

## Cardiovascular risk factors affect brain volume in young multiple sclerosis patients

<sup>1,3</sup>R. Bonacchi, <sup>2</sup>D. Mistri, <sup>1</sup>A. Meani, <sup>1</sup>A. Zanghi, <sup>1,3,4,5</sup>M. Filippi, <sup>2,3,5</sup>MA Rocca

<sup>1</sup>Neuroimaging Research Unit, <sup>2</sup>Neuroimaging of CNS White Matter Unit, Institute of Experimental Neurology, Division of Neuroscience, <sup>3</sup>Neurology Unit, <sup>4</sup>Neurophysiology Unit, San Raffaele Scientific Institute, <sup>5</sup>Vita-Salute San Raffaele University, Milan, Italy

### Short title: comorbidity impact on brain atrophy in MS

**Background.** Previous studies demonstrated an impact of cardiovascular (CV) risk factors on clinical and MRI outcomes in multiple sclerosis (MS) patients without setting an age-limit, but older patients present cerebral small vessel disease-related damage.

**Objectives.** To investigate impact of CV risk factors on brain atrophy in MS patients under age 50.

**Methods.** One-hundred and twenty-four (79 relapsing-remitting, 45 progressive) MS patients, and 95 age- and sex-matched healthy controls (HC) underwent brain 3T MRI with sequences for assessing lesions and atrophy. Traditional CV risk factors were assessed: having smoked  $\geq 5$  pack-years (py), and presence of hypertension, dyslipidemia, diabetes/prediabetes. More stringent cut-offs were also assessed: having smoked  $\geq 10$ py, and hypertension, dyslipidemia or diabetes under treatment. Linear models adjusted for age, sex, disease duration, phenotype and treatment were used to determine the impact of CV risk factors on MRI variables.

**Results.** Nineteen HC and 48 MS patients had 1 traditional CV risk factor, 4 HC and 15 MS patients had  $>1$ . Ten HC and 30 MS patients had 1 stringent CV risk factor, 3 and 8 had  $>1$ . In MS patients, the presence of  $\geq 2$  traditional CV risk factors was associated with reduced normalized grey matter volume (NGMV) ( $p=0.01$ ), white matter volume (NWMV) ( $p=0.03$ ) and brain volume (NBV) ( $p=0.003$ ), and not with T2-lesion volume (T2-LV) ( $p=0.27$ ). In MS patients, the presence of  $\geq 1$  stringent CV risk factor was associated with reduced NGMV ( $p=0.006$ ), NWMV ( $p=0.003$ ) and NBV ( $p<0.001$ ), and higher T2-LV ( $p=0.03$ ). In HC, no differences were observed according to either traditional or stringent risk factor presence.

**Conclusions.** The presence of CV risk factors is associated with brain atrophy in MS patients, even under age 50. CV risk factors seem to have synergistic effects, determining brain atrophy even for levels of exposure that may often be overlooked by clinicians, when present in combination.

**Funding:** Partially supported by grants from Fondazione Italiana Sclerosi Multipla (FISM/2018/R/16).