 doi:10.20944/preprints202204.0134.v1

Article

Motoric Cognitive Risk Syndrome, Subtypes and 8-year all-cause Mortality in Aging Phenotypes: The Salus in Apulia Study

Ilaria Bortone[1]*, Roberta Zupo[1], Fabio Castellana[1], Simona Aresta[1], Luisa Lampignano[1], Sabrina Sciarra[1], Chiara Griseta[1], Tommaso Antonio Stallone[2], Giancarlo Sborgia[3], Madia Lozupone[4], Francesco Panza[4], Gianvito Lagravinese[5], Petronilla Battista[5,6] and Rodolfo Sardone[1]

1 Unit of Research Methodology and Data Sciences for Population Health, National Institute of Gastroenterology "Saverio de Bellis," Research Hospital, Castellana Grotte, Bari, Italy
2 General Direction, National Institute of Gastroenterology "Saverio de Bellis," Research Hospital, Castellana Grotte, Bari, Italy
3 Eye Clinic, Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari, Bari, Italy
4 Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy
5 ICS Maugeri, Istituto Maugeri IRCCS Bari, Bari, Italy
6 Global Brain Health Institute, University of California, San Francisco, USA Affiliation 1; e-mail@e-mail.com
* Correspondence: ilariabortone@gmail.com

Abstract: Background: This study aims to set out key clinical features of different Motoric Cognitive Risk (MCR) subtypes based on individual quantitative measures of cognitive impairment and to compare their predictive power on survival over an 8-year observation time. **Methods:** We analyzed data from a population-based study of 1138 subjects aged 65 years and older in south Italy. These individuals were targeted and allocated to subtypes of the MCR phenotype according to the slowness criterion plus one other different cognitive domain for each characterized phenotype. Clinical evaluation and laboratory assays, along with a comprehensive battery of neuropsychological and physical tests, completed the sample investigation. **Results:** MCR prevalence was found to be 9.8% (N=112), 3.6% (N=41), 3.4% (N=39), and 1.8% (N=21) for the MCR, MCR-GlobalFunction, MCR-StructuredSCC, and MCR-SCC&GlobalFunction, respectively. Univariate Cox survival analysis showed an association only of the MCR-GlobalFunction subtype with a significant, 1.5-fold increased risk of overall death as compared to the other counterparts (HR 2.53, 95%CI 1.28 to 4.99, P-value<0.01) over an 8-year observation period, even after major adjustment (HR 2.02, 95%CI 1.02 to 4.02). **Conclusions:** MCR phenotypes assigned to the MMSE cognitive domain are more likely to have an increased risk of overall mortality, 1.5-fold higher than counterparts, over 8-year observation.

Keywords: frailty; older people; cognitive impairment; assessment; gait

1. Introduction

Motoric cognitive risk (MCR) syndrome is characterized by cognitive complaints and slow gait speed in the absence of dementia [1]. The inherent value of this syndromic pattern as a further clinical tool to promptly and better organize therapeutic targets in aging has led to a growing scientific interest in MCR syndrome [2]. From the preventive perspective, approaching the best MCR phenotype in terms of the associated risk of adverse outcomes is critical. Employing the construct proposed by Verghese and colleagues in 2013 [3,4], we recently derived a prevalence of MCR of 9.9% in our southern Italian elderly population, surveying a combination of physical exhaustion, low muscle strength, and physical activity [5].

Since MCR is a relatively new pre-dementia syndrome relying on cumulative multi-facet constructs, the natural history of MCR has not been well characterized, and further longitudinal studies are needed to assess the causal direction, without which it would be considered simply a predictor of probable cognitive impairment [6]. To our knowledge, only a few longitudinal surveys of MCR have been conducted, and only two reports explored the association between MCR syndrome and mortality [7,8]. Ayers and colleagues showed that MCR syndrome was associated with a 70% increased risk of mortality in over 11,000 older adults aged 65 years from three established cohort studies based in 12 countries in the United States and Europe. Furthermore, they found that MCR predicted death over the first 2 years of follow-up, a clinically relevant time interval for clinicians assessing patients. [7]. Subsequently, Beauchet and colleagues confirmed the association of MCR with an increased risk for mortality, although no significant association of MCR and its individual components with the occurrence of death during the first 5 years of the EPIDOS follow-up was reported [8]. However, the authors did not find any association between SCC and incident mortality, suggesting that this stage of SCC without cognitive impairment may be too early in the course of dementia to be associated with an increased risk for mortality while slow walking speed may be an early marker of global deterioration of health as reported with frailty in older adults [8,9].

With this evidence, we hypothesized that MCR subtypes, based on different cognitive subdomains (general cognitive function, subjective cognitive complaint, memory impairment), could be differentially associated with specific cognitive domains. We then aimed at investigating MCR and its different phenotypic subtypes as a predictor for overall mortality in the "Salus in Apulia Study" population over an 8-year observation period.

2. Materials and Methods

2.1. Study Population

Participants of the present study were recruited from the electoral rolls of Castellana Grotte, Bari, Southern Italy. The sampling framework was the health registry office list on December 31, 2014, which included 19,675 subjects, 4021 of which were aged 65 years or older. All subjects had been enrolled included in the "Salus in Apulia Study," a public health initiative funded by the Italian Ministry of Health and Apulia Regional Government and conducted at IRCCS "S. De Bellis" Research Hospital. The study focused on lifestyle factors including physical activity [10], diet [11], and age-related sensory impairments [12,13] or frailty phenotypes [14]. For this analysis we used data on a subpopulation of the Salus in Apulia Study, numbering 1657 older subjects who had undergone all the assessments. All participants provided written informed consent to enrollment in the study. The Institutional Review Board of IRCCS "S. De Bellis" Institute approved the "Salus in Apulia Study" with its measurements and data collections before the study started, in accordance with the Helsinki Declaration of 1975.

2.2. Neuropsychological assessment

The present study administered a comprehensive neuropsychological assessment consisting of standardized test batteries to assess specific cognitive domains: verbal memory, assessed by the immediate or delayed recall of a list of words from the Rey Auditory-Verbal Learning Test (RAVLT) [15]; subjective memory impairments, assessed using the Memory Assessment Clinic-Q (MAC-Q) score [16]; processing speed, as assessed with the Trail Making Test, structured in parts A and B (TMT-A and TMT-B)[17]: part A requires subjects to connect a series of consecutively numbered circles and thus involves visual scanning, number recognition, number sequence, and motor speed,

 doi:10.20944/preprints202204.0134.v1

while part B requires subjects to connect a series of numbered and lettered circles, alternating between the two sequences; and executive function, set using the Clock Drawing Test (CDT) [18], which focuses on visual-spatial and planning skills.

2.3. Motor Cognitive Risk Syndrome Subtypes

We considered MCR if subjects were dementia-free, had preserved activities of daily living (ADLs), but reported cognitive complaints, and exhibited slow gait speed [1]. Cognitive complaints were coded as present if there was a positive response to item GDS-30 (SCC, Subjective Cognitive Complaint): "Do you feel you have more problems with memory than most?" [19]. Slowness was evaluated using a 5-m walking test, assuming a cut-off point of 0.6 m/s [5].

MCR subtypes were identified by replacing the cognitive complaint criterion with:

MCR-GlobalFunction: the Mini-Mental State Examination (MMSE) with a cut-off of 24 for identifying impairment in cognitive function [20];

MCR-StructuredSCC: Cognitive Complaints in Age Questionnaire (MAC-Q) scoring equal to or greater than 25 to assess subjective memory impairments [16];

MCR-SCC&GlobalFunction: the co-occurrence of both SCC and MMSE.

2.4. Mortality

The mortality data were obtained from the Electronic Health Records (EHRs) of the Regione Puglia.

2.5. Clinical and laboratory assessment

All information was collected based on surveys, including on-site interviews and health examinations. For each participant, we assessed education level, living conditions, and smoking status [14]. Education was defined by years of schooling. Smoking status was assessed with the single categorical question "Are you a current smoker?" (yes/no). Height and weight measurements were performed by registered dietitians under the supervision of a senior nutritionist (RZ) using a Seca 220 stadiometer and a Seca 711 scale. Body mass index (BMI) was calculated as kg/m2. Serum high-sensitivity C-reactive protein (CRP) was assayed using a latex particle-enhanced immunoturbidimetric assay (Kamiya Biomedical Company, Seattle, WA) (reference range: 0–5.5 mg/L; interassay coefficient of variation: 4.5%). Serum IL-6 and tumour growth factor-α (TNF-α) were assayed using the quantitative sandwich enzyme technique ELISA (QuantiKine High Sensitivity Kit, R&D Systems, Minneapolis, MN and QuantiGlo immunoassay from R&D Systems, Minneapolis, MN). Interassay coefficients of variation were 11.7% for IL-6 and 13.0% for TNFα. Inflammatory marker assays were analyzed at the same laboratory following strict quality control procedures.

2.6. Statistical Analysis

The normal distribution of variables for each group was tested using Shapiro's test. The Participant characteristics were reported as mean ± Standard Deviation (SD) for continuous variables to ensure better comparability with similar studies, and frequencies and percentages for categorical variables. Differences in prevalence exposure groups (MCR subtypes) and other categorical variables and their means and SDs (otherwise expressed as % for proportions) were computed as summarized in Table 1, then used to assess important practical differences in the magnitude of association, i.e., effect size (ES) [21].

 doi:10.20944/preprints202204.0134.v1

Individual descriptive supplementary tables according to the different MCR phenotypic subtypes (presence/absence) and their differences are reported in detail as Supplementary material.

Differences in continuous variables were computed using Cohen's d difference between the means and Glass's delta when the assumption of similar variance was violated, with their ES and confidence intervals.

Multivariable nested Cox models were run to estimate the hazard ratio (HR) of death for the main variables (MCR and its subtypes), adjusted for covariates assumed to have a confounding effect. The Cox proportional hazards model was fitted to the data, and the proportional hazards hypothesis was assessed by means of Schoenfeld residuals (SRT). All model fits were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). Risk estimators were expressed as HR and 95% CI. Multicollinearity of the models was assessed by a variance inflation factor (VIF), using a score of 2 as the cut-off for exclusion. Major confounding factors, such as age, gender, BMI, and education for Cox models, were implemented in the adjusted model, selected from those assumed to be related to exposure (MCR and Subtypes) and to overall mortality (outcomes). In addition, to assess separately the effect of gender on the outcome, Generalized Estimating Equations (GEE) for clustered survival data were implemented, considering gender as the cluster level. In those models the standard errors were adjusted for the variance of the cluster variable, allowing for different variances in the cluster and in the other variables.

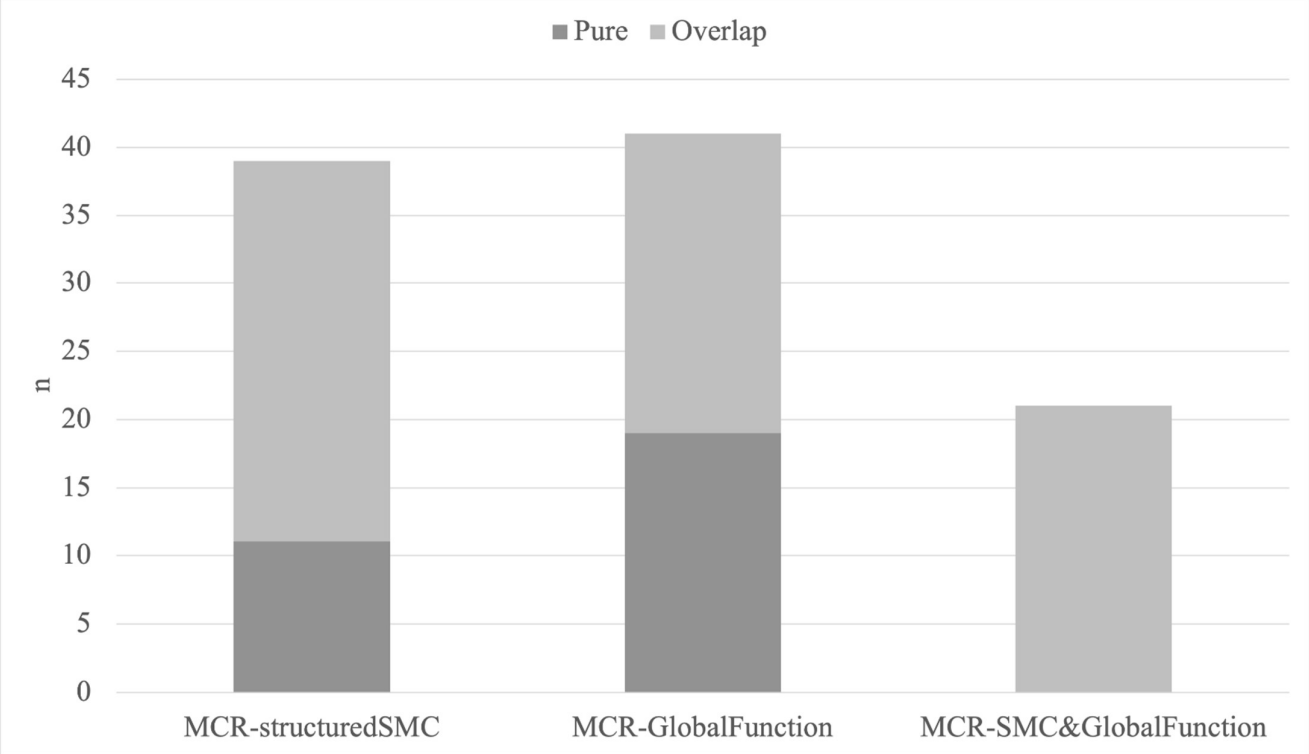
The methodological approach and analyses were designed and operated by a senior epidemiologist (RS) and biostatistician (FC), using RStudio software, version 1.2.5042. R Packages: tidyverse, gmodels, kableExtra, rstatix, effsize, EpiR, car, survival, survaminer.

3. Results

From the original Salus in Apulia aging cohort, 1657 participants underwent comprehensive neuropsychological and physical assessments. A total of 434 participants were then excluded due to a diagnosis of dementia (26.20%), and 85 participants were excluded due to their inability to walk (5.5%). At baseline, the mean age of the 1138 participants was 74.51 ± 6.11 years (age range 65 to 96 years), 51.5% were female and mean education was 7.11 ± 3.76 years. The MCR prevalence was found to be 9.8% (N = 112) for MCR, 3.6% (N = 41) for MCR-GlobalFunction, 3.4% (N = 39) for MCR-StructuredSCC, and 1.8% (N = 21) for MCR-SCC&GlobalFunction. As MCR subtypes were not mutually exclusive, 30 participants (2,7%) met the criteria for any one of the three MCR subtypes, and among them, 22 participants (2%) met criteria for more than one MCR subtype. Overlap between MCR subtypes was illustrated in Figure 1.

Figure 1. Overlap between MCR subtypes

 doi:10.20944/preprints202204.0134.v1



Clinical features of each MCR subtype are presented in Table 1, and demographic data for their non-MCR counterparts are provided in Supplemental Material (Stable1). Descriptive analyses showed that MCR and its phenotypic subtypes shared older age and lower educational levels than their non-MCR counterparts. Meaningful differences were observed for smoking habits for MCR-StructuredSMC and MCR with general cognitive function component. Only the MRC subtype referred to general cognitive function showed higher BMI than the non-MCR counterpart. Regarding fluid inflammatory biomarkers, higher serum IL-6 levels were found for subjects allocated to the MCR phenotype than their counterparts, with a medium effect size for the MRC subtype with general cognitive function.

Table 1. Clinical Characteristics of MCR Subtypes * (N: 1138).

	MCR	MCR Global Function	MCR Structured SCC	MCR SCC & Global Function
Proportions (%)	112 (9.80)	41 (3.60)	39 (3.40)	21 (1.80)
Age (*years*)	75.57 ± 6.16 ↟	77.83 ± 5.97 ↟	77.85 ± 6.12 ↟	76.57 ± 4.71
Gender				
Male	48 (42.90)	16 (39.00)	17 (43.60)	9 (42.90)
Female	64 (57.10)	25 (61.00)	22 (56.40)	12 (57.10)
BMI (Kg/m²)	28.95 ± 5.22	30.43 ± 5.66	29.86 ± 5.56	29.15 ± 6.32
Education (years)	6.29 ± 4.05 ↟	4.02 ± 2.44 ↟	6.97 ± 4.69	3.67 ± 2.31 ↟
Smokers	7 (6.20)	1 (2.4)	1 (2.60)	--
Interleukin 6	4.58 ± 6.36 ↟	7.29 ± 9.99	4.47 ± 7.26	7.95 ± 10.75
TNF-alpha	3.08 ± 4.58	3.42 ± 3.46	2.64 ± 1.85	2.82 ± 1.07

 doi:10.20944/preprints202204.0134.v1

CRP	0.64 ± 0.71	0.54 ± 0.59	0.75 ± 0.69	0.62 ± 0.73
Time of observation (*months*)	63.56 ± 21.53	53.66 ± 22.53	62.38 ± 22.15	55.76 ± 23
Survival mean time (*months*)	83.40 ± 8.35	77.20 ± 13.32	80.20 ± 10.94	78.50 ± 7.87

** MCR subtypes are not mutually exclusive. Significant differences are reported as compared to the respective no MCR group.*

BMI: Body Mass Index; TNF-alpha: Tumour Necrosis Factor alpha; CRP: C Reactive Protein

In Table 2 we reported the comparison of MCR and its subtypes in terms of both neuropsychological and physical assessments. General cognitive function (MMSE) was significantly lower in MCR and its subtypes with respect to non-MCR groups, except for the MCR phenotype referred to as structured SCC. However, both the original construct of MCR and MCR-StructuredSCC showed similar scores. Nor immediate or delayed recall variables (RAVLTi and RAVLTd, respectively) used to estimate verbal memory showed significant differences between MCR and MCR-StructuredSCC phenotypes and their counterparts. However, MCR constructs with global cognitive function showed lower scores in both immediate and delayed RAVLT. Also, executive function, focused on visuospatial and planning skills, and assessed by the CDT, showed markedly poorer ratings in all MCR phenotypes than their counterparts: larger effect sizes were observed again for MCR with global cognitive function in the construct (ES 0.81, 95%CI 0.49 to 1.12; ES 1.20, 95%CI 0.76 to 1.63). On processing speed, as assessed by TMT and structured in parts A and B (TMT-A and TMT-B), a significantly longer time taken to complete tasks was noted in all MCR types compared to non-MCR counterparts in terms of prevalence difference.

Table 2. Cognitive and Physical Profiles of MCR Subtypes (N: 1138).

	MCR	MCR Global Function	MCR Structured SCC	MCR SCC & Global Function
MMSE	26.42 ± 2.98	21.81 ± 1.51	26.49 ± 2.86	21.49 ± 1.56
RAVLTi	35.0 ± 8.60	29.05 ± 6.46	33.21 ± 7.83	26.89 ± 6.24
RAVLTd	6.68 ± 2.55	5.44 ± 3.07	6.3 ± 2.62	4.84 ± 2.52
CDT	9.96 ± 2.87	8.02 ± 3.35	9.61 ± 3.01	7.43 ± 3.12
MAC-Q	22.8 ± 2.15	22.41 ± 2.05	26.08 ± 1.35	23.19 ± 2.4
SCC (*impaired*)	112 (100.00)	21 (52.10)	27 (69.20)	21 (100.00)
TMT-A	99.20 ± 54.20	138.29 ± 68.17	104.59 ± 51.33	146.48 ± 52.75
TMT-B	200 ± 111.00	241.85 ± 105.36	195.79 ± 107.18	260.48 ± 114.63
Slowness (*impaired*)	112 (100.00)	41 (100.00)	39 (100.00)	21 (100.00)

** MCR subtypes are not mutually exclusive. Significant differences are reported as compared to the respective no MCR group.*

MMSE: Mini Mental Statement Examination; RAVLT: Rey Auditory Verbal Learning Test (i, immediate; d, delayed); CDT: Clock Drawing Test; MAC-Q: Memory Assessment Clinic-Q; SCC: Subjective Cognitive Complaint; TMT: Trail Making Test

 doi:10.20944/preprints202204.0134.v1

Table 3 shows multivariable Cox survival analysis for each of the four MCR phenotypes. The MCR-GlobalFunction subtype was found to be associated with a 1.5-fold increased risk of overall death compared with its counterpart (HR 2.53, 95%CI 1.28 to 4.99, P-value < 0.01) over an 8-year observation time. However, the same was not shown for MCR and the other subtypes (HR 1.51, 95%CI 0.91 to 2.49, and HR 1.94, 95%CI 0.94 to 3.97, and HR 2.02, 95%CI 0.74 to 5.48, for MCR, MCR-StructuredSCC, and MCR-SCC&GlobalFunction, respectively). Then, we performed further analyses on the MCR-GlobalFunction subtype by adjusting for the main confounders, i.e., age and gender, and found that significance on 8-year survival was kept (HR 2.02, 95%CI 1.02 to 4.02).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 April 2022 doi:10.20944/preprints202204.0134.v1

Table 3. Results Cox Regression Models for each type of MCR.

	MCR						MCR Global Function					
	Raw			*corrected*			*Raw*			*corrected*		
	HR	*CI 95%*	*s.e*	*HR*	*CI 95%*	*s.e.*	*HR*	*CI 95%*	*s.e.*	*HR*	*CI 95%*	*s.e.*
Type of MCR	1.51	0.91 to 2.49	0.25	1.63	0.60 to 4.45	0.51	2.53	1.28 to 4.99	0.34	1.71	0.84 to 3.48	0.36
Age (years)	--	--		1.11	1.08 to 1.14	0.01	--	--	--	1.10	1.07 to 1.13	0.01
Gender (Female)	--	--		0.35	0.23 to 0.54	0.20	--	--	--	0.35	0.23 to 0.53	0.20
BMI (Kg/m^2)	--	--		1.01	0.97 to 1.05	0.01	--	--	--	1.01	0.97 to 1.04	0.01
	MCR Structured SCC									MCR SCC & Global Function		
	Raw			*corrected*			*Raw*			*corrected*		
	HR	*CI 95%*	*s.e.*	*HR*	*CI 95%*	*s.e.*	*HR*	*CI 95%*	*s.e.*	*HR*	*CI 95%*	*s.e.*
Type of MCR	1.94	0.94 to 3.97	0.36	1.42	0.69 to 2.93	0.36	2.02	0.74 to 5.48	0.50	1.65	0.60 to 4.45	0.51
Age (years)	--	--	--	1.10	1.07 to 1.14	0.01	--	--	--	1.11	1.08 to 1.14	0.01
Gender (Female)	--	--	--	0.34	0.23 to 0.53	0.20	--	--	--	0.35	0.23 to 0.54	0.20
BMI (Kg/m^2)	--	--	--	1.01	0.97 to 1.05	0.01	--	--	--	1.01	0.97 to 1.05	0.01

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 April 2022 doi:10.20944/preprints202204.0134.v1

Since gender seems to be the most important effect modifier of the relation between MCR phenotype and mortality, we used Generalized estimating equations (GEE) for clustered survival data, using gender as cluster level (Table 4). In those models the standard errors were adjusted for the variance of the cluster variable, allowing for different variances in the cluster and in the other variables. Using GEE, the global effect of each adjusted model showed an important decrease in terms of HR, CI, and SE, demonstrating that gender was a fundamental term in the association between MCRs and mortality.

Table 4. Generalized estimating equations for clustered survival data on MCR.

	MCR						MCR Global Function					
	Raw			*Adjusted*			*Raw*			*Adjusted*		
	HR	*CI 95%*	*Robust s.e*	*HR*	*CI 95%*	*Robust s.e.*	*HR*	*CI 95%*	*Robust s.e.*	*HR*	*CI 95%*	*Robust s.e.*
Type of MCR	1.51	1.30 to 1.75	0.07	1.38	1.12 to 1.69	0.1	2.53	2.52 to 2.53	0.01	1.68	1.64 to 1.73	0.01
Age (years)				1.11	1.09 to 1.13	0.01				1.11	1.08 to 1.13	0.01
BMI (Kg/m²)				1.01	0.96 to 1.05	0.02				1.01	0.96 to 1.05	0.02
	MCR Structured SCC						MCR SCC & Global Function					
	Raw			*Adjusted*			*Raw*			*Adjusted*		
	HR	*CI 95%*	*Robust s.e.*	*HR*	*CI 95%*	*Robust s.e.*	*HR*	*CI 95%*	*Robust s.e.*	*HR*	*CI 95%*	*s.e.*
Type of MCR	1.93	1.06 to 1.83	0.36	1.94	1.60 to 2.35	0.09	2.02	1.82 to 2.25	0.05	1.63	1.45 to 1.83	0.06
Age (years)				1.11	1.09 to 1.13	0.01				1.11	1.09 to 1.13	0.01
BMI (Kg/m²)				1.01	0.97 to 1.05	0.01				1.01	0.96 to1.05	0.02

4. Discussion

The present study probed different MCR subtypes to investigate the association of each with mortality in a large sample of non-demented older subjects from Southern Italy. The major finding of this study was that MCR is an important predictor for the risk of mortality, even when adjusted for age and BMI and clustered by gender, which is the most important effect modifier in the association.

Along with the MCR phenotype, that used subjective cognitive complaints as the cognitive domain, we explored three other subtypes by replacing the cognitive domain with global cognitive function, as measured by the MMSE, or the structured SCC, i.e., MACQ, or by using the coexistence of these two, but without ever replacing the functional criterion of slow gait.

On a descriptive level, all four MCR phenotypic subtypes shared older age and lower levels of education than their non-MCR counterparts. Consistency in the evidence that additional years of education are associated with higher cognitive outcomes and a slower cognitive decline in the adult population adds confidence to the internal validity of our data [22]. Further analysis of a battery of cognitive tests indicated significantly worse scores for executive function focused on visuospatial and planning skills, only when subjective cognitive complaints were used as the cognitive domain of the MCR phenotype.

Since deficit accumulation algorithms are a good way to simplify screening in clinical settings and improve the understanding of risk trajectories, we chose to span different phenotypic constructs of MCR, to see which operated best in predicting mortality risk. Our findings indicated that assuming the same physical domain, namely slow gait, a cognitive domain represented by the MMSE score worked much better than others. Furthermore, this holds good even after correcting for major effect confounders like age and gender. In previous investigations, Allali and colleagues found that MCR syndrome was associated with a 70% increased risk of mortality over a period of 5 years in over 11,000 older adults from three large cohorts studies [7]. However, the authors also reported that MCR did not significantly predict death in those participants who were diagnosed with dementia at or before death. No significant association of MCR and its individual components with the occurrence of death was also reported during the first 5 years of the EPIDOS follow-up [8]; however, slow walking speed and MCR were associated with an increased risk for mortality at medium and long terms with the same magnitude, whereas no association was found with SCC, suggesting that slow walking speed may be the early marker of global deterioration of health as reported with frailty in older adults [8,9].

In our study, we found no association between the original MCR construct and mortality. One explanation could be the fact that hat this stage of SCC without cognitive impairment may be too early in the course of dementia to be associated with an increased risk for mortality. In fact, when introducing more structured components of the cognitive domain, such as MMSE, the relationship between MCR and mortality is then consistent with previous results found on the increased risk of mortality in an older individual with cognitive frailty, which associates physical frailty and cognitive impairment in individuals free of dementia [14,23]. Furthermore, decreased cognitive function is associated with an increased risk of transitioning to dementia, and therefore, associated with

mortality [23,24]. As a result, predementia syndromes may raise mortality risk by contributing to geriatric syndromes with high death rates in aging.

Some potential limitations need to be considered when interpreting our findings. Firstly, mortality was not attributed to any specific disease, and thus we could not analyze associations with cause-specific death. The strengths of this study included its long-term prospective observation time (84 months of follow-up), the large population-based sample size, and the generalizability of the results to southern Mediterranean populations. Further study of risk factors, as well as fall mechanisms in MCR, are needed to improve our understanding of this geriatric syndrome, as well as to guide future interventions [25].**5.**

Conclusions

Defining different subtypes of MCR using alternate quantitative cognitive parameters may provide new insights into preclinical markers of dementia and help improve the identification of patients at high risk for dementia. To our knowledge, this is the first study to analyze several constructs of the MCR predementia syndrome combining gait with other cognitive domain features. In our sample, MCR phenotypes allocated via the MMSE cognitive domain approached an increased risk of overall mortality over 8 years of observation. These findings provide further support for the usefulness of MCR as a clinical assessment tool and its better phenotyping as a risk management utility. Moreover, this tool is also inexpensive, efficient, and easily applicable in clinical settings worldwide to identify adults at high risk for dementia and death. Further studies across different populations are needed to strengthen our data.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Conceptualization, I.B., P.B., F.P. and R.S.; methodology, R.S.; formal analysis, F.C. and I.B.; investigation, R.Z., A.A., L.L., M.L., G.S., G.L., C.G., S.S.; data curation, X.X.; writing—original draft preparation, I.B; writing—review and editing, R.S. and P.B.; visualization, I.B..; supervision, R.S., P.B., and F.P.; project administration, R.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the Italian Ministry of Health, under the Aging Network of Italian Research Hospitals.

Institutional Review Board Statement: The Institutional Review Board of IRCCS "S. De Bellis" Institute approved the "Salus in Apulia Study" with its measurements and data collections before the study started, in accordance with the Helsinki Declaration of 1975. (Approval Code: 68/CE De Bellis; Approval Date: April 9, 2019)

Informed Consent Statement: All participants provided written informed consent to enrollment in the study.

Data Availability Statement: Data are available on request from the corresponding author.

Acknowledgements: We thank the "Salus in Apulia" Research Team. This manuscript is the result of the research work on frailty undertaken by the "Italia Longeva: Research Network on Aging" team, supported by the resources of the Italian Ministry of Health—Research Networks of National

Health Institutes. We thank the General Practitioners of Castellana Grotte, for their fundamental role in the recruitment of participants to these studies: Cecilia Olga Maria Campanella, Annamaria Daddabbo, Giosuè Dell'aera, Rosalia Francesca Giustiniano, Massimo Guzzoni Iudice, Savino Lomuscio, Rocco Lucarelli, Antonio Mazzarisi, Mariana Palumbo, Maria Teresa Persio, Rosa Vincenza Pesce, Gabriella Puzzovivo, Pasqua Maria Romano, Cinzia Sgobba, Francesco Simeone, Paola Tartaglia, and Nicola Tauro

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Verghese, J.; Wang, C.; Lipton, R.B.; Holtzer, R. Motoric Cognitive Risk Syndrome and the Risk of Dementia. J. Gerontol. A Biol. Sci. Med. Sci. 2013, 68, 412–418, doi:10.1093/gerona/gls191.
2. Sekhon, H.; Allali, G.; Launay, C.P.; Barden, J.; Szturm, T.; Liu-Ambrose, T.; Chester, V.L.; Wong, C.H.; Beauchet, O.; Canadian Gait Consortium Motoric Cognitive Risk Syndrome, Incident Cognitive Impairment and Morphological Brain Abnormalities: Systematic Review and Meta-Analysis. Maturitas 2019, 123, 45–54, doi:10.1016/j.maturitas.2019.02.006.
3. Maggio, M.; Lauretani, F. Prevalence, Incidence, and Clinical Impact of Cognitive-Motoric Risk Syndrome in Europe, USA, and Japan: Facts and Numbers Update 2019. J. Cachexia Sarcopenia Muscle 2019, 10, 953–955, doi:10.1002/jcsm.12476.
4. Verghese, J.; Annweiler, C.; Ayers, E.; Barzilai, N.; Beauchet, O.; Bennett, D.A.; Bridenbaugh, S.A.; Buchman, A.S.; Callisaya, M.L.; Camicioli, R.; et al. Motoric Cognitive Risk Syndrome: Multicountry Prevalence and Dementia Risk. Neurology 2014, 83, 718–726, doi:10.1212/WNL.0000000000000717.
5. Bortone, I.; Griseta, C.; Battista, P.; Castellana, F.; Lampignano, L.; Zupo, R.; Sborgia, G.; Lozupone, M.; Moretti, B.; Giannelli, G.; et al. Physical and Cognitive Profiles in Motoric Cognitive Risk Syndrome in an Older Population from Southern Italy. Eur. J. Neurol. 2021, 28, 2565–2573, doi:10.1111/ene.14882.
6. Semba, R.D.; Tian, Q.; Carlson, M.C.; Xue, Q.-L.; Ferrucci, L. Motoric Cognitive Risk Syndrome: Integration of Two Early Harbingers of Dementia in Older Adults. Ageing Res. Rev. 2020, 58, 101022, doi:10.1016/j.arr.2020.101022.
7. Ayers, E.; Verghese, J. Motoric Cognitive Risk Syndrome and Risk of Mortality in Older Adults. Alzheimers. Dement. 2016, 12, 556–564, doi:10.1016/j.jalz.2015.08.167.
8. Beauchet, O.; Sekhon, H.; Launay, C.P.; Chabot, J.; Rolland, Y.; Schott, A.-M.; Allali, G. Motoric Cognitive Risk Syndrome and Mortality: Results from the EPIDOS Cohort. Eur. J. Neurol. 2019, 26, 794–e56, doi:10.1111/ene.13891.
9. Bortone, I.; Sardone, R.; Lampignano, L.; Castellana, F.; Zupo, R.; Lozupone, M.; Moretti, B.; Giannelli, G.; Panza, F. How Gait Influences Frailty Models and Health-Related Outcomes in Clinical-Based and Population-Based Studies: A Systematic Review. J. Cachexia Sarcopenia Muscle 2021, 12, 274–297, doi:10.1002/jcsm.12667.
10. Bortone, I.; Castellana, F.; Lampignano, L.; Zupo, R.; Moretti, B.; Giannelli, G.; Panza, F.; Sardone, R. Activity Energy Expenditure Predicts Clinical Average Levels of Physical Activity in Older Population: Results from Salus in Apulia Study. Sensors 2020, 20, doi:10.3390/s20164585.
11. Zupo, R.; Sardone, R.; Donghia, R.; Castellana, F.; Lampignano, L.; Bortone, I.; Misciagna, G.; De Pergola, G.; Panza, F.; Lozupone, M.; et al. Traditional Dietary Patterns and Risk of Mortality in a Longitudinal Cohort of the Salus in Apulia Study. Nutrients 2020, 12, doi:10.3390/nu12041070.
12. Sardone, R.; Sborgia, G.; Niro, A.; Giuliani, G.; Pascale, A.; Puzo, P.; Guerra, V.; Castellana, F.; Lampignano, L.; Donghia, R.; et al. Retinal Vascular Density on Optical Coherence Tomography Angiography and Age-Related Central and Peripheral Hearing Loss in a Southern Italian Older Population. J. Gerontol. A Biol. Sci. Med. Sci. 2020, doi:10.1093/gerona/glaa269.
13. Sardone, R.; Lampignano, L.; Guerra, V.; Zupo, R.; Donghia, R.; Castellana, F.; Battista, P.; Bortone, I.; Procino, F.; Castellana, M.; et al. Relationship between Inflammatory Food Consumption and Age-Related Hearing Loss in a Prospective Observational Cohort: Results from the Salus in Apulia Study. Nutrients 2020, 12, doi:10.3390/nu12020426.
14. Castellana, F.; Lampignano, L.; Bortone, I.; Zupo, R.; Lozupone, M.; Griseta, C.; Daniele, A.; De Pergola, G.; Giannelli, G.; Sardone, R.; et al. Physical Frailty, Multimorbidity, and All-Cause Mortality in an Older Population From Southern Italy: Results From the Salus in Apulia Study. J. Am. Med. Dir. Assoc. 2021, doi:10.1016/j.jamda.2020.12.026.

15. Carlesimo, G.A.; Caltagirone, C.; Gainotti, G.; Fadda, L.; Gallassi, R.; Lorusso, S.; Marfia, G.; Marra, C.; Nocentini, U.; Parnetti, L. The Mental Deterioration Battery: Normative Data, Diagnostic Reliability and Qualitative Analyses of Cognitive Impairment. Eur. Neurol. 1996, 36, 378–384, doi:10.1159/000117297.
16. Crook, T.H., 3rd; Feher, E.P.; Larrabee, G.J. Assessment of Memory Complaint in Age-Associated Memory Impairment: The MAC-Q. Int. Psychogeriatr. 1992, 4, 165–176, doi:10.1017/s1041610292000991.
17. Giovagnoli, A.R.; Del Pesce, M.; Mascheroni, S.; Simoncelli, M.; Laiacona, M.; Capitani, E. Trail Making Test: Normative Values from 287 Normal Adult Controls. Ital. J. Neurol. Sci. 1996, 17, 305–309, doi:10.1007/BF01997792.
18. Caffarra, P.; Gardini, S.; Zonato, F.; Concari, L.; Dieci, F.; Copelli, S.; Freedman, M.; Stracciari, A.; Venneri, A. Italian Norms for the Freedman Version of the Clock Drawing Test. J. Clin. Exp. Neuropsychol. 2011, 33, 982–988, doi:10.1080/13803395.2011.589373.
19. Yesavage, J.A.; Brink, T.L.; Rose, T.L.; Lum, O.; Huang, V.; Adey, M.; Leirer, V.O. Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. J. Psychiatr. Res. 1982, 17, 37–49, doi:10.1016/0022-3956(82)90033-4.
20. Measso, G.; Cavarzeran, F.; Zappalà, G.; Lebowitz, B.D.; Crook, T.H.; Pirozzolo, F.J.; Amaducci, L.A.; Massari, D.; Grigoletto, F. The Mini-mental State Examination: Normative Study of an Italian Random Sample. Dev. Neuropsychol. 1993, 9, 77–85, doi:10.1080/87565649109540545.
21. Grissom, R.J.; Kim, J.J. Effect Sizes for Research: A Broad Practical Approach. 2005.
22. Zahodne, L.B.; Stern, Y.; Manly, J.J. Differing Effects of Education on Cognitive Decline in Diverse Elders with Low versus High Educational Attainment. Neuropsychology 2015, 29, 649–657, doi:10.1037/neu0000141.
23. Solfrizzi, V.; Scafato, E.; Seripa, D.; Lozupone, M.; Imbimbo, B.P.; D'Amato, A.; Tortelli, R.; Schilardi, A.; Galluzzo, L.; Gandin, C.; et al. Reversible Cognitive Frailty, Dementia, and All-Cause Mortality. The Italian Longitudinal Study on Aging. J. Am. Med. Dir. Assoc. 2017, 18, 89.e1–e89.e8, doi:10.1016/j.jamda.2016.10.012.
24. Park, J.E.; Lee, J.-Y.; Suh, G.-H.; Kim, B.-S.; Cho, M.J. Mortality Rates and Predictors in Community-Dwelling Elderly Individuals with Cognitive Impairment: An Eight-Year Follow-up after Initial Assessment. International Psychogeriatrics 2014, 26, 1295–1304.
25. Verghese, J. Motoric Cognitive Risk Syndrome: Next Steps. Eur. J. Neurol. 2021, doi:10.1111/ene.14949.