no brain imaging data on the subset of GAIT participants selected for this study.

Conclusion

The findings revealed that individuals with MCRf are distinct from those with MCRs. MCRf status does not relate to MCI status in the same way that MCRs does. A-MCI related negatively to MCRs, whereas it related positively to na-MCI. All these results suggest that using FTSS time in the definition of MCR is not appropriate in order to identify older adults who are at risk of dementia.

Author Contributions

HS and OB studied the concept and design. OB and CL acquired the data. HS, CL, GA, and OB analyzed and interpretated the data. HS drafted the manuscript. CL, JC, GA, and OB critically revised the manuscript for important intellectual content.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. Comparison of participants' characteristics according to motoric cognitive risk syndrome definitions (n=633)

	Non-MCR (n=503)	MCR (n=130)				P-value				
		Walking speed* (n=76)	FTSS* (n=39)	Walking speed and FTTS (n=15)	Walking speed and/or FTTS (n=130)	Overall†	Walking speed versus FTSS‡	Walking speed versus walking speed and FTTS‡	FTSS versus walking speed and FTTS‡	MCR# versus non-MCR¶
Age, mean±SD (y)	71.8±4.5	71.3±3.3	72.7±4.4	72.8±5.6	71.9±4.0	0.330	0.148	0.464	0.977	0.849
Female, n (%)	215 (42.7)	28 (36.8)	9 (23.1)	3 (20.0)	40 (30.8)	**0.029**	0.135	0.208	0.808	**0.013**
Number of drugs daily taken, mean±SD	2.7±2.6	4.5±4.0	3.1±2.8	3.9±3.0	4.0±3.6	0.194	0.072	0.808	0.343	**≤0.001**
Body masse index, mean±SD (kg/m^2)	25.6±3.5	28.7±5.6	27.2±3.5	28.1±3.7	28.2±4.9	0.413	0.251	0.773	0.255	**≤0.001**
Education level **, n (%)	337 (67)	29 (38.2)	25 (64.1)	8 (53.3)	62 (47.7)	**≤0.001**	**0.008**	0.274	0.467	**≤0.001**

Handgrip strength †† ($N.m^{-2}$), mean ± SD	32.2±9.3	32.1±8.4	31.9±8.8	32.4±10.1	32.2±8.7	0.771	0.901	0.406	0.416	0.745
Distance vision acuity ‡‡ (/10.9040), mean ± SD	8.1±1.6	7.9±1.6	8.0±1.5	7.8±1.3	7.9±1.5	0.268	0.917	0.624	0.641	0.113
Lower-limb proprioception score ¶¶ (/8), mean ± SD	5.2±1.5	5.0±1.1	4.9±1.7	4.8±1.6	4.9±1.3	**0.048**	0.843	0.904	0.903	**0.042**
MMSE (/30), mean±SD	28.0±1.6	27.2±2.1	27.7±2.1	27.3±1.8	27.4±2.1	0.228	0.093	0.895	0.298	**≤0.001**
FAB (/18), mean±SD	16.3±1.5	15.4±1.8	16.0±1.8	14.6±2.8	15.5±2.0	0.094	0.062	0.422	0.090	**≤0.001**
Mild cognitive impairment, n (%)										
All categories	208 (41.4)	40 (52.6)	21 (53.8)	10 (66.7)	71 (54.6)	**0.039**	0.902	0.318	0.393	**0.007**
Amnestic	57 (11.3)	2 (2.6)	6 (15.4)	3 (20.0)	11 (8.5)	**0.023**	**0.010**	**0.018**	0.935	**0.044**
Non- Amnestic	151 (30.0)	38 (50.0)	15 (38.5)	7 (46.7)	60 (46.2)	**0.025**	**0.010**	**0.018**	0.935	**0.049**
Walking speed, mean±SD (m/s)	115.3±17.7	82.0±9.5	108.1±16.6	76.2±13.8	89.2±17.7	**≤0.001**	**≤0.001**	0.094	**≤0.001**	**≤0.001**

FTSS, mean±SD (s)	12.6±2.6	13.6±2.4	19.8±2.9	20.9±3.9	16.3±4.2	**≤0.001**	**≤0.001**	**≤0.001**	0.401	**≤0.001**

MCR: Motoric Cognitive Risk syndrome; FTTS: Five Times Sit-to-Stand; SD: Standard deviation; MMSE: Mini Mental Status Examination; FAB: Frontal Battery Assessment; *: Exclusive (i.e., only participants with mean value of the motor test below 1 standard deviation); †: Comparisons between the different subgroups of MCR based on Kruskal-Wallis or Chi square test, as appropriate; ‡: Based on Mann-Whitney or Chi square test; #: All subgroups of MCR merged together; ¶: Based on independent *t*-test; ††: mean value of the highest value of maximal isometric voluntary contraction strength measured with computerized dynamometers expressed in Newton per square meter; ‡‡: binocular vision acuity at distance of 5 m with a standard Monoyer letter chart; ¶¶: mean value of left and right side and based on graduated tuning fork placed on the tibial tuberosity; P-value significant (i.e., P<0.05) indicated in bold.

Table 2. Logistic regressions showing the association between Motoric Cognitive Risk syndrome and Mild Cognitive Impairment (n=633)

	OR [95%CI] P-value*							
	Walking speed†		FTSS†		Walking speed and FTTS		Walking speed and/or FTTS	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Mild cognitive impairment								
All categories	1.60	0.99	1.40	1.29	2.34	1.87	1.7	1.95
	[0.97;2.12]	[0.57;1.71]	[0.69;2.64]	[0.63;2.64]	[0.77;7.11]	[0.59;5.94]	[1.14;2.53]	[0.78;1.89]
	0.064	0.965	0.383	0.485	0.134	0.287	**0.010**	0.385
Amnestic	0.13	0.17	1.23	1.60	1.34	1.72	0.47	0.63
	[0.03;0.57]	[0.04;0.75]	[0.45;3.32]	[0.56;4.56]	[0.34;5.40]	[0.39;7.55]	[0.23;0.97]	[0.30;1.34]
	0.007	**0.019**	0.686	0.578	0.677	0.475	**0.040**	0.232
Non-amnestic	2.70	2.40	0.90	0.78	0.86	0.76	1.44	1.25
	[1.31;5.59]	[1.15;5.04]	[0.54;1.47]	[0.46;1.32]	[0.43;1.72]	[0.36;1.60]	[1.01;2.06]	[0.86;1.82]

	0.007	**0.020**	0.664	0.358	0.666	0.469	**0.046**	0.249

OR: Odd Ratio; CI: Confidence Interval; MCR: Motoric Cognitive Risk syndrome; FTTS: Five Times Sit-to-Stand; *: Separate model for gait speed, FTSS, gait speed and FTTS, gait speed and/or FTTS; †: Exclusive (i.e., only participants with mean value of the motor test below 1 standard deviation); Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, number of drugs daily taken, body mass index, educational level, handgrip strength, distance vision acuity and lower-limb proprioception

Chapter 6 The association of anxio-depressive disorders and depression with motoric cognitive risk syndrome: Results from the baseline assessment of the Canadian longitudinal study on aging

The third manuscript examines the association between motoric cognitive risk syndrome (MCR) and depression or anxio-depressive disorders.

MCR has not been well studied in the Canadian population. MCR is comprised of slow walking speed and subjective cognitive impairment which can also be symptoms of depression or anxio-depressive disorders. Moreover, both MCR as well as depression and anxio-depressive disorders are prevalent globally, more information on the two are provided in the literature review (chapter 2). As such, it is important to examine the association between MCR as well as depression and anxio-depressive disorders as this could greatly influence MCR diagnosis. This association has not been considered in great depth, the few studies that have examined this association have done so only as a secondary objective. Moreover, previous studies have reported diverging results regarding the association between MCR as well as depression and anxio-depressive disorders. This is also the first time that MCR is considered in a younger (<60) population.

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Running title: The association of depression with motoric cognitive risk syndrome

ABSTRACT

Motoric cognitive risk syndrome (MCR), anxio-depressive disorders (ADD) and depression are associated with cognitive complaint and slow gait speed. The study aims to examine 1) the association of ADD and depression with MCR, and 2) the influence of the type and the severity of ADD and age on this association in older adults. A total of 29,569 participants free from cognitive impairment with walking speed measure recruited at baseline in the Canadian Longitudinal Study on Aging (CLSA) Comprehensive were selected in this cross-sectional study. They were separated into different sub-groups based on their age groups (i.e., 45-54, 55-64, 65-74 and ≥ 75) and the presence of MCR. Anxiety, mood and depressive disorders (defined ADD) were assessed. Depression was defined by the Center for epidemiological studies – depression scale (CES-D) score ≥10. The overall prevalence of MCR was 7.0% and was greater in the youngest age group (8.9%) as compared to the other age groups ($P<0.05$). There was a higher prevalence of ADD and depression in individuals with MCR compared to those without MCR for all age groups ($P\leq0.001$). Depression was significantly associated with MCR regardless of age-group (Odd ratio ≥3.65 with $P\leq0.001$. The association of ADD with MCR depended on the accumulation of disorders and not their type, and was weaker and more inconstant in the oldest age group as compared to younger age groups. MCR is associated with ADD and depression in both young and old individuals. This association is stronger for depression and younger individuals.

Key words: Epidemiology; Walking speed; Cognitive complaint; Depression; Older adults; CLSA

Introduction

Motoric cognitive risk syndrome (MCR) is a new clinical syndrome, defined by subjective cognitive complaint and objective slow gait speed, with a high prevalence around 10% in the population aged 60 and above (1-3). MCR predicts mild and major neurocognitive disorders (1, 2). MCR does not rely on complex time-consuming assessments, making it applicable to screen individuals at risk for mild and major neurocognitive disorders in any type of healthcare setting (1, 2).

Slow gait speed and cognitive complaint are unspecific symptoms that can be found to a wide variety of morbidities (i.e., having a disease or a symptom of the disease), thus causing overlap with other syndromes, which may influence the value of MCR risk for mild and major neurocognitive disorders. For instance, there is an overlap between MCR and Mild Cognitive Impairment (MCI) which is, a pre-dementia syndrome similar to MCR (4). Patients diagnosed with MCR can also be diagnosed with MCI, although this is not always the case. It has been suggested that patients cumulating both syndromes are more at risk for mild and major neurocognitive disorders compared to patients with MCR or MCI alone (4). Similarly, anxio-depressive disorders (ADD) defined by anxiety, mood or depressive disorders as well as depression are associated with slow gait speed and cognitive complaint (5-7). Prevalence of ADD and depression similar to MCR is high and estimated to be around 9% with some age variation, younger adults being at higher prevalence compared to older adults (6, 7). Due to the high prevalence of MCR, ADD and depression, there is a high probability of overlap. This

probability is particularly high as subjective cognitive complaint used in MCR is often extracted from an item of depressive scales (1, 8, 9).

Few studies have examined the association of ADD and depression with MCR, and reported diverging results, as studies found both significant and not significant associations (1-3, 5, 8-13). These mixed results may be explained by the definition used for ADD and depression which may be based on standardized questionnaires or antidepressant use (2, 5, 8, 10). Moreover, the divergence between studies may also be related to the type of the ADD symptomology (e.g., anxiety mood, depressive disorders), and age because of age-related change in ADD prevalence (6, 7, 14). Thus, to better understand the relationship of ADD and depression with MCR, it seems important to examine this association taking into consideration parameters that may influence it.

We have the opportunity with the baseline assessment of a large population-based observational, prospective study in Canada - the Canadian Longitudinal Study on Aging (CLSA) - to better understand the parameters influencing the association of ADD and depression with MCR (15). We hypothesized that there was an association of ADD and depression with MCR in the Canadian Population and that this association may be influenced by the type of ADD and age. The study aims to examine 1) the association of ADD and depression with MCR, and 2) the influence of the type and the severity of ADD and age on this association in the participants of the CLSA.

Material and Methods

Population and study design

Data for this cross-sectional study are a subset of individuals recruited in the CLSA, which is a population-based, 20-year prospective cohort study (15, 16). This observational cohort is composed of over 50,000 Canadians, 45-85 years of age at the time of recruitment. The CLSA is accessible upon approval from the CLSA Data and Sample Access Committee (15, 16). The data collection methods have been previously described in detail (16). For this study, we selected a subset of CLSA Comprehensive cohort. The inclusion criteria for this study were available walking speed measure and no diagnosis of dementia or Alzheimer's disease (AD) (defined as "Has a doctor ever told you that you have dementia or Alzheimer's disease?"). A total of 30,097 participants in the CLSA Comprehensive have comprehensive physical examinations with information about these two criteria and, thus, were considered for selection for this study (15, 16). After applying the inclusion criteria, 98.2% (n=29,569) participants were selected. One hundred thirty-six (0.5%) were excluded because of lack of walking speed measure, 375 (1.3%) because of having dementia or AD, and 17 (0.1%) because accumulating both exclusion criterion. Figure 1 shows the flow diagram for the selection of recruited participants. Selected participants were separated into four age groups based on their age at the time of the first baseline data collection: 45-54, 55-64, 65-74 and ≥75.

Clinical assessment

All participants selected for this study had comprehensive full clinical examinations recording the following variables: age, sex, aboriginal identity (self-identifying as Aboriginal), country of

birth (Canada versus other), independent place of living (i.e., not residing in an assisted living dwelling/institution), living alone (i.e. single, separated, divorced or widowed), low household income (i.e., CAD, <$50,000 annual), high education level (i.e., grade 9 or higher), total number of medications daily taken, mean value of Body Mass Index (BMI) in kg/m2 and category overweight/obese defined with - BMI≥ 25 kg/m2 and walking speed. Mean walking speed was considered using the time taken to complete the 4 Meter Walking Test (seconds and milliseconds). The participants were instructed to stand behind the start line with their toes touching the start line, and to walk (once instructed) until past the finish line (16). The participants were also allowed to practice once (16). The stopwatch was started after the instructions were given. The Research Staff Member then said (Ready, Set) "Go" to indicate that the participant should start walking and the stopwatch was stopped once the participant had completely passed the finish line (16). In addition, participants were considered to have subjective cognitive complaint if they self-reported 'sometimes, occasionally or always' for the variable trouble concentrating or 'yes' for the variable memory problem on standardized questionnaires. Trouble concentrating was determined by asking the participants "How often did you have trouble keeping your mind on what you were doing?". Memory problem was determined by asking the participant "Has a doctor ever told you that you have a memory problem?".

Definition of motoric cognitive risk syndrome

MCR was defined by the association of subjective cognitive complaint and slow walking speed. Subjective cognitive complaint was defined using the variable trouble concentrating or the self-

reported memory problem. Slow walking speed was defined as walking speed one standard deviation (SD) below the average of the cohort. The cohort was defined using sex and age group. The mean walking speed cut-off was found to be 0.85 m/s (for 45-54-year-old males), 0.84 m/s (for 45-54-year-old females), 0.81 m/s (for 55-64-year-old males), 0.79 m/s (for 55-64-year-old females), 0.77 m/s (for 65-74-year-old males), 0.73 m/s (for 65-74-year-old females), 0.68 m/s (for 75+ males) and 0.64 m/s (for 75+ females).

Definition of anxio-depressive disorders and depression

Expression of ADD and depression were distinguished based on the items recorded. First, ADD was defined to have one of the following components: anxiety, mood or depressive disorders. Anxiety disorder was determined by asking the participant “Has a doctor ever told you that you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?”. Mood disorder was determined by asking the participant “Has a doctor ever told you that you have a mood disorder such as depression (including manic depression), bipolar disorder, mania, or dysthymia?”. Depressive disorder was determined by asking the participant “Has a doctor ever told you that you suffer from clinical depression?”. In addition, ADD severity was estimated using the accumulation of ADD components expressed per individual and separated into three levels: at least 1, 2 or all 3 components. In addition, depression was also considered and defined by the Center for epidemiological studies – depression scale (CES-D) score ≥10 (17).

Ethics

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). Participants in the CLSA provided were included after obtaining their written and informed consent for the CLSA. The Jewish General Hospital Ethics Committee approved the study protocol. This research has been conducted using the CLSA Baseline Comprehensive dataset version 3.0 under Application Number 180902, and data access was approved by the CLSA Data and Sample Access Committee.

Statistics

Participants' characteristics were summarized using means and standard deviations (SD) or frequencies and percentages, as deemed appropriate. Participants were categorized by age groups (45-54, 55-65, 65-74, 75+) and in each age group they were separated in participants with and without MCR. Between group comparisons were completed using unpaired t-test or Chi-square test, as deemed appropriate. Due to multiple comparisons (n=84), P-values significant was fixed ≤ 0.0006. Multiple logistic regressions were performed to examine the association of ADD and depression (used as independent variable separately) and MCR (used as a dependent variable) for all population and the different age groups (i.e., 45-54; 55-64; 65-74; ≥75). This analysis was adjusted for age (only in the total population category), sex, aboriginal identity, country of birth-Canada, independent place of living, living alone, low household income, high education level, number of medications taken daily and BMI. P-values

less than 0.05 were considered as statistically significant for logistic regressions. All statistics were performed using SPSS (version 23.0; SPSS, Inc., Chicago, IL).

Results

Table 1 provides a comparison of participants' characteristics according to age groups (i.e., 45-54, 55-64, 65-74, ≥ 75) in participants with and without MCR. The overall prevalence of MCR was 7.0% and differed significantly when comparing age groups (P≤0.001). The prevalence of MCR in 45-54 (8.9%) was higher as compared to 55-64 (6.8%, P≤0.001), 65-74 (5.0%, P≤0.001) and ≥75 (7.4%, P=0.004). This prevalence of MCR in 55-64 was also significantly higher compared to 65-74 (P≤0.001) but not different for ≥75 (P=0.198), whereas it was lower in 65-74 compared to ≥75 (P≤0.001).

In each age-group, the following participants' characteristics were found to be significant (P≤0.001): sex (higher prevalence of females in participants with MCR compared to those without MCR in 45-54 and 65-74, with opposite results in other age-group), number of medications taken (higher prevalence in participants with MCR compared to those without MCR, in all age groups), at least 1 and 2 ADD component (higher prevalence in participants with MCR compared to those without MCR, in all age groups), 3 ADD components cumulated (higher prevalence in participants with MCR compared to those without MCR, in all age groups except in the oldest) and depression (higher prevalence in participants with MCR compared to those without MCR, in all age groups).

Significant (P≤0.001) difference between MCR and non-MCR participants was found for specific age groups for the following characteristics: mean age (older participants with MCR compared to those without MCR, in 65-74, ≥ 75, other age groups were not significant), aboriginal identity (higher prevalence in participants with MCR compared to those without MCR in 45-54, other age groups were not significant), living alone (higher prevalence in participants with MCR compared to those without MCR, in 45-54, 55-64, 65-74, the other age group was not significant), low household income (higher prevalence in participants with MCR compared to those without MCR in 45-54, 55-64, 65-74, older age-group was not significant), high education level (lower prevalence in participants with MCR compared to those without MCR in 65-74, other age groups were not significant), mean value of BMI (higher prevalence in participants with MCR compared to those without MCR in 45-54, 55-64, 65-74, older age-group was not significant), Overweight/obese (higher prevalence in participants with MCR compared to those without MCR, in the ≥75, other age groups were not significant), and 3 ADD components (higher prevalence in participants with MCR compared to those without MCR in 45-54, 55-64, 65-74, the oldest age group was not significant).

Table 2 shows the results of multiple logistic regressions examining the association of ADD and depression (used as an independent variable separately) and MCR (used as a dependent variable) for all population and the different age groups (i.e., 45-54; 55-64; 65-74; ≥75) adjusted on participant's clinical characteristics. Mood disorder was positively associated with MCR in the total population (OR=1.49 with P=0.001) and in 55-64 (OR=1.66 with P=0.013). For the age groups 45-54, 55-64 and 65-74, to have one, two or all ADD components, as well as depression, was positively associated with MCR (OR ≥1.55 with P≤0.002). For the oldest

age-group (i.e., ≥75) only to have at least one ADD components, as well as depression, was positively associated with MCR (OR=1.52 with P=0.003 and OR=3.74 with P≤0.001).

Discussion

Our findings show that firstly the highest prevalence of MCR was observed in the youngest age group. Second, there was a higher prevalence of ADD and depression in individuals with MCR compared to those without MCR, for all age groups. Third, this prevalence of ADD and depression was lower in the oldest individuals with MCR compared to the other MCR age groups. Fourth, ADD and depression were positively associated with MCR, irrespective of age group, but this association was weaker for ADD in oldest age groups compared to the other age groups.

The study showed a higher prevalence of MCR in younger individuals as compared to older individuals. This result is not consistent with previous studies that found an opposite association (1-3). There are potential reasons for this discrepancy. Firstly, it is the first study that includes the prevalence of MCR in a young age group like 45-54. The majority of previous studies examined the prevalence of MCR in individuals age 65 and above (5). The youngest age group examined in the literature was individuals age 60 and over with a mean of 74.9 (5). It has been found that the prevalence of MCR increased with age, particularly after 75 (1). Our study showed a similar trend as the highest prevalence of MCR was found in the oldest age group when using the 55-64 age group as the reference group (excluding the 45-54 group). Second, previous studies have mainly recruited individuals from geriatric or memory clinics,

thus resulting in a bias of selection of older individuals who had a high prevalence of cognitive complaint. In contrast, the CLSA is a population-based study including community dwelling individuals, who have less complaint compared to those consulting in geriatric or memory clinics. Furthermore, as age is associated with slow gait speed, there is a higher probability to have more individuals with MCR in those consulting in geriatric or memory clinics compared to those who are not seen in these clinics who are younger. This last point may explain the fact that we found a lower prevalence of MCR in older age groups compared to the usual prevalence reported in the literature, respectively 7% versus 10%.

The second main result of our study is that ADD and depression were more prevalent in individuals with MCR compared to those without MCR, regardless of the age groups. There are two complementary explanations for this result. First, MCR, ADD and depression present similar symptoms associating slow gait and cognitive complaint, which may result in the overlap. Moreover, it has also been previously reported that depression may be an early manifestation of neurocognitive disorders dues to neurodegenerative or vascular brain diseases, thus explaining the prevalence of ADD and depression in individuals with MCR which is a condition at risk for mild and major neurcognitive disorders (18, 19). Second, MCR and ADD or depression are highly prevalent in the Canadian population and thus, there is a high probability to have an individual with both syndromes (6, 7). Third, it is important to consider that MCR diagnosis in previous studies usually used criteria extracted from depression scales. This association is important to take into consideration as depression may negatively impact the effect of another morbidity. For instance, it has been reported that

comorbidity associated with depression worsens greater health condition compared to depression alone or any morbidity alone (20).

Another main result of our study is that ADD and depression were more prevalent in younger adults compared to older adults, regardless of the MCR status. The prevalence reported in the sample of younger as well as older MCR participants was similar to that reported in the Canadian population. The prevalence of major depressive disorders is reported to be almost double in younger Canadians (25-64), as compared to elderly Canadians (≥65), 12.5% and 7.2%, respectively (14). To explain this trend of higher prevalence in younger individuals, it can be suggested that they are very active and involved in various roles and activities, increasing their levels of stress. Moreover, older adults are less likely to express their ADD (possible underreporting and diagnosis in this age cohort) as compared to younger adults, possibly due to a shift in recent times of increasing awareness and lessening stigma surrounding mental health (21, 22). Similar to the Canadian population, the age trend was observed more strongly in participants with MCR, as compared to participants without MCR, possibly due to the fact that those with MCR have reported cognitive complaint and, thus, are more likely to express and be open to discussing ADD symptomology/complaint. Lastly, it must also be considered that the scale used to detect depression in the CLSA, the CES-D is not a scale specific to the geriatric population, rather a general scale (23).

Finally, our study underscores that MCR is positively associated with ADD and depression in all age groups. However, this association was weaker in older individuals as compared to younger individuals, suggesting that the nature of the disease explaining the symptomatology influence this association. In younger individuals, MCR may be a clinical manifestation of ADD

and depression, whereas in older adults it may be related both to depression or pre-dementia stage, thus explaining the higher prevalence of MCR in the younger population (1-3). Over the past 5 years, two clinical characteristics have been reported as a predictor of dementia. First, individuals with perceived changes in memory and/or cognition in the absence of objective evidence are commonly given a 'diagnosis' of subjective cognitive impairment (SCI) (24). SCI has been defined as a pre-mild cognitive impairment stage and thus, is considered the earliest clinical stage of AD. Second, low gait performance, such as slow walking speed, has been also associated with the occurrence of dementia (25, 26). MCR is a combination of these two symptoms and has been recognized as a pre-dementia stage like MCI (1-4).

Our study has various strengths. The CLSA Comprehensive is a multicenter population-based cohort study with over 30,000 participants and a wide age range of 45-85 years at the time of recruitment. Moreover, a comprehensive clinical assessment of the participants has been completed. However, there are limitations that must be considered. Firstly, the cross-sectional design of our study does not afford causal inferences between depression and depressive symptomatology and MCR. Secondly, this study is a secondary analysis of the existing data, and the CLSA was not specially designed for our research question, explaining that characterization of ADD and depression were not supported by a psychiatric diagnosis but as answers to questions or questionnaires like the CES-D. Thirdly, it must be noted that the definition of cognitive complaint of MCR came from one item of the CES-D. Moreover, it must be considered that the question regarding cognitive complaint may not only refer to subjective cognitive complaint, but to objective cognitive complaint as well. Finally, even if we took into

consideration various variables were when analyzing the possible association of MCR with ADD and depression, it is possible that there are other confounders not considered.

In conclusion, the findings of this study underscore that ADD and depression are associated with MCR, aging leading to a weaker strength of association for depression and mixed results for ADD. These findings suggest that MCR may be a clinical manifestation of ADD or depression in younger individuals, whereas it may be related both to depression and pre-dementia stage in older adults.

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Author's contribution

Study design HS and OB. Study conduct: HS and OB. Data collection: CLSA team. Data interpretation: HS and OB. Drafting manuscript: HS and OB. Revising manuscript content: GA. Approving final version of manuscript HS, OB and GA. HS takes responsibility for the integrity of the data analysis.

Disclosures

The authors declare no conflict of interest. The opinions expressed in this manuscript are the authors' own and do not reflect the views of the Canadian Longitudinal Study on Aging.

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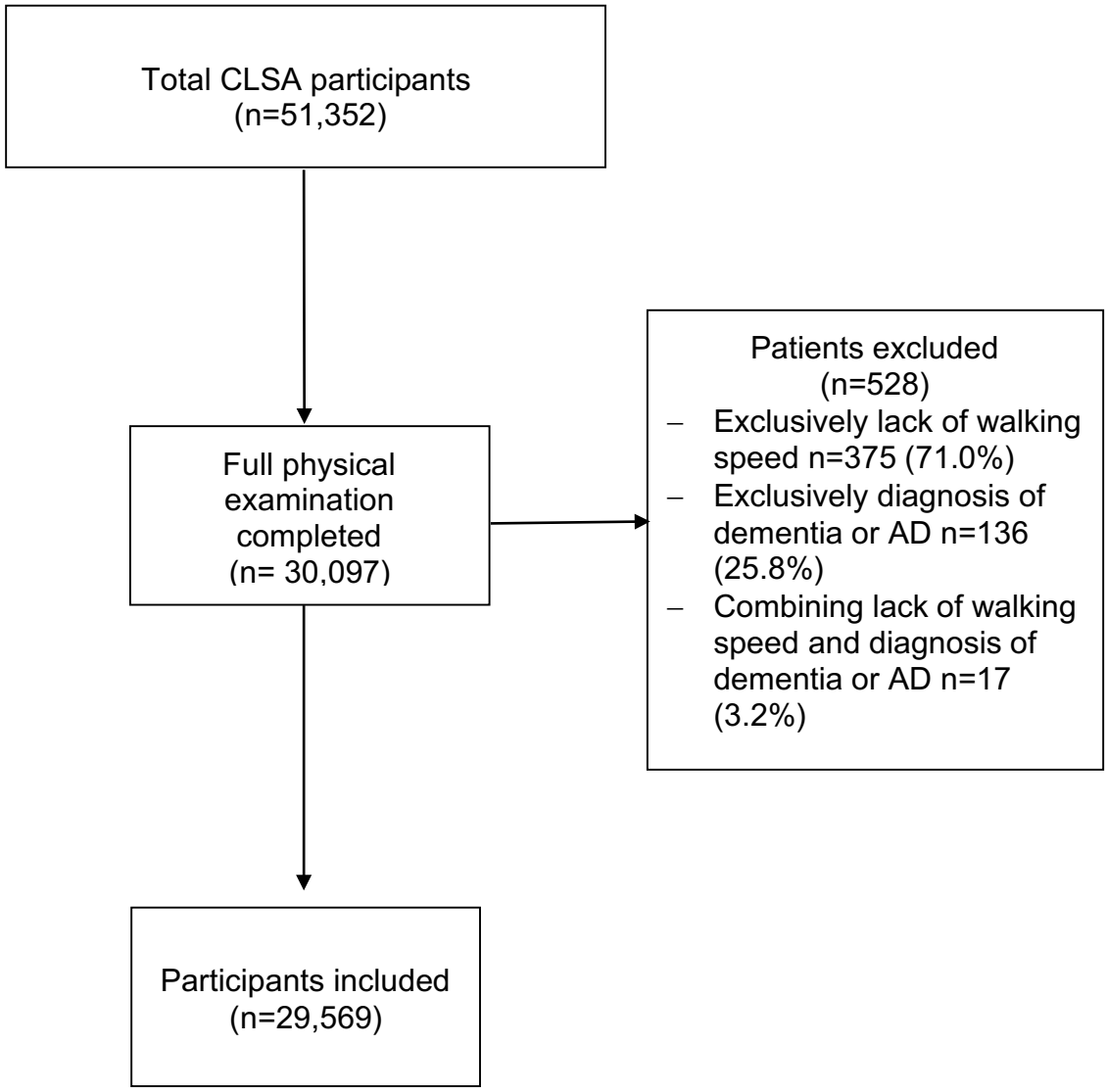

Figure 1. Flow diagram of selection of participants

Table 1. Comparisons of participants' characteristics according to age groups (i.e., 45-64, 55-64, 65-74, ≥ 75) and Motoric Cognitive Risk syndrome in participants of the Canadian longitudinal study on aging (n=29,569).

	Age 45-54		P-value*	Age 55-64		P-value*	Age 65-74		P-value*	Age ≥ 75		P-value*
	No-MCR (n=6863)	MCR (n=666)		No-MCR (n=9036)	MCR (n=663)		No-MCR (n=6850)	MCR (n=359)		No-MCR (n=4752)	MCR (n=380)	
Age, mean value±SD	50.3±2.7	50.4±2.6	0.721	59.7±2.8	59.9±2.8	0.118	68.9±2.8	69.5±2.9	**≤0.001**	78.8±2.9	79.8±3.1	**≤0.001**
Female, n (%)	3492 (50.9)	403 (60.5)	**≤0.001**	4818 (53.3)	190 (28.7)	**≤0.001**	3368 (49.2)	252 (70.2)	**≤0.001**	2389 (50.3)	149 (39.2)	**≤0.001**
Aboriginal, n (%)	371 (5.4)	58 (8.7)	**≤0.001**	334 (3.7)	32 (4.8)	0.028	195 (2.8)	16 (4.5)	0.182	84 (1.8)	6 (1.6)	0.001
Country of Birth Canada, n (%)	5802 (84.5)	545 (81.8)	0.064	7739 (85.6)	556 (83.9)	0.207	5339 (77.9)	287 (79.9)	0.377	3650 (76.8)	303 (79.7)	0.194
Independent place of living†, n (%)	6859 (99.9)	666 (100)	0.824	9018 (99.8)	660 (99.5)	0.176	6822 (99.6)	348 (96.9)	**≤0.001**	4663 (98.1)	362 (95.3)	0.001
Living alone‡, n (%)	1614 (23.5)	203 (30.5)	**≤0.001**	2520 (27.9)	234 (35.3)	**≤0.001**	2172 (31.7)	163 (45.4)	**≤0.001**	2094 (44.1)	182 (47.9)	0.340
Low household income‖	832 (12.1)	171 (25.7)	**≤0.001**	1890 (20.9)	225 (33.9)	**≤0.001**	2264 (33.1)	202 (56.3)	**≤0.001**	1914 (40.3)	190 (50.0)	0.002
High education level¶, n (%)	6840 (99.7)	661 (99.2)	0.147	8984 (99.4)	654 (98.6)	0.023	6701 (97.8)	340 (94.7)	**≤0.001**	4546 (95.7)	356 (93.7)	0.197
Number of medications daily taken	2.1±1.8	2.8±2.2	**≤0.001**	2.5±2.0	3.3±2.3	**≤0.001**	2.7±2.0	3.7±2.3	**≤0.001**	3.05±2.0	3.6±2.4	**≤0.001**
Body mass index (kg/m^2)												
Mean value±SD	27.7±5.5	29.5±7.1	**≤0.001**	28.3±5.6	30.6±7.0	**≤0.001**	28.2±5.1	30.8±7.4	**≤0.001**	27.3±4.5	27.9±5.3	0.008
Overweight/Obese§, n (%)	4453 (64.9)	490 (73.6)	**≤0.001**	6341 (70.2)	535 (80.7)	0.001	4993 (72.9)	281 (78.3)	0.021	3216 (67.7)	264 (69.5)	0.408
Anxio-depressive disorders												
Type of disorders												

Anxiety Disorder‡‡ †††	234 (3.4)	28 (4.2)	0.285	289 (3.2)	29 (4.4)	0.101	223 (3.3)	13 (3.6)	0.704	120 (2.5)	7 (1.8)	0.409
Mood Disorder|||| †††	188 (2.7)	22 (3.3)	0.399	250 (2.8)	30 (4.5)	0.009	190 (2.8)	19 (5.3)	0.006	108 (2.3)	13 (3.4)	0.156
Depressive disorder†† †††	148 (2.2)	12 (1.8)	0.545	251 (2.8)	13 (2.0)	0.212	160 (2.3)	17 (4.7)	0.004	75 (1.6)	12 (3.2)	0.022
Number of disorders, n (%)												
≥1,	1609 (23.4)	265 (39.8)	**≤0.001**	2317 (25.6)	265 (40)	**≤0.001**	1462 (21.3)	144 (40.1)	**≤0.001**	665 (14.0)	83 (21.8)	**≤0.001**
≥2	1039 (15.1)	203 (30.5)	**≤0.001**	1527 (16.9)	193 (29.1)	**≤0.001**	889 (13.0)	95 (26.5)	**≤0.001**	362 (7.6)	51 (13.4)	**≤0.001**
3	309 (4.5)	87 (13.1)	**≤0.001**	426 (4.7)	72 (10.9)	**≤0.001**	222 (3.2)	36 (10.0)	**≤0.001**	80 (1.7)	13 (3.4)	0.015
Depression ***	970 (14.1)	278 (41.7)	**≤0.001**	1250 (13.8)	288 (43.4)	**≤0.001**	840 (12.3)	143 (39.8)	**≤0.001**	643 (13.3)	135 (25.5)	**≤0.001**

MCR: Motoric Cognitive Risk; *: Comparison based on unpaired t-test or Chi square test, as appropriate; †: Defined as not residing in an assisted living dwelling/institution; ‡: Defined as single, separated, divorced or widowed; ||: Defined as CAD $ <50,000; ¶: High education level- is defined as grade 9 or higher; §: Overweight defined as body mass index ≥ 25 kg/m^2; #: Trouble Concentrating: How often did you have trouble keeping your mind on what you were doing?; **: Memory Problem: Has a doctor ever told you that you have a memory problem?

††: Defined as “Has a doctor ever told you that you suffer from clinical depression?”; ‡‡: Defined as “Has a doctor ever told you that you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?”; ||||: Defined as “Has a doctor ever told you that you have a mood disorder such as depression (including manic depression), bipolar disorder, mania, or dysthymia?”; †††: Exclusive (i.e., no overlap with another depressive symptom); ***: Center for epidemiological studies – depression scale (CES-D) Score (/X) ≥ 10

P value significant ≤ 0.0006 because of multiple comparisons (n=84) indicated in bold

Table 2. Multiple logistic regressions presenting the association of Motoric Cognitive Risk syndrome (dependent variable) with depressive symptoms (independent variable, separated models for each symptom) in all population and the different age groups (i.e., 45-54; 55-64; 65-74; ≥75) adjusted on participant's clinical characteristics* (n=29,569).

	OR [95%CI] P-Value				
	Total	Age groups*			
	population * (n=29,569)	45-54 (n=7,529)	55-64 (n=9,699)	65-74 (n=7,209)	≥75 (n=5,132)
Anxio-depressive disorders					
Type of disorders					
Clinical	0.85	0.57	0.59	1.40	1.49
Depression‡#	[0.64;1.14]	[0.31;1.06]	[0.33;1.05]	[0.82;2.39]	[0.79;2.83]
	0.273	0.074	0.072	0.214	0.221
Anxiety	1.23	1.34	1.42	1.10	0.77
Disorder‖#	[0.96;1.56]	[0.90;2.01]	[0.95;2.11]	[0.62;1.97]	[0.36;1.69]
	0.097	0.153	0.091	0.736	0.523
Mood	1.49	1.16	1.66	1.63	1.67
Disorder¶#	[1.18;1.88]	[0.73;1.82]	[1.11;2.47]	[0.99;2.70]	[0.92;3.03]
	0.001	0.531	**0.013**	0.055	0.090
Number of disorders					
≥1	1.64	1.64	1.78	1.69	1.52
	[1.48;1.82]	[1.37;1.97]	[1.48;2.13]	[1.33;2.15]	[1.15;2.00]
	≤0.001	**≤0.001**	**≤0.001**	**≤0.001**	**0.003**
≥2	1.68	1.79	1.81	1.55	1.53

		[1,50;1.88]	[1.47;2.18]	[1.48;2.21]	[1.18;2.02]	[1.10;2.14]
		≤0.001	**≤0.001**	**≤0.001**	**0.002**	0.074
	3	2.10	2.28	2.08	2.15	1.72
		[1.78;2.47]	[1.74;2.99]	[1.56;2.77]	[1.44;3.21]	[0.93;3.18]
		≤0.001	**≤0.001**	**≤0.001**	**≤0.001**	0.085
Depression §#		4.03	3.75	4.85	3.65	3.74
		[3.65;4.45]	[3.15;4.47]	[4.06;5.81]	[2.88;4.63]	[2.95;4.75]
		≤0.001	**≤0.001**	**≤0.001**	**≤0.001**	**≤0.001**

OR: Odd Ratio; CI: Confidence Interval; *: All models adjusted for age (only in the “All Age Groups” category) sex, aboriginal, country of birth Canada, independent place of living, living alone, low household income, high education level, number of medications daily taken and body mass index; ‡: Defined as “Has a doctor ever told you that you suffer from clinical depression?”

||: Defined as “Has a doctor ever told you that you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?”; ¶: Defined as “Has a doctor ever told you that you have a mood disorder such as depression (including manic depression), bipolar disorder, mania, or dysthymia?”; §: Center for epidemiological studies – depression scale (CES-D) Score (/X) ≥ 10; #: Exclusive (i.e., no overlap with another depressive symptom); P-value significant (i.e., ≤0.05) in bold

Chapter 7 Motoric cognitive risk syndrome and cardiovascular diseases and risk factors in the Canadian population: Results from the baseline assessment of the Canadian longitudinal study on aging

The fourth manuscript examines the association of motoric cognitive risk syndrome (MCR) with cardiovascular disease and risk factors.

MCR has not been well studied in the Canadian population. As discussed in the literature review (chapter 2) MCR is a better predictor of vascular dementia than AD. Previous studies examining the association between MCR and cardiovascular disease and risk factors have reported diverging findings regarding this association. A recent systematic review found that MCR and cardiovascular disease and risk factors are indeed positively associated. Cardiovascular diseases are rampant and a leading cause of death among Canadians. This is the first time that this association was considered in the Canadian context. Lastly, this is also the first time that younger adults (45-60) are included.

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Running title: The association of cardiovascular diseases and risk factors with motoric cognitive risk syndrome

ABSTRACT

Background: Motoric Cognitive Risk Syndrome (MCR) is a pre-dementia syndrome associated with cardiovascular diseases and risk factors (CVDRF). There is no information on this association in the Canadian population. The aim of this study was to examine whether there is: 1) an association between MCR and CVDRF in the Canadian population, and 2) a specific MCR-related CVDRF profile (i.e., cardiovascular diseases (CVD) *versus* cardiovascular risk factors (CVRF) *versus* both) when comparing different age groups.

Methods: A total of 29,569 participants free of dementia recruited in the Canadian Longitudinal Study on Aging (CLSA) Comprehensive, who had a baseline assessment with the 4-meter walking test and information on cognitive complaint, were selected in this cross-sectional study. Participants were categorized into groups by their age (i.e. 45-54, 55-64, 65-74 and ≥ 75) and MCR status (with MCR *versus* without MCR). Overweight/obese, smoking, Waist to Hip Circumference Ratio (WHCR), systolic blood pressure and diastolic blood pressure levels were CVRF considered. Diabetes type I and II, hypertension, heart disease and attack, peripheral vascular disease, angina, stroke and rhythmic disease were CVD considered.

Results: There was a higher prevalence of CVD in individuals with MCR compared to those without MCR for all age groups. A higher prevalence of CVRF in MCR was shown in the youngest age groups (i.e., 45-54 and 55-64) compared to the other age groups. MCR was positively associated with CVDRF, except in the oldest age group (i.e., ≥75). In this group, the only significant association with CVRF was with diastolic blood

pressure, which was negatively associated with MCR. Diabetes and hypertension were not associated with MCR.

Conclusions: In the Canadian population, MCR is associated with CVDRF in both younger and older individuals. A stronger association was present for CVRF factors in younger adults and for CVD in older adults.

Key words: Epidemiology; Walking speed; Cognitive complaint; Cardiovascular disease and risk factors; Older adults; CLSA

Introduction

Motoric Cognitive Risk Syndrome (MCR), which is defined by the association of slow gait speed and cognitive complaint, has been associated with cognitive impairment and decline (1). Thus, MCR may be used to screen individuals at risk of dementia (1). MCR is usable in various primary care settings and at the population level because its two components are easy to assess and are already a part of the physician regular visit for older patients (2-5). Dementia is a major chronic morbidity without any curative treatment; but the onset and progression can be delayed and slowed down by identifying individuals at risk and controlling for cognitive decline risk factors (6-9). Better understanding the dementia-related risk factors associated with MCR may be helpful for improving dementia prevention.

The physiopathology of MCR is still a matter of debate (1, 10-12). MCR has been associated with the occurrence of both Alzheimer Disease (AD) and Vascular Dementia (VD) (1, 10-12). However, MCR is a stronger predictor of VD compared to AD (10). Recently, it has been demonstrated in a meta-analysis that MCR was significantly associated with cardiovascular diseases and risk factors (CVDRF) (13). This meta-analysis underscored that few studies have examined the association between MCR and CVDRF, and most of them recruited older adults referred to memory or geriatric centres with a lack of focus on general population (13). It must be noted that the Canadian population was not considered in any of those studies or the meta-analysis (13). This is concerning as CVDRF are highly prevalent in the Canadian population, as the second leading cause of death in Canada, with a trend for increased prevalence

(14, 15). Moreover, the fact that there are major differences in lifestyle (i.e. diet, physical activity, etc.) and genetics (i.e. ethnic backgrounds, geographical variation, etc.) between the populations included in the meta-analysis and the Canadian population emphasizes the need for targeting the Canadian population (13). Furthermore, it has been showed that cardiovascular risk factors (CVRF) in middle life are important risk factors for dementia, suggesting that the profile of association of CVRF and cardiovascular diseases (CVD) with a pre-dementia stage like MCR may change with group age (16,17).

We have the opportunity with the Canadian Longitudinal Study on Aging (CLSA), which is a population-based prospective and observational study to overcome the previously described limitations of our meta-analysis (18). Indeed, the CLSA has various strengths for examining the association of MCR with CVDRF, CVD and CVRF; such as a very large sample size (n=51,352), recruitment of participants who are community dwellers in the general population and varying in age (45–85 years old) (18). Thus, not limited to the older population (12, 18).

The aim of this study was to examine whether there is 1) an association between MCR and CVDRF in the Canadian population, and 2) a specific MCR-related CVDRF profile (CVD versus CVRF versus both) when comparing different age groups. We hypothesized that there was a positive association between MCR and CVDRF in the Canadian population and that this association may be influenced by age.

Methods

Population and study design

Participants selected in the present study are a Comprehensive Cohort of the CLSA baseline data. A total of 51,388 participants have been recruited in the CLSA. Among them, 21,241 completed a computer-assisted telephone interview (Tracking Cohort) and 30,097 completed both face-to-face, laptop computer-assisted in-home interviews and data collection site visits for additional computer-assisted interviews and clinical assessments (Comprehensive Cohort) (18). Thus, only participants in the Comprehensive Cohorts were potential participants for this study. The subset of CLSA participants, who had a baseline assessment including a physical examination with a completed 4-meter walking test and the absence of a dementia diagnosis, were selected for this study (n= 29,569; 98.2%). Of participants not included in this study, 0.45% (n=136) lacked walking speed, 1.25% (n=375) had dementia or AD, and 0.06% (n=17) did not meet either criteria.

Clinical assessment

The CLSA Comprehensive participants selected for this study had comprehensive, standardized physical examinations and questionnaire-based measures of demographics (e.g., age, sex), physiological, psychological, and social functioning, lifestyle, behavior, and sociodemographic. Of these variables, the following were recoded for this study: country of birth (Canada *versus* other), high education level (i.e.,

grade 9 or higher), total number of medications taken, independent place of living (i.e., not residing in an assisted living dwelling/institution), Indigenous identity (self-identifying as Aboriginal), living alone (i.e. single, separated, divorced or widowed), low household income (i.e., CAD, <$50,000 annual). The variable country of birth was combined from various questions inquiring about the participants' country of birth (i.e. the US, Germany, India, etc.), it was categorized as those born in Canada *versus* any other country. The variable high education level was coded from the question "What is the highest grade of elementary or high school you have ever completed?", where options were combined as lower than grade 9 or grade 9 and higher. The variable total number of medications taken was coded by considering all variables relating to the participant taking medications or undergoing other treatment, these were considered/tallied and included. The variable "Dwelling type" was recoded with "House (single detached, semi-detached, duplex or townhouse)", "Apartment or condominium" and "Hotel, rooming or lodging house" being considered as not residing in an assisted living dwelling/institution. The variable "Aboriginal Identity" was included as is, with participants asked to self-identify as aboriginal. The variable "Marital/partner status" was recoded with "Single, never married or never lived with a partner", "Widowed", "Divorced" and "Separated" being merged into living alone. The variable "Total household income" was recoded with "Less than $20,000" and "$20,000 or more, but less than $50,000" tallied together after considering the Canadian household low-income cutoff for an average family of 4 (19).

Definition of motoric cognitive risk syndrome

Subjective cognitive complaint using the variable ‘trouble concentrating’ or the self-reported ‘memory problem’ variable combined with slow gait defines MCR. Participants who self-reported “sometimes”, “occasionally” or “always” for the variable “trouble concentrating” and/or “yes” for the variable “memory problem” were considered to have a subjective cognitive complaint. To determine the ‘trouble concentrating’ variable, participants were asked the following: “How often did you have trouble keeping your mind on what you were doing?”. Moreover, the variable ‘memory problem’ was determined by the question “Has a doctor ever told you that you have a memory problem?”.

Mean walking speed was considered using the time taken to complete the 4 Meter Walking Test (seconds and milliseconds). The participants were instructed to stand behind the start line with their toes touching the start line, and to walk (once instructed) until past the finish line (18). The participants were also allowed to practice once (18). The stopwatch was started after the instructions were given and the research staff member said (Ready, Set) "Go" and the stopwatch was stopped once the participant had completely passed the finish line (18). Slow gait, was defined by walking speed one standard deviation (SD) below the average of the cohort for each individual sex and age group. The mean walking speed cut-offs for each sub-group were: 0.68 m/s (for 75+ males), 0.64 m/s (for 75+ females), 0.77 m/s (for 65-74-year-old males) 0.73 m/s (for 65-74-year-old females), 0.81 m/s (for 55-64-year-old males), 0.79 m/s (for 55-64-year-

old females), 0.85 m/s (for 45-54-year-old males) and 0.84 m/s (for 45-54-year-old females).

Definition of cardiovascular diseases and risk factors

Overweight/obese, smoking, waist to hip circumference ratio (WHCR), systolic blood pressure, diastolic blood pressure, diabetes Type I and II, hypertension, heart disease and attack, peripheral vascular disease, angina, stroke and rhythmic disease were CVDRF measured in the CLSA. Overweight/obese was defined by body mass index (BMI) ≥ 25 kg/m^2. Smoking was measured as a current or former smoker for the question “What is your smoking status?". When considering both systolic and diastolic blood pressure the average for all 6 readings for each was considered. Diabetes was defined by a yes to the question, "Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?”. Hypertension was defined by a yes to the question, “Has a doctor ever told you that you have high blood pressure or hypertension?”. Heart disease and attacked was defined by a yes to any of the following two questions: (A) “Has a doctor ever told you that you have heart disease (including congestive heart failure, or CHF)?” or (B) “Has a doctor ever told you that you have had a heart attack or myocardial infarction?”. Peripheral vascular disease was defined by a yes to “Has a doctor ever told you that you have peripheral vascular disease or poor circulation in your limbs?”. Angina was defined by a yes to “Has a doctor ever told you that you have angina (or chest pain due to heart disease)?”. Stroke was defined by a yes to any of the following questions “Has a doctor ever told you that you have

experienced a Stroke or CVA? (cerebrovascular accident)?" and/or "Has a doctor ever told you that you have experienced a ministroke or TIA (Transient Ischemic Attack)?" and/or "Has a doctor ever told you that you suffer from the effects of a stroke, CVA (cerebrovascular accident), mini-stroke or TIA (Transient Ischemic Attack)?".

Ethics

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). Participants in the CLSA provided written and informed consent for the CLSA. The Jewish General Hospital Ethics Committee (Montreal, Quebec, Canada) approved the study protocol. This research has been conducted using the CLSA Baseline Comprehensive dataset version 3.0 under Application Number 161002, and data access was approved by the CLSA Data and Sample Access Committee.

Statistics

Means and standard deviations (SD) or frequencies and percentages were used as appropriate to examine participants' characteristics. Participants were separated by age groups (i.e., 45-54, 55-65, 65-74 and 75+) and MCR diagnosis (i.e., with *versus* without MCR). An unpaired t-test or Chi-square test were used as appropriate, for between-group comparisons. As numerous analyses were carried out, the P-values were calculated to be ≤0.0007 (number of comparison 76). Moreover, multiple logistic regressions were performed to examine the association of MCR (dependent variable)

with CVDRF, CVD and CVRF (used as independent variables) in the entire population and the different age groups (i.e., 45-54; 55-64; 65-74; ≥75) using 3 different models. The following clinical characteristics were adjusted by age (only in the total population category), sex, Indigenous identity, country of birth-Canada, independent place of living, living alone, low household income, high education level and the number of medications taken daily. P-values ≤0.05 were considered statistically significant for the multiple logistic regression. All statistics were performed using SPSS (version 23.0; SPSS, Inc., Chicago, IL).

Results

Table 1 provides a comparison of participants' characteristics according to their age groups (i.e., 45-54, 55-64, 65-74, ≥ 75) and MCR diagnosis. Country of birth, Canada, was the only variable not significant in any age group. Participants with MCR were older than those without MCR within the age groups 65-74 and ≥ 75. A higher prevalence of females in participants with MCR compared to those without MCR in the age groups 45-54 and 65-74 were noted, whereas, opposite results were shown in the other age groups. Diabetes and peripheral vascular disease were more prevalent in participants with MCR compared to those without MCR. Participants with MCR had a significantly higher prevalence of CVRF and CVD compared to those without MCR: overweight/obese category (age group 45-54); smoking (age groups 45-54 and 55-64); systolic blood pressure (age group 55-64); diastolic blood pressure (age group 55-64);

hypertension (age groups 45-54 and 55-64); heart disease or attack (age group 55-64); angina (age groups 45-54, 55-64 and 65-74) and stroke (age groups 55-64 and 65-74). Comparatively, a lower prevalence of participants with MCR compared to those without MCR for diastolic blood pressure in age group 65-74, for heart disease or attack and for stroke in the age group ≥75 was reported. For the other participants' characteristics, significant differences were observed (please see Table 1).

Table 2 shows the results of logistic regressions exploring the association of MCR with CVDRF. The only negative association that was found was for diastolic blood pressure in age groups 65-74 and ≥75 (OR ≤0.99 with P≤0.015). Diastolic blood pressure was positively associated with MCR in the age group 45-54 (OR=1.01 with P=0.019). The overweight/obese category was positively associated with MCR in age groups 45-54, 55-64, 65-74 (OR≥1.30 with P≤0.034). Smoking was positively associated with MCR in the total population and in age groups 45-54 and 55-64 (OR≥ 1.44 with P≤0.001). WHCR was positively associated with MCR in the total population and in age groups 45-54, 55-64 and 65-74 (OR≥14.45 with P≤0.001). Systolic blood pressure was positively associated with MCR in the age group 45-54 (OR=1.01 with P=0.002). Diabetes was positively associated with MCR in the total population and in age groups 45-54, 55-64 and 65-74 (OR≥1.46 with P≤0.001). Hypertension was positively associated with MCR in the total population and in age groups 45-54 (OR≥1.11 with P≤0.038). Heart disease or attack was positively associated with MCR in the total population and in age groups 55-64, 65-74 and ≥75 (OR≥1.29 with P≤0.029). Peripheral vascular disease was positively associated with MCR in the total population as well as

age groups 45-54, 55-64, 65-74 and ≥75 (OR≥1.77 with P≤0.003). Angina was positively associated with MCR in the total population and in age groups 45-54, 55-64, 65-74 and ≥75 (OR≥1.38 with P≤0.041). Stroke was positively associated with MCR in the total population and in age groups 55-64, 65-74 and ≥75 (OR≥1.50 with P≤0.045).

Discussion

Our study found that there is a higher prevalence of CVD, in individuals with MCR as compared to those without MCR for all age groups, whereas, the higher prevalence of CVRF in MCR was shown in the youngest age groups (i.e., 45-54 and 55-64). In addition, MCR was positively associated with CVDRF, except in the oldest age group (i.e., ≥75). In this group, the only significant association was with diastolic blood pressure, which was negatively associated with MCR. Diabetes and hypertension were not associated with MCR.

The first main finding of this study was an overall higher prevalence of CVD in individuals with MCR compared to individuals without MCR. This result is consistent with our recent meta-analysis (13). The novelty of this last study is that younger (i.e., age group 45-54 and 55-64) adults are included as compared to previous literature, which only focused on individuals ≥60. Our findings also showed that this higher prevalence was shown for CVRF but only in the youngest age groups (i.e., 45-54 and 55-65) and not in the oldest age groups (i.e., 65-74 and ≥75). This result may be explained by the rate of death of patients with CVD, which increases with age (19).

Thus, the probability to die because of CVD before 75 is high. The absence of higher prevalence of high blood pressure in the oldest age group may be related to the use of anti-hypertensive drugs, whereas, in the youngest group this disease could be ignored because it is more frequent and controlled with age (19). These results are consistent with the fact that we demonstrated a positive association of MCR with CVDRF, except for CVRF in the oldest age group and for diastolic pressure.

The lack of association between MCR and CVRF in ≥75 age group is opposite to the findings in the last meta-analysis (13). This contradictory finding may be due to some specific characteristics of the Canadian population, such as ethnicity, lifestyle and environment. In addition, the absence of significant association with diabetes and hypertension may be due to the fact that these two CVDs do not assess the consequences of CVDRF on a specific organ, as compared to the other CVDs used in our study.

The findings of our study revealed a negative association of MCR with high diastolic pressure in the older age group (i.e., 64-74 and ≥75). This association with diastolic blood pressure may be explained by the fact that it has been especially related to the occurrence of brain vascular diseases (20,21). However, the negative association with MCR is difficult to understand because in the majority of cases a high diastolic blood pressure has been related to adverse effects (21). However, it has been shown in the older population that lower blood pressure levels may be paradoxically associated with adverse effects like increased rate of death (22). In addition, some studies conducted in

older adults (i.e., ≥75) demonstrated that low systolic and diastolic blood pressure have been associated with incident dementia (22/23).

This study has various strengths. First, there is a large number of community-dwelling population-based participants in Canada. Second, the participants are aged from 45 to 85 at the time of recruitment, not only older adults. Third, as the participants were not recruited from memory clinics, they were older population-based community-dwelling adults. However, some limitations need to be considered. This study is a secondary analysis of the existing study, whose study and data collection protocol were not created with the specific research questions of this study. Thus, the characterization of the outcomes may be non-optimal, as was explained above, because various variables from the CLSA were recoded and combined for this study. Moreover, it must be considered that one of the variables used to identify participants with subjective cognitive impairment was from the CESD-10 depression scale. Furthermore, as using the baseline data of the CLSA, this study was a cross-sectional study no causal inferences can be made. Lastly, the authors tried to be exhaustive in the CVDRF variable considered, but other potential confounders may have been missed.

Conclusion

MCR is associated with CVDRF in the Canadian population. Specifically, a stronger association was reported for CVRF factors in younger adults and CVD in older adults.

These results suggest that CVDRF are involves in the physiopathology of MCR and emphasizes its complexity which required more research.

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Author's contribution

Study design HS and OB. Study conduct: HS and OB. Data collection: CLSA team. Data interpretation: HS and OB. Drafting manuscript: HS and OB. Revising manuscript content: GA. Approving final version of manuscript HS, OB and GA. HS takes responsibility for the integrity of the data analysis.

Disclosures

The authors declare no conflict of interest. The opinions expressed in this manuscript are the authors' own and do not reflect the views of the Canadian Longitudinal Study on Aging.

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Table 1. Comparisons of participants' characteristics according to age groups (i.e., 45-64, 55-64, 65-74, ≥ 75) and Motoric Cognitive Risk syndrome in participants of the Canadian longitudinal study on aging (n=29,569).

	Age 45-54		P-value*	Age 55-64		P-value*	Age 65-74		P-value*	Age ≥ 75		P-value*
	No-MCR (n=6863)	MCR (n=666)		No-MCR (n=9036)	MCR (n=663)		No-MCR (n=6850)	MCR (n=359)		No-MCR (n=4752)	MCR (n=380)	
Age, mean value±SD	50.3±2.7	50.4±2.6	0.721	59.7±2.8	59.9±2.8	0.118	68.9±2.8	69.5±2.9	**≤0.001**	78.8±2.9	79.8±3.1	**≤0.001**
Female, n (%)	3492 (50.9)	403 (60.5)	**≤0.001**	4818 (53.3)	190 (28.7)	**≤0.001**	3368 (49.2)	252 (70.2)	**≤0.001**	2389 (50.3)	149 (39.2)	**≤0.001**
Aboriginal, n (%)	371 (5.4)	58 (8.7)	**≤0.001**	334 (3.7)	32 (4.8)	0.028	195 (2.8)	16 (4.5)	0.182	84 (1.8)	6 (1.6)	0.001
Country of Birth Canada, n (%)	5802 (84.5)	545 (81.8)	0.064	7739 (85.6)	556 (83.9)	0.207	5339 (77.9)	287 (79.9)	0.377	3650 (76.8)	303 (79.7)	0.194
Independent place of living†, n (%)	6859 (99.9)	666 (100)	0.824	9018 (99.8)	660 (99.5)	0.176	6822 (99.6)	348 (96.9)	**≤0.001**	4663 (98.1)	362 (95.3)	0.001
Living alone‡, n (%)	1614 (23.5)	203 (30.5)	**≤0.001**	2520 (27.9)	234 (35.3)	**≤0.001**	2172 (31.7)	163 (45.4)	**≤0.001**	2094 (44.1)	182 (47.9)	0.340
Low household income‖	832 (12.1)	171 (25.7)	**≤0.001**	1890 (20.9)	225 (33.9)	**≤0.001**	2264 (33.1)	202 (56.3)	**≤0.001**	1914 (40.3)	190 (50.0)	0.002
High education level¶, n (%)	6840 (99.7)	661 (99.2)	0.147	8984 (99.4)	654 (98.6)	0.023	6701 (97.8)	340 (94.7)	**≤0.001**	4546 (95.7)	356 (93.7)	0.197
Number of medications daily taken	2.1±1.8	2.8±2.2	**≤0.001**	2.5±2.0	3.3±2.3	**≤0.001**	2.7±2.0	3.7±2.3	**≤0.001**	3.05±2.0	3.6±2.4	**≤0.001**
Cardiovascular risk factors												
Overweight/Obese§, n (%)	4453 (64.9)	490 (73.6)	**≤0.001**	6341 (70.2)	535 (80.7)	0.001	4993 (72.9)	281 (78.3)	0.021	3216 (67.7)	264 (69.5)	0.408
Smoking††	782 (11.4)	129 (19.4)	**≤0.001**	929 (10.3)	112 (16.9)	**≤0.001**	459 (6.7)	34 (9.5)	0.043	169 (3.6)	20 (5.3)	0.089
Systolic Blood Pressure	116.0±14.5	118.1±15.4	0.001	120.8±16.0	123.3±17.2	**≤0.001**	125.7±16.9	126.2±17.8	0.575	128.5±18.0	128.2±18.9	0.717

Diastolic Blood Pressure	75.7±9.9	76.5±10.3	0.055	75.6±9.7	77.5±10.8	**≤0.001**	73.8±9.5	71.2±9.9	**≤0.001**	70.6±9.8	69.3±9.7	0.017
Cardiovascular Diseases												
Diabetes||||	682 (9.9)	126 (18.9)	**≤0.001**	1507 (16.7)	203 (30.6)	**≤0.001**	1434 (20.9)	122 (34.0)	**≤0.001**	1002 (21.1)	117 (30.8)	**≤0.001**
Hypertension¶¶	1299 (18.9)	181 (27.2)	**≤0.001**	3000 (33.2)	303 (45.7)	**≤0.001**	3105 (45.3)	190 (52.9)	0.005	2576 (54.2)	228 (60.0)	0.029
Heart Disease or Attack§§	244 (3.6)	26 (3.9)	0.644	771 (8.5)	113 (17.0)	**≤0.001**	1131 (16.5)	82 (22.8)	0.002	1209 (25.4)	129 (33.9)	**≤0.001**
Peripheral Vascular Disease##	179 (2.6)	35 (5.3)	**≤0.001**	345 (3.8)	56 (8.4)	**≤0.001**	396 (5.8)	66 (18.4)	**≤0.001**	422 (8.9)	72 (18.9)	**≤0.001**
Angina***	58 (0.8)	17 (2.6)	**≤0.001**	236 (2.6)	47 (7.1)	**≤0.001**	402 (5.9)	41 (11.4)	**≤0.001**	440 (9.3)	55 (14.5)	0.001
Stroke†††	81 (1.2)	17 (2.6)	0.003	225 (2.5)	43 (6.5)	**≤0.001**	337 (4.9)	34 (9.5)	**≤0.001**	481 (10.1)	68 (17.9)	**≤0.001**

MCR: Motoric Cognitive Risk. Comparison based on unpaired t-test or Chi-square test, as appropriate; †: Defined as not residing in an assisted living dwelling/institution; ‡: Defined as single, separated, divorced or widowed; ||: Defined as CAD $ <50,000; ¶: High education level- is defined as grade 9 or higher; §: Overweight defined as body mass index ≥ 25;; ††: Smoking: Defined as current or former for “What is your smoking status?”; ||||: Diabetes: Defined as “Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?”; ¶¶: Hypertension: Defined as “Has a doctor ever told you that you have high blood pressure or hypertension?”; §§: Heart Disease or Attack: Defined as “Has a doctor ever told you that you have heart disease (including congestive heart failure, or CHF)?” or Defined as “Has a doctor ever told you that you have had a heart attack or myocardial infarction?”; ##: Peripheral Vascular Disease: Defined as “Has a doctor ever told you that you have peripheral vascular disease or poor

circulation in your limbs?"; ***: Angina: Defined as "Has a doctor ever told you that you have angina (or chest pain due to heart disease)?"; †††: Stroke: Defined as "Has a doctor ever told you that you have experienced a Stroke or CVA? (cerebrovascular accident)?" and/or "Has a doctor ever told you that you have experienced a ministroke or TIA (Transient Ischemic Attack)?" and/or "Has a doctor ever told you that you suffer from the effects of a stroke, CVA (cerebrovascular accident), ministroke or TIA (Transient Ischemic Attack)?"; P-value significant ≤ 0.0007 because of multiple comparisons (n=76) indicated in bold

Table 2. Multiple logistic regressions presenting the association of Motoric Cognitive Risk syndrome (dependent variable) with Cardiovascular Diseases and Risk Factors in all population and the different age groups (i.e., 45-54; 55-64; 65-74; ≥75) in different models (n=29,569).

	OR [95%CI] P-Value				
	Total	Age-groups			
	Population[2] (n=29,569)	45-54 (n=7,529)	55-64 (n=9,699)	65-74 (n=7,209)	≥75 (n=5,132)
Cardiovascular risk factors					
Overweight/Obese*	1.30	1.54	1.46	1.33	1.00
	[1.17;1.45]	[1.28;1.85]	[1.19;1.79]	[1.02;1.73]	[0.79;1.26]
	≤0.001	**≤0.001**	**≤0.001**	**0.034**	0.998
Smoking†	1.55	1.75	1.44	1.31	1.42
	[1.36;1.78]	[1.42;2.17]	[1.16;1.80]	[0.90;1.92]	[0.88;2.30]
	≤0.001	**≤0.001**	**0.001**	0.158	0.155
Waist to Hip	14.45	12.58	47.74	59.70	2.39
Circumference Ratio	[7.42;28.14]	[3.69;42.88]	[14.76;154.47]	[11.77;302.78]	[0.48;11.81]
	≤0.001	**≤0.001**	**≤0.001**	**≤0.001**	0.286
Systolic Blood Pressure	1.00	1.01	1.00	1.00	1.00
	[1.00;1.01]	[1.00;1.01]	[1.00;1.01]	[0.99;1.01]	[0.99;1.01]
	0.185	**0.002**	0.271	0.965	0.899

Diastolic Blood Pressure	1.00	1.01	1.00	0.98	0.99
	[0.99;1.00]	[1.00;1.02]	[1.00;1.01]	[0.97;0.99]	[0.98;1.00]
	0.213	**0.019**	0.476	**≤0.001**	**0.015**
Cardiovascular Diseases					
Diabetes‖	1.46	1.53	1.53	1.63	1.26
	[1.30;1.63]	[1.21;1.93]	[1.25;1.87]	[1.27;2.10]	[0.99;1.62]
	≤0.001	**≤0.001**	**≤0.001**	**≤0.001**	0.064
Hypertension¶	1.11	1.24	1.19	1.04	1.05
	[1.01;1.23]	[1.02;1.51]	[0.99;1.42]	[0.82;1.30]	[0.83;1.32]
	0.038	**0.035**	0.060	0.765	0.695
Heart Disease or Attack§	1.38	0.99	1.58	1.52	1.29
	[1.22;1.57]	[0.65;1.51]	[1.26;1.98]	[1.16;1.99]	[1.03;1.62]
	≤0.001	0.949	**≤0.001**	**0.002**	**0.029**
Peripheral Vascular	2.23	1.77	1.89	3.00	2.18
Disease#	[1.91;2.59]	[1.21;2.59]	[1.39;2.57]	[2.23;4.04]	[1.65;2.89]
	≤0.001	**0.003**	**≤0.001**	**≤0.001**	**≤0.001**
Angina**	1.70	2.31	1.87	1.97	1.38
	[1.42;2.04]	[1.31;4.08]	[1.33;2.63]	[1.38;2.82]	[1.01;1.88]
	≤0.001	**0.004**	**≤0.001**	**≤0.001**	**0.041**
Stroke††	1.52	1.25	1.65	1.50	1.50
	[1.27;1.83]	[0.72;2.19]	[1.15;2.37]	[1.01;2.22]	[1.11;2.02]
	≤0.001	0.429	**0.007**	**0.045**	**0.009**

OR: Odd Ratio; CI: Confidence Interval; 1 (Model 1): Unadjusted model. Independent variable, separated models for each variable; 2 (Model 2): Adjusted on participant's clinical characteristics. Independent variable, separated models for each variable; 3 (Model 3): Adjusted on participant's clinical characteristics and all Cardiovascular Diseases and Risk Factors; *: Overweight defined as body mass index ≥ 25; †: Smoking: Defined as current or former for "What is your smoking status?"; ||: Diabetes: Defined as "Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?"; ¶: Hypertension: Defined as "Has a doctor ever told you that you have high blood pressure or hypertension?"; §: Heart Disease: Defined as "Has a doctor ever told you that you have heart disease (including congestive heart failure, or CHF)?"; #: Heart Attack: Defined as "Has a doctor ever told you that you have had a heart attack or myocardial infarction?"; **: Peripheral Vascular Disease: Defined as "Has a doctor ever told you that you have peripheral vascular disease or poor circulation in your limbs?"; ††: Angina: Defined as "Has a doctor ever told you that you have angina (or chest pain due to heart disease)?"; ‡‡‡: Stroke: Defined as "Has a doctor ever told you that you have experienced a Stroke or CVA? (cerebrovascular accident)?" and/or "Has a doctor ever told you that you have experienced a ministroke or TIA (Transient Ischemic Attack)?" and/or "Has a doctor ever told you that you suffer from the effects of a stroke, CVA (cerebrovascular accident), ministroke or TIA (Transient Ischemic Attack)?"; P-value significant (i.e., ≤0.05) in bold

Chapter 8 Discussion

The research question, population and conclusion of each of the four studies of this thesis have been summarized in table 1 (page 269) and confirmed that MCR (SCI and slow gait speed) is strongly associated with incident cognitive impairment but also with depressive symptoms and CVDRF. In contrast, MCR pathophysiology remains unclear. Study one, which is a systematic review and meta-analysis, found that MCR is associated with incident cognitive impairment. Study two, was completed to determine whether the FTSS could be used in lieu for the definition of MCR. The study found that FTSS is not a good substitute for walking speed, because when it is used in the definition of MCR it was not a good predictor of dementia or MCI. In study three, it was examined whether there is an association between MCR as well as depression and depressive symptomology. It was found that mood disorder, depression and cumulative depressive symptoms were associated with MCR, with some variation based on age groups. Lastly, study four examined whether there is an association between MCR and CVDRF in the Canadian population. Both CVD and CVRF were found to be associated with MCR, with some variation and strength of association based on age groups.

8.1 Motoric Cognitive Risk Syndrome and Incident Cognitive Impairment

A total of 11 studies were included in the systematic review and meta-analysis after applying the inclusion criteria for the first study, which set out to examine MCR's

predictive value of cognitive performance and incident cognitive impairment, as well as its physiopathology of MCR. The prevalence of MCR reported in the studies ranged from 6-18.2%. The results reported that MCR is indeed a better predictor of incidence of dementia than either SCI or slow walking speed. MCR was also found to be associated with cognitive impairment (with a pooled HR of 1.70, 95% CI, 1.46 - 1.98). All studies reported significant findings (with a HR ranging from 1.48 - 3.59).

MCR was also significantly associated with incidence of dementia (with a pooled HR of 2.50, 95% CI, 1.75 - 2.39). The association between MCR and incidence of dementia in individual studies varied greatly with five of the six studies reporting significant findings (with HR ranging from 1.79 - 3.18). Only one study, the Kurihara project, was not found to be significant for the same (with a HR of 1.50, 95% CI, 0.73 - 3.07). Mixed findings were reported for the association of MCR with cognitive performance, such as executive function, memory and global executive function.

8.2 Gait Speed Seems to be the Right Criteria to Define Motoric Cognitive Risk Syndrome

The second study, which set out to determine if a FTSS could be used in lieu of walking speed to further simplify MCR, found that overall FTSS was not a good substitute for walking speed, as, when used in terms of the definition of MCR, it was not found to be a

good predictor of dementia, nor MCI. Individuals identified when using the FTSS test for the definition of MCR differed greatly from the individuals identified when using walking speed. A significantly ($p \leq 0.001$) larger proportion of individuals (12%) were identified when using slow walking speed, as compared to FTSS (6.2%). Only 2.4% of individuals identified, overlapped between the groups.

8.3 Overlap between Motoric Cognitive Risk Syndrome and Mild Cognitive Impairment

The second study also set out to consider if using FTSS would capture the same participants as slow gait speed and how this would impact the overlap between MCI and MCR. It was found that the association of MCI with MCR differed based on whether walking speed or FTSS was used. Overall, MCI was found to be prevalent in individuals with MCR, as compared to individuals without MCR. The type of MCI, amnestic (a-MCI) and non-amnestic (na-MCI), also affected the association. The prevalence of a-MCI was higher in individuals with MCR defined by FTSS than in individuals with MCR defined by walking speed. Comparatively, the prevalence of na-MCI was higher in individuals with MCR defined by walking speed than in individuals with MCR defined by FTSS. These findings highlight that FTSS cannot be used in lieu of walking speed for the definition of MCR.

8.4 Motoric Cognitive Risk Syndrome and Depression: Interference

As both MCR and depression exhibit similar symptoms, study three set out to determine whether there is overlap between the same, and if the interaction is age dependent. This study was also the first to consider the prevalence of MCR in the Canadian population. The pooled prevalence of MCR was found to be 7% for all participants that were selected. Interestingly, a higher number of younger individuals met the criteria for MCR as compared to older adults, 8.9% and 6.8% as compared to 5.0% and 7.4% for age groups 45-54, 55-64, 65-74 and over 75, respectively. These results could be explained by the fact that this is the first-time younger age groups are being considered. Moreover, it must be noted that the criteria for MCR, slow walking speed and cognitive complaint can also be observed in individuals with depression. Thus, the younger individuals identified with MCR may in fact be depressed or exhibit some depressive symptoms. Future work on the same is required to better understand these results. Clinical depression and anxiety disorder individually were not found to be significantly associated with MCR in any age group or the total population. Comparatively, mood disorder, one depressive symptom or more, two depressive symptoms or more, three depressive symptoms and depression (CES-D) were all found to be positively associated with MCR.

Specifically, mood disorder was only significantly associated with MCR in the age group 55-64 (with an OR of 1.66, p=0.013) and in the total population (with an OR of 1.49,

p=0.001). Both one and more depressive symptoms and depression (CES-D) were associated with MCR in all age groups (with an OR ≥1.52, p≤0.003) and the total population (with an OR ≥3.65, p≤0.001). Two or more depressive symptoms were also significantly associated with MCR in the age groups 45-54 (with an OR of 1.79, p≤0.001), 55-64 (with an OR of 1.81, p≤0.001), 65-74 (with an OR of 1.55, p≤0.001) as well as the total population (with an OR of 1.68, p≤0.001). Three depressive symptoms were also significantly associated with MCR in the age groups 45-54 (with an OR of 2.28, p≤0.001), 55-64 (with an OR of 2.08, p≤0.001) as well as the total population (with an OR of 2.10, p≤0.001).

More young participants reported depression and depressive symptoms than their older counterparts. Furthermore, it was also reported that there is a higher prevalence of MCR in younger adults. Additionally, as discussed above regarding the similar expression of symptoms for both MCR and depression/depressive symptomology, MCR diagnosis in younger and older adults may be representative of different health conditions.

8.5 Motoric Cognitive Risk Syndrome and Cardiovascular Diseases and Risk Factors

The association between CVDRF and MCR which has been reported as significant in some studies and insignificant in others was studied in the Canadian population for the

first time in study four, it was found that individuals with MCR had a higher prevalence of CVD in age groups 45-54, 55-64 and 65-74. Similarly, individuals with MCR had a higher prevalence of CVRF in age groups 45-54 and 55-64. When considering all individuals, irrespective of MCR status, it was found that older individuals had a higher prevalence of CVD. The same was also true for CVRF, though this association was weaker than what was observed with CVD. One possible reason for this is that CVRF typically present prior to CVD and thus earlier at a younger age. Following which the CVRF lead to CVD as some individuals age, thus explaining the age-related trend with CVRF and CVD.

All CVDRF were more prevalent in individuals with MCR, except systolic blood pressure in the age group ≥75 as well as diastolic blood pressure in the age group 65-74 and ≥75. When no variables were adjusted for, an association for all CVRF and MCR was found, with some variation based on age groups. Diastolic blood pressure was the only variable found to be negatively associated with MCR in the older age groups, though a positive association was reported for the age group 55-64. More homogeneous findings were reported for CVD, which were (except rhythmic disease) found to be significantly associated with MCR.

After adjusting for participants' clinical characteristics and all CVDRF, no significant association was found for hypertension, heart disease/attack, rhythmic disease or systolic blood pressure with MCR. All other CVDRF (except diastolic blood pressure)

were found to have a significant positive association with MCR for some or all age groups. In Model 3, a negative association between diastolic blood pressure and MCR was still reported, this time for age groups 65-74, ≥75 and the total population. The findings confirmed that, overall, there is an association between CVDRF and MCR in the Canadian population. Further work is needed to replicate these findings in a longitudinal study and to address other limitations of this manuscript as outlined below in the limitations section.

8.6 Limitations

The four studies of this thesis had various strengths. The strengths of study one includes that articles were searched for in two large databases, strict exclusion criteria were followed and two authors independently underwent the process of screening manuscripts. Study two's strengths include the completion of standardized clinical examination as well as a comprehensive neuropsychological assessment. Studies three and four, which utilized the CLSA had strengths such as a large number of participants, participants with varied ages, in depth data collection, detailed questionnaires and imaging.

However, the studies also had a few limitations that must be addressed. In manuscript one, it must be noted that as MCR is a relatively newly defined syndrome, it had a

limited number of published manuscripts. Secondly, there was variation in the variables considered, follow up period and statistical analysis performed, making it more difficult to compare their overall findings and conclusions. Moreover, the criteria used to identify individuals with MCR also differed based on manuscripts as different variables were used for the SCI and slow walking speed components. Lastly, the studies were typically focused on higher income countries, with a lack of representation of lower income countries.

The second manuscript also had a few limitations that must be considered. Firstly, individuals who used a mobility device were not included in the database. Secondly, individuals were recruited from a single site. Thirdly, all individuals recruited were patients of a memory clinic, thus all participants had memory concerns, which provides no cognitively healthy comparison group. Fourth, all individuals recruited in the GAIT study were proficient in French, thus individuals not proficient in French were excluded.

Studies 3 and 4 both used data from the CLSA. Studies 3 and 4 both have some limitations that must be considered. The participants that were recruited by the CLSA were limited to ages 45-85 (at the time of the first data collection), thus missing the chance to incorporate the important age category considered “old-old” (i.e. individuals age>85). Individuals living on Indigenous reserves were also excluded, thus, failing to provide a comparison and insight to how a large component of Indigenous individuals age. Moreover, individuals included in the CLSA had to be proficient in English or

French, as Canada is a very diverse country with immigrants from many countries. This excludes the important category of older individuals who may be immigrants and not proficient in English or French.

A general limitation that must be considered is that as pre-collected databases were used, the variables and research questions are not specific to our study. The same can be observed with the CES-D, which is a general depression scale. This was used instead of a scale specific to the geriatric population. Moreover, the results above must be replicated with a longitudinal design as the current cross-sectional design does not allow casual associations to be made. This can be addressed in the future by using the follow up data from the CLSA, once released. Lastly, though the databases and the authors of the manuscripts have attempted to be exhaustive in considering possible confounding variables it is possible that some confounders were missed.

8.7 Conclusions

In conclusion, the systematic review reported that MCR does indeed successfully predict dementia and cognitive impairment, though further research is needed on its pathophysiology. Moreover, slow walking speed was identified to be a better component of MCR than time to complete FTSS. MCR is reported to be a predictor of dementia or an indicator of depression/depressive symptomology in older adults, whereas, it is only

an indicator of depression/depressive symptomology in younger adults. Lastly, MCR was found to be associated with CVDRF in the Canadian population, with some variation regarding the strength of association based on age.

8.8 Future Perspectives

Future steps should include the replication of these studies in diverse populations globally and within Canada. The latter is especially important as the Canadian population is very diverse and certain sub-populations in Canada may be at more risk of dementia due to increased risk factors (e.g. Indigenous population, due to higher smoking rates). Moreover, further emphasis on the association of MCR with other co-morbidities must be examined. As pre-collected datasets were used for these studies with pre-determined questionnaires and data collection tools, these findings must be replicated. Furthermore, information on the pathophysiology of MCR must be studied. Pilot studies on the inclusion of MCR in clinical practice must be conducted to truly determine its feasibility and wide scale applicability.

Table 1. Summary of research question, population and conclusion of the four studies of this thesis

Study	Research Question	Population	Conclusion
Motoric cognitive risk syndrome, incident cognitive impairment and brain structures abnormalities: Systematic review and meta-analysis	Is MCR associated with incident cognitive impairment, cognitive performance and brain structures?	- US population in 4 studies - Japanese population in 2 studies - Irish population in 1 study - Indian population in 2 studies - French population in 2 studies	- MCR predicts cognitive impairment including dementia, - It is associated with both low brain gray matter volume and lacunar lesions
Motoric cognitive risk syndrome: Could increased five-times-sit-to-stand test time be used instead of slow walking speed for the definition?	Could FTSS be used instead of slow walking speed for the definition of MCR?	- Participants from the French data base "Gait and Alzheimer Interactions Tracking" study	- FTSS cannot replace slow walking speed in the definition of MCR - MCR defined with FTSS is not associated with MCI status compared to

			MCR defined by slow walking speed
The Association of Depression with Motoric Cognitive Risk Syndrome: Results from the Canadian Longitudinal Study on Aging	Is MCR associated with depression and depressive symptomologies in the Canadian population?	- Participants from the Canadian database, the "Canadian Longitudinal Study on Aging"	- MCR diagnosed in younger adults may in fact be an identification of individuals with depression or depressive symptomology - Comparatively, MCR diagnosis in older adults may be an indication of either/both depression or a pre-dementia stage
The Association of Motoric Cognitive Risk Syndrome with Cardiovascular Diseases and Risk factors: Results from the Canadian	Is MCR associated with cardiovascular disease and risk factors in the Canadian population?	- Participants from the Canadian database, the "Canadian Longitudinal Study on Aging"	- MCR is associated with CVDRF in the Canadian population. - CVRF factors are more strongly associated in younger adults - Comparatively, CVD are more strongly

Longitudinal Study on Aging			associated in older adults