ORIGINAL ARTICLE

The Framingham cardiovascular risk score in multiple sclerosis

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Background and purpose: Cardiovascular risk factors can increase the risk of multiple sclerosis (MS) and modify its course. However, such factors possibly interact, determining a global cardiovascular risk. Our aim was to compare the global cardiovascular risk of subjects with and without MS with the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR) and to evaluate its importance on MS-related outcomes.

Methods: Age, gender, smoking status, body mass index, systolic blood pressure, type II diabetes and use of antihypertensive medications were recorded in subjects with and without MS to estimate the FR, an individualized percentage risk score estimating the 10-year likelihood of cardiovascular events.

Results: In total, 265 MS subjects were identified with 530 matched controls. A *t* test showed similar FR in cases and controls ($P = 0.212$). Secondary progressive MS presented significantly higher FR compared to relapsing–remitting MS ($P < 0.001$). Linear regression analysis showed a direct relationship between FR and Expanded Disability Status Scale ($P < 0.001$) and MS Severity Scale ($P < 0.001$).

Conclusion: The FR, evaluating the global cardiovascular health by the interaction amongst different risk factors, relates to MS disability, severity and course.

Introduction

Multiple sclerosis (MS) is a chronic disorder of the central nervous system whose pathogenesis and clinical course are influenced by the interaction of environmental, genetic and autoimmune factors [1]. Intriguingly, risk factors for MS also include cardiovascular risk factors that can be modified, with subsequent possible effects on MS evolution.

In particular, the prevalence of cardiovascular disorders is slightly higher or, probably, not different in MS subjects, as compared to the general population [2–6]. However, MS subjects presenting vascular comorbidities seem to have higher chances of ambulatory disability [7]. Moreover, being overweight apparently increases MS risk and MS-related morbidity [8–10]. Similarly, MS subjects are more at risk of insulin resistance, another factor possibly increasing MS-related disability [10]. In addition, cigarette smokers are more at risk of MS and have worse MS clinical and neuroradiological outcomes, with higher risk of secondary progression and increased mortality rate [11–15]. Finally, high sodium intake, a regulating factor of blood pressure, has been related to clinical and radiological MS exacerbations [16].

In conclusion, there are several studies evaluating single cardiovascular risk factors in MS and their impact on the course of the disease [2–17]. However, it is possible that MS outcomes are affected by the interaction of different cardiovascular risk factors, and studies evaluating single factors have missed this perspective. Therefore the present study aims to evaluate (i) the global cardiovascular risk in MS with the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR), a standardized algorithm estimating the 10-year likelihood of cardiovascular

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events [22]; (ii) differences in FR between subjects with and without MS; (iii) possible relationships between FR and MS-related disability, severity and treatment choice.

Methods

Study design

This is a cross-sectional case–control study evaluating the FR in subjects with and without MS and its relationships with MS clinical features. Considering that all clinical assessments were part of clinical practice in a university setting, specific ethical approval was not required. All subjects signed the general informed consent form, authorizing the use of observational clinical data for research purposes. The study was performed in accordance with good clinical practices and the Declaration of Helsinki.

Subjects with MS

Multiple sclerosis subjects were consecutively identified at the MS Centre of 'Federico II' University Hospital in Naples, Italy, whilst attending their scheduled visit in September 2014, according to clinical practice. The main inclusion criterion was a diagnosis of definite MS according to Poser or McDonald criteria [19,20]. Subjects presenting MS-related conditions possibly affecting neurological or cardiovascular evaluation, such as current clinical relapse, recent disease-modifying treatment (DMT) change (<6 months, a time usually assumed as necessary for DMTs to achieve their clinical efficacy) or recent corticosteroid treatment (<1 month), were excluded.

Trained physicians evaluated all MS subjects for MS clinical features. Kurtzke's Expanded Disability Disease Score (EDSS) was adopted to evaluate current MS-related disability [21]. In order to rate disease severity, disease duration (years since clinical onset) was recorded and the MS Severity Scale (MSSS) was calculated [22]. Current DMT was recorded and MS subjects were categorized according to the treatment (interferon, natalizumab or fingolimod) or as not undergoing any DMT. DMTs were prescribed according to current European Medicines Agency indications [23]. MS subjects were categorized according to the clinical course in relapsing–remitting MS (RRMS) or secondary progressive MS (SPMS) [24]. For RRMS, the occurrence of clinical relapse during the previous 12 months was recorded. Finally, all MS subjects were investigated for FR items [18].

Subjects without MS

Controls were identified amongst subjects visiting the same hospital within the same period (September 2014) for their scheduled visit at the Occupational Medicine Unit, in accordance with Italian regulations for preventive purposes. All subjects without MS underwent a detailed medical history and examination; comorbidities and current medications were recorded. FR was subsequently calculated [18].

Framingham risk score assessment

Cardiovascular risk factors were directly assessed to calculate the FR in subjects with and without MS. In particular, from age, gender, smoking status, body mass index (BMI), systolic blood pressure, type II diabetes and use of antihypertensive medications it is possible to calculate the FR based on non-laboratory predictors, an individualized percentage risk score estimating the 10-year likelihood of cardiovascular events (coronary, cerebrovascular, peripheral arterial disease and heart failure) [18].

The FR single item evaluation was performed as previously suggested [18,25]. In particular, smoking habits were recorded and persons who smoked regularly during the previous 12 months were classified as smokers. Height and weight were measured with standardized hospital clinical methods, and BMI was calculated. Two blood pressure determinations were made after the participant had been sitting at least 5 min, and the average was used for analyses. Type II diabetes was considered present if the participant was under treatment with insulin or oral hypoglycaemic agents or if fasting blood glucose exceeded 126 mg/dl in previous blood examinations (all subjects performed at least two different blood tests in the previous 12 months, according to clinical practice) [18].

Subjects presenting serious concomitant illnesses (i.e. cancer or hepatitis) or treatments (i.e. chemotherapy) possibly interfering with cardiovascular risk were excluded.

Considering that the FR is composed of both modifiable (smoking, BMI, systolic blood pressure, type II diabetes and use of antihypertensive medications) and not-modifiable (age, gender) risk factors, statistical analysis has been adjusted for age and gender in order to better understand the impact of modifiable cardiovascular risk factors on MS.

Sample size estimation

Considering the main outcome of the present study (difference in FR between subjects with and without

MS), a sample of 105 subjects for each group was considered necessary to obtain an acceptable estimate ($\alpha = 0.05$; power = 0.8; effect size $d = 0.5$).

Statistical analysis

In the first part of the study, a cross-sectional case–control evaluation was performed to assess differences in the FR between cases and controls. MS subjects were individually matched to subjects without MS according to age (within 2 years) and gender, with a case:control matching ratio of 1:2. Differences in demographics and in cardiovascular risk factors (FR, smoking status, BMI, systolic blood pressure, use of antihypertensive drugs, diabetes) between cases and controls were explored with the χ^2 test, McNemar's test or t test, as appropriate. Subsequently, the model considering the FR was included in an analysis of variance (ANOVA) adjusted for age, gender and then FR items (smoking status, BMI, systolic blood pressure, use of antihypertensive drugs, diabetes).

In the second part of the present study, relationships between FR and MS clinical features were evaluated. The analysis of the FR was performed with linear regression analysis (EDSS, MSSS) or ANOVA (current DMT, clinical course, occurrence of a relapse), as appropriate. The model was adjusted for age, gender and then FR components (smoking status, BMI, systolic blood pressure, use of antihypertensive drugs, diabetes).

Stata 12.0 and Microsoft Excel were used for data processing and analysis. Each of the analyses was tested for normal distribution of residuals by using both statistical and graphical methods. Results were considered statistically significant for $P < 0.05$.

Results

In the first part of our study, 265 MS subjects were included and 530 controls were subsequently matched for age and gender. Cases and controls were similar for age, gender, BMI and smoking status ($P = 0.275$, $P = 0.999$, $P = 0.159$ and $P = 0.169$, respectively) (Table 1). Controls presented higher systolic blood pressure ($P = 0.010$) and use of antihypertensive drugs ($P < 0.001$) compared to MS subjects (Table 1). MS subjects presented higher prevalence of diabetes compared to controls ($P < 0.001$) (Table 1). The FR was not different between cases and controls ($P = 0.212$) (Table 1). The latter result was confirmed with ANOVA adjusted for age and gender ($P = 0.486$; adjusted $R^2 = 0.618$) and for FR items ($P = 0.476$; adjusted $R^2 = 0.812$), and in particular was influenced by age ($P < 0.001$), gender ($P < 0.001$), smoking status ($P < 0.001$), BMI ($P < 0.001$), systolic blood pressure ($P < 0.001$), use of antihypertensive drugs ($P < 0.001$) and diabetes ($P < 0.001$).

In the second part of our study, only MS subjects were evaluated. Linear regression analysis showed a direct relationship between FR and EDSS before ($P < 0.001$) but not after correction for age, gender ($P = 0.285$) and FR items ($P = 0.217$) (Table 2). Furthermore, linear regression analysis showed a direct relationship between FR and MSSS before ($P < 0.001$) (Fig. 1) and after correction for age, gender ($P = 0.003$) and FR items ($P = 0.022$) (Table 2).

DMTs performed in the population were interferon ($n = 148$; FR = 6.7 ± 6.1), natalizumab ($n = 63$; FR = 4.6 ± 5.3), fingolimod ($n = 36$; FR=6.3 ± 6.4) or no current treatment ($n = 18$; FR = 8.7 ± 9.9). None of the subjects was treated with glatiramer acetate. ANOVA did not show differences in FR amongst subjects undergoing different DMTs before ($P = 0.057$) and after correction for age, gender ($P = 0.277$) and FR items ($P = 0.165$) (Table 2).

The t test showed significantly higher FR in SPMS compared to RRMS ($P < 0.001$) (Fig. 2; Table 2). ANOVA analysis confirmed the latter result after adjusting for age, gender ($P = 0.001$) and FR items ($P = 0.029$) (Table 2).

When evaluating RRMS, 54 subjects (out of 215 RRMS) experienced a clinical relapse during the previous 12 months. FR showed no difference between subjects presenting a clinical relapse during the previous 12 months (4.9 ± 5.5) and those not (4.9 ± 5.7) on t test ($P = 0.434$) and on ANOVA adjusted for age, gender ($P = 0.160$) and FR items ($P = 0.644$) (Table 2).

Discussion

This is the first study that not only separately considered cardiovascular risk factors but also evaluated their biological interactions by the FR, assessing the global cardiovascular health in MS subjects.

Considering our primary objective, subjects with and without MS presented only slight differences in systolic blood pressure, use of antihypertensive drugs and diabetes prevalence, whereas they did not differ in the predicted risk of cardiovascular events within 10 years. Interestingly, previous studies investigating the prevalence of cardiovascular events in MS [2,26,27] suggested an increased frequency of ischaemic stroke possibly biased by magnetic resonance imaging surveillance [2] or mediated, at least in part, by widespread cerebral hypoperfusion due to impaired neuroaxonal metabolism [6]. In addition, an increased frequency of venous thromboembolic disorders has

Table 1 Cardiovascular risk in MS subjects and controls

	Subjects with MS (n = 265)	Subjects without MS (n = 530)	P value
Gender: male/female	101/164	202/328	0.999
Age, years ± SD (range)	42.2 ± 10.9 (18–65)	42.9 ± 9.7 (20–65)	0.275
Age at onset, years ± SD (range)	29.9 ± 8.2 (14.5–52.0)	–	–
Disease duration, years ± SD (range)	8.2 ± 6.5 (0.5–29.7)	–	–
Smokers, n (%)	99 (37.4)	192 (36.2)	0.169
BMI, kg/m^2 ± SD (range)	26.3 ± 4.5 (16.5–44.7)	26.6 ± 4.9 (17.5–50.2)	0.159
Systolic blood pressure, mmHg ± SD (range)	118.9 ± 13.6 (90–170)	121.6 ± 14.6 (70–180)	0.010
Use of antihypertensive drugs, n (%)	35 (13.2%)	42 (7.9%)	<0.001
Diabetes, n (%)	5 (1.9%)	4 (0.7%)	<0.001
FR, mean ± SD (range)	6.5 ± 6.3 (0.2–37.2)	6.9 ± 7.0 (0.2-37.1)	0.212
Male	9.9 ± 7.6 (0.5–37.2)	10.5 ± 8.4 (1.1–37.1)	0.122
Female	4.7 ± 4.7 (0.2–30.0)	4.8 ± 4.7 (0.2–30.2)	0.364

MS, multiple sclerosis; BMI, body mass index; FR, simplified 10-year Framingham General Cardiovascular Disease Risk Score.

Demographics, cardiovascular risk factors and Framingham risk score in subjects with and without MS. Results are shown from the χ^2 test, McNemar's test or t test, as appropriate.

been found, suggesting immobility as a possible factor [2]. However, such cardiovascular events might have been related also to an increased cardiovascular risk that, unfortunately, these studies did not investigate.

In the second part of the present study, MS subjects were analysed for clinical correlates of the FR. In particular, both EDSS and MSSS were evaluated. Although they ultimately refer to MS-related disability, the MSSS accounts for both disease duration and disability and is a reliable marker of severity in MS evolution [22]. In more detail, cardiovascular risk factors and, in particular, modifiable ones appeared to affect the speed in disability accrual (evaluated by the MSSS) more than the disability itself. In addition, this association was not influenced by single cardiovascular factors but by their interaction, evaluated with the FR. Moreover, the global predicted cardiovascular risk related to a secondary progressive course, and this association was only in part influenced by single cardiovascular risk factors. Therefore the biological interaction of different cardiovascular risk factors determining a global cardiovascular risk (FR) is strongly associated with increased MS disability and severity and with a secondary progressive course. Considering possible biological mechanisms, it has been hypothesized that cardiovascular comorbidities might increase peripheral low-grade inflammation, with subsequent progressive activation of the systemic inflammatory cascade, worsening demyelination and neurodegeneration in MS [28].

Finally, some limitations need to be reported, such as the cross-sectional design, not exploring a possible causality. For instance, an increase in the cardiovascular risk might also be related to disability-related reduced mobility, with subsequent differences between RRMS and SPMS. Furthermore, there is a risk of a surveillance bias for MS subjects undergoing periodic medical visits. In addition, it is possible to calculate the FR considering lipid profile instead of BMI. Unfortunately, standardized cholesterol measurements were not available for all subjects, and further studies are warranted on this issue, since an adverse lipid profile has been associated with MS evolution [28,29]. However, both FR versions are a reliable index of the 10-year risk of cardiovascular events [22]. Moreover, the inclusion of subjects visiting our centre in a limited time (September 2014) might have determined a selection bias with an increased prevalence of those subjects more frequently visiting our centre (i.e. natalizumab-treated subjects). In line with this, the absence of primary progressive MS and of subjects treated with glatiramer acetate must be reported, raising some generalizability concerns on this population. However, the present study should be considered preliminary and further investigations are warranted to explore these open issues.

In conclusion, the global cardiovascular risk does not appear to be different between subjects with and without MS. However, the FR is related to MS disability, severity and course. Therefore, modifiable cardiovascular risk factors should be investigated and corrected with a possible effect on MS-related outcomes.

Table 2 FR and MS-related outcomes

		Unadjusted model					Partially adjusted model (age, gender)					Fully adjusted model (age, gender, BMI, systolic blood pressure, use of antihypertensive drugs, smoking status, diabetes)				
				95% CI					95% CI					95% CI		
	Subjects with MS (n = 265)	Coefficient	R^2	Lower	Upper	Significance	Coefficient	R^2	Lower	Upper	Significance	Coefficient	R^2	Lower	Upper	Significance
EDSS, mean ± SD (range)	3.8 ± 1.5 (1–7.5)	0.081	–	0.055	0.107	***	0.020	–	–0.017	0.059	ns	0.033	–	−0.019	0.086	ns
Age		–	–	–	–	–	0.052	–	0.031	0.073	***	0.058	–	0.359	0.081	***
Gender		–	–	–	–	–	0.105	–	–0.279	0.491	ns	0.082	–	−0.316	0.482	ns
BMI		–	–	–	–	–	–	–	–	–	–	−0.011	–	−0.049	0.026	ns
Systolic blood pressure		–	–	–	–	–	–	–	–	–	–	−0.012	–	−0.027	0.002	*
Use of antihypertensive drugs		–	–	–	–	–	–	–	–	–	–	−0.360	–	−0.885	0.165	ns
Smoking status		–	–	–	–	–	–	–	–	–	–	0.272	–	−0.111	0.657	ns
Diabetes		–	–	–	–	–	–	–	–	–	–	−0.006	–	−1.235	1.222	ns
MSSS, mean ± SD (range)	4.9 ± 2.0 (0.49–9.26)	0.071	–	0.035	0.107	***	0.083	–	0.027	0.138	***	0.089	–	0.012	0.165	**
Age		–	–	–	–	–	–0.020	–	–0.050	0.010	ns	−0.012	–	−0.045	0.020	ns
Gender		–	–	–	–	–	0.399	–	–0.157	0.956	ns	0.412	–	−0.161	0.985	ns
BMI		–	–	–	–	–	–	–	–	–	–	0.039	–	−0.014	0.093	ns
Systolic blood pressure		–	–	–	–	–	–	–	–	–	–	–0.028	–	−0.049	–0.006	***
Use of antihypertensive drugs		–	–	–	–	–	–	–	–	–	–	–0.011	–	−0.766	0.742	ns
Smoking status		–	–	–	–	–	–	–	–	–	–	0.418	–	−0.133	0.970	ns
Diabetes		–	–	–	–	–	–	–	–	–	–	0.109	–	−1.654	1.872	ns
DMT		–	0.028	–	–	*	–	0.590	–	–	ns	–	0.837	–	–	ns
Age		–	–	–	–	–	–	–	–	–	***	–	–	–	–	***
Gender		–	–	–	–	–	–	–	–	–	***	–	–	–	–	***
BMI		–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns
Systolic blood pressure		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***
Use of antihypertensive drugs		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***
Smoking status		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***
Diabetes		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***

(continued)

Table 2 *(Continued)*

		Unadjusted model					Partially adjusted model (age, gender)					Fully adjusted model (age, gender, BMI, systolic blood pressure, use of antihypertensive drugs, smoking status, diabetes)				
				95% CI					95% CI					95% CI		
	Subjects with MS (n = 265)	Coefficient	R^2	Lower	Upper	Significance	Coefficient	R^2	Lower	Upper	Significance	Coefficient	R^2	Lower	Upper	Significance
RRMS/SPMS, n (%)	215/50 (81.1/18.9)	–	0.085	–	–	***	–	0.588	–	–	***	–	0.836	–	–	**
Age		–	–	–	–	–	–	–	–	–	***	–	–	–	–	***
Gender		–	–	–	–	–	–	–	–	–	**	–	–	–	–	*
BMI		–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns
Systolic blood pressure		–	–	–	–	–	–	–	–	–	–	–	–	–	–	**
Use of antihypertensive drugs		–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns
Smoking status		–	–	–	–	–	–	–	–	–	–	–	–	–	–	**
Diabetes		–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns
Relapses, number in RRMS (%)	54 (25.1)	–	0.029	–	–	ns	–	0.714	–	–	ns	–	0.887	–	–	ns
Age		–	–	–	–	–	–	–	–	–	***	–	–	–	–	***
Gender		–	–	–	–	–	–	–	–	–	***	–	–	–	–	***
BMI		–	–	–	–	–	–	–	–	–	–	–	–	–	–	ns
Systolic blood pressure		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***
Use of antihypertensive drugs		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***
Smoking status		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***
Diabetes		–	–	–	–	–	–	–	–	–	–	–	–	–	–	***

FR, Framingham General Cardiovascular Disease Risk Score; MS, multiple sclerosis; BMI, body mass index; 95% CI, 95% confidence interval; EDSS, Expanded Disability Status Scale; MSSS, MS Severity Scale; DMT, disease-modifying treatment; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.

FR has been related to MS-related outcomes (EDSS, MSSS, DMT, disease course, occurrence of clinical relapse during previous 12 months) with analysis of variance or linear regression analysis, as appropriate. Models have been corrected for age, gender and then FR components (BMI, systolic blood pressure, use of antihypertensive drugs, smoking status, diabetes). Coefficients, R^2 or adjusted R^2, 95% confidence intervals and statistical significance are shown (ns, $P > 0.100$; *$P < 0.100$; **$P < 0.050$; ***$P < 0.010$), according to statistical methods.

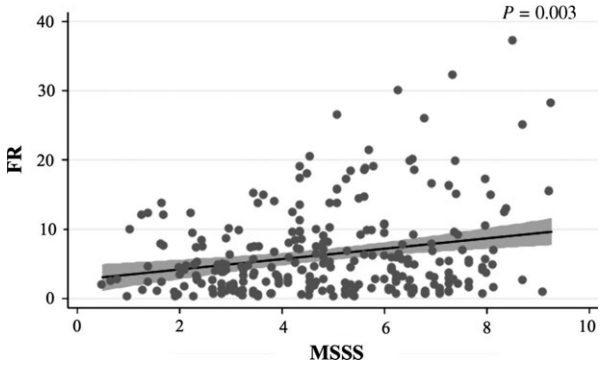

Figure 1 Scatter plot showing the relationship between the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR) and the Multiple Sclerosis Severity Scale (MSSS). *P* value from linear regression analysis adjusted for age and gender is shown; 95% confidence intervals are represented as a grey shadow.

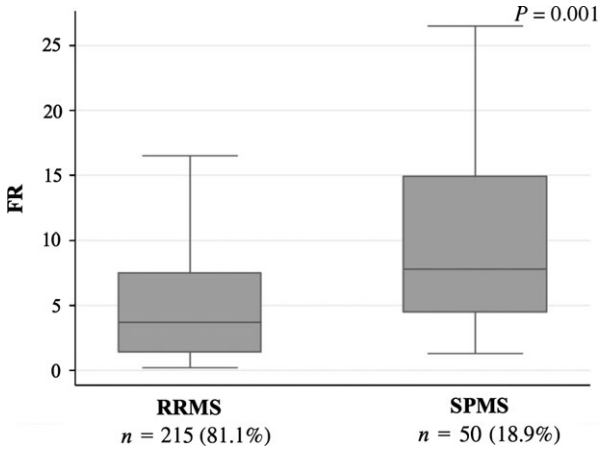

Figure 2 Box-and-whisker plot showing the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR) in relapsing–remitting multiple sclerosis (RRMS) (n = 215; FR = 5.4 ± 5.5) and in secondary progressive multiple sclerosis (SPMS) (n = 50; FR = 10.3 ± 8.0). *P* value from analysis of variance adjusted for age and gender is shown.

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Ethics approval

Considering that all clinical assessments were part of clinical practice in a university setting, specific ethical approval was not required.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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