

**Title:** Evaluating the risk of macrovascular events and mortality in individuals with multiple sclerosis in England: a population-based nested case-control study

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**Abstract**

**Background:** Individuals with Multiple Sclerosis (MS) are at increased cardiovascular risk and mortality; however, evidence from population-based studies is sparse. We assessed whether the risk of macrovascular events and mortality differs in individuals with MS as compared with a matched non-MS population in England.

**Methods:** Individuals with a diagnosis of MS after 1 Jan 1987 and registered with English general practices were identified from the UK Clinical Practice Research Datalink database and matched with up to 6 controls by age, sex, and general practice. Clinical data were linked with hospital and mortality data. We included individuals with  $\geq 3$  MS diagnoses recorded over the study period (in primary and secondary care settings). First MS diagnosis was considered as index date and a matched index date was assigned to controls. Study baseline was the year of MS diagnosis. We used multivariable Cox proportional hazard regression model to compare the risk of acute coronary events and cerebrovascular disease and mortality between individuals with a without MS. Models were adjusted for age, sex, ethnicity (white/non-white), deprivation index, smoking status, diabetes, depression, urinary-tract infection, medication (antihypertensive, lipid-lowering, antidiabetic, anti-platelet, and anti-coagulant), and number of primary care visits in the index year.

**Results:** 12,251 individuals with MS were matched to 72,573 controls. Individuals with MS were younger (42.0 years  $\pm$  13.0, controls: 44.9  $\pm$  13.3) than controls, more likely to smoke (38.3% vs. controls: 29.6%), have diabetes (6.9% vs. controls: 5.0%), and depression (20.9% vs. controls: 8.7%); 93.9% were white (controls: 91.8%). They were similar to controls for sex, index of deprivation, and medications. As compared with controls, individuals with MS had increased rates of incident acute coronary events (HR 1.25, 95%CI 1.07-1.47) and cerebrovascular disease (HR 1.81, 95% CI 1.51-2.16). Rate of any macrovascular event was 34% increased (HR 1.34, 95% CI 1.16-1.53). They also had >3-fold increased risk of mortality (HR 3.19, 95% CI 3.03-3.36) and 91% increased risk of fatal macrovascular event (HR 1.92, 95% CI 1.68-2.19).

**Conclusions:** Individuals with MS are at increased risk of macrovascular events and cardiovascular disease mortality; the risk persists after adjusting for cardiovascular risk factors. Further studies are warranted to assess the effect of tight cardiovascular risk factor management on these outcomes.

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